Neurotoxicity: Identifying and Controlling Poisons of the Nervous System

April 1990

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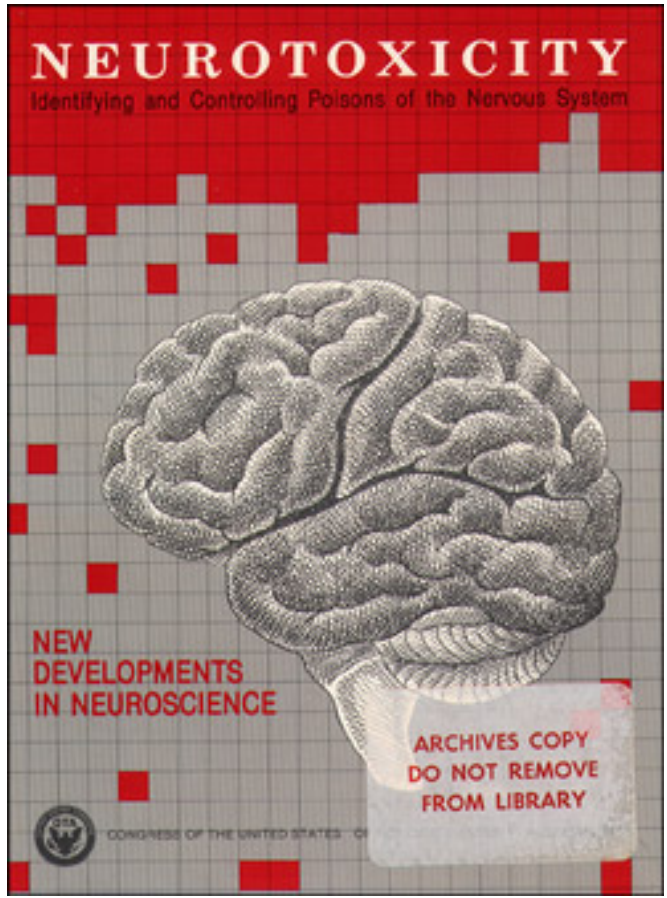

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Foreword

Extraordinary developments in the neuroscience in recent years have been paralleled by a growing congressional interest in their policy implications. The designation of the 1990s by the 101st Congress as the "Decade of the Brain" is one indication of the promise shown by scientific advances for treating diseases of the nervous system and for increased general understanding of the human mind. Other advances, however, have led us to the disturbing realization that many commonly used chemicals can adversely affect the human nervous system. Concern about this issue provided the motivation for hearings held in October 1985 on ''Neurotoxins in the Home and in the Workplace' by the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology.

Another result of heightened congressional interest was a request that OTA undertake a series of assessments on major public policy issues related to the neuroscience. Requesting committees included the House Committees on Science, Space, and Technology; Energy and Commerce; Appropriations; and Veterans' Affairs; and the Senate Subcommittee on Science, Technology, and Space of the Committee on Commerce, Science, and Transportation. In addition, the Senate Committee on Environment and Public Works recently requested a study of the noncancer health risks posed by toxic substances. This Report, the first of the neuroscience series, discusses the risks posed by neurotoxic substances—substances that can adversely affect the nervous system—and evaluates the Federal research and regulatory programs now in place to address these risks.

One finding of this Report is that considerably more research and testing are necessary to determine which substances have neurotoxic potential. Neurotoxic effects can often go unrecognized because symptoms are varied and may not appear for months or even years. Adverse effects range from impaired movement, anxiety, and confusion to memory loss, convulsions, and death. Another important finding is the need for greater public awareness. Neurotoxic chemicals constitute a major public health threat; the social and economic consequences of excessive exposure to them are potentially very large. Minimizing exposure requires action not just by regulatory and other public officials, but also by individual citizens who can take steps to avoid these substances both at home and in the workplace.

Many individuals and institutions contributed their time and expertise to the project. Scientists and regulatory officials in several Federal agencies and experts in academia and industry served on the project's advisory panel, in workshop groups, and as reviewers. OTA gratefully acknowledges the assistance of these contributors. As with all OTA assessments, however, responsibility for the content of the Report is OTA's alone and does not necessarily constitute the consensus or endorsement of the advisory panel or the Technology Assessment Board.



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NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the advisory and study panel members. The panels do not, however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

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Summary, Policy Issues, and Options for Congressional Action

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Chapter 1

Summary, Policy Issues, and Options for Congressional Action

SUMMARY

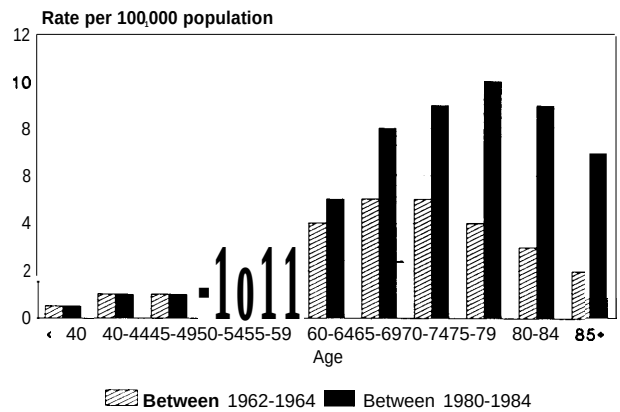
Chemicals are an integral part of our daily lives and are responsible for substantially improving them. Chemicals can also endanger our health, even our survival. This assessment focuses on neurotoxic substances, those chemicals that adversely affect the nervous system. Included among such substances are industrial chemicals, pesticides, therapeutic drugs, abused drugs, food, food additives, cosmetic ingredients, and naturally occurring **substances. Whether** a substance causes an adverse health effect depends on many factors, including the toxicity of the substance, the extent of exposure, and the age and state of health of an exposed individual. Minimizing public health risks requires information about the properties and mechanisms of action of potentially toxic substances to which humans may be exposed. This information provides the foundation for safety standards.

More than 65,000 chemicals are in the U.S. Environmental Protection Agency's (EPA) inventory of toxic chemicals; and the Agency annually receives approximately 1,500 notices of intent to manufacture new substances. Since few of these chemicals have been tested to determine if they adversely affect the nervous system, no precise figures are available on the total number of chemicals in existence that are potentially neurotoxic to humans. Some estimates have been developed, however, based on analyses of certain subsets of chemicals. These estimates vary considerably, depending on the definition of neurotoxicity used and the subset of substances examined. For example, some 600 active pesticide ingredients are registered with EPA, a large percentage of which are neurotoxic to varying degrees. One investigator estimated that 3 to 5 percent of industrial chemicals, excluding pesticides, have neurotoxic potential. Another investigator found that 28 percent of industrial chemicals for which occupational exposure standards have already been developed produce neurotoxic effects. In addition, a substantial number of therapeutic drugs have neurotoxic potential.

In recent years, concern about the neurotoxic effects of chemicals has increased as evidence has become available linking exposure to chemicals and drugs with long-term changes in the nervous system. Some scientists believe that neurotoxic substances play a role in triggering some neurological disorders, including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. For example, investigators recently found evidence that the incidence of motor neuron disease (primarily amyotrophic lateral sclerosis) is increasing particularly in the elderly (figure 1-1). Exposure to toxic chemicals may be one of the factors contributing to this increase. More research is necessary to confirm this trend and to determine the underlying causative factors.

Human *exposure* to significant concentrations of most known neurotoxic substances is normally quite limited. Consequently, the number of substances that pose an actual threat to public health is considerably less than the total

Figure I-l—Average Annual Motor Neuron Disease* Mortality in the United States, White Males



*Most motor neuron disease is diagnosed as amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease.

SOURCE: Adapted from D.E. Lilienfeld, et al., "Rising Mortality From Motoneuron Disease in the U. S., 1962-1884," *The Lancet,* Apr. 1, 1989, pp. 710-713.

number of neurotoxic substances in existence. **The number of substances that pose a significant risk to public health and the extent of that risk are unknown because the potential neurotoxicity of only a small number of chemicals has been evaluated adequately.**

Scope of This Study

This study examines many, but not all, of the classes of neurotoxic substances. **The assessment includes discussion of industrial chemicals, pesticides, therapeutic drugs, substance drugs, foods, food additives, cosmetic ingredients, and such naturally occurring substances as lead and mercury.** It does not include radioactive chemicals, nicotine (from cigarette smoke), alcohol (ethanol), biological and chemical warfare agents, microbial, plant, and animal toxins, and physical agents such as noise.

What Is Neurotoxicity?

The nervous system comprises the brain, the spinal cord, and a vast array of nerves and sensory organs that control major body functions. Movement, thought, vision, hearing, speech, heart function, respiration, and numerous other physiological processes are controlled by this complex network of nerve processes, transmitters, hormones, receptors, and channels (figure 1-2).

Every major body system can be adversely affected by toxic substances, but the nervous system is particularly vulnerable (see box l-A). Many toxic substances can alter the normal activity of the nervous system. Some produce effects that occur almost immediately and last for several hours. Examples include an alcoholic beverage or fumes from a can of paint. The effects of other neurotoxic substances may appear only after repeated exposures over weeks or even years: e.g., regularly breathing the

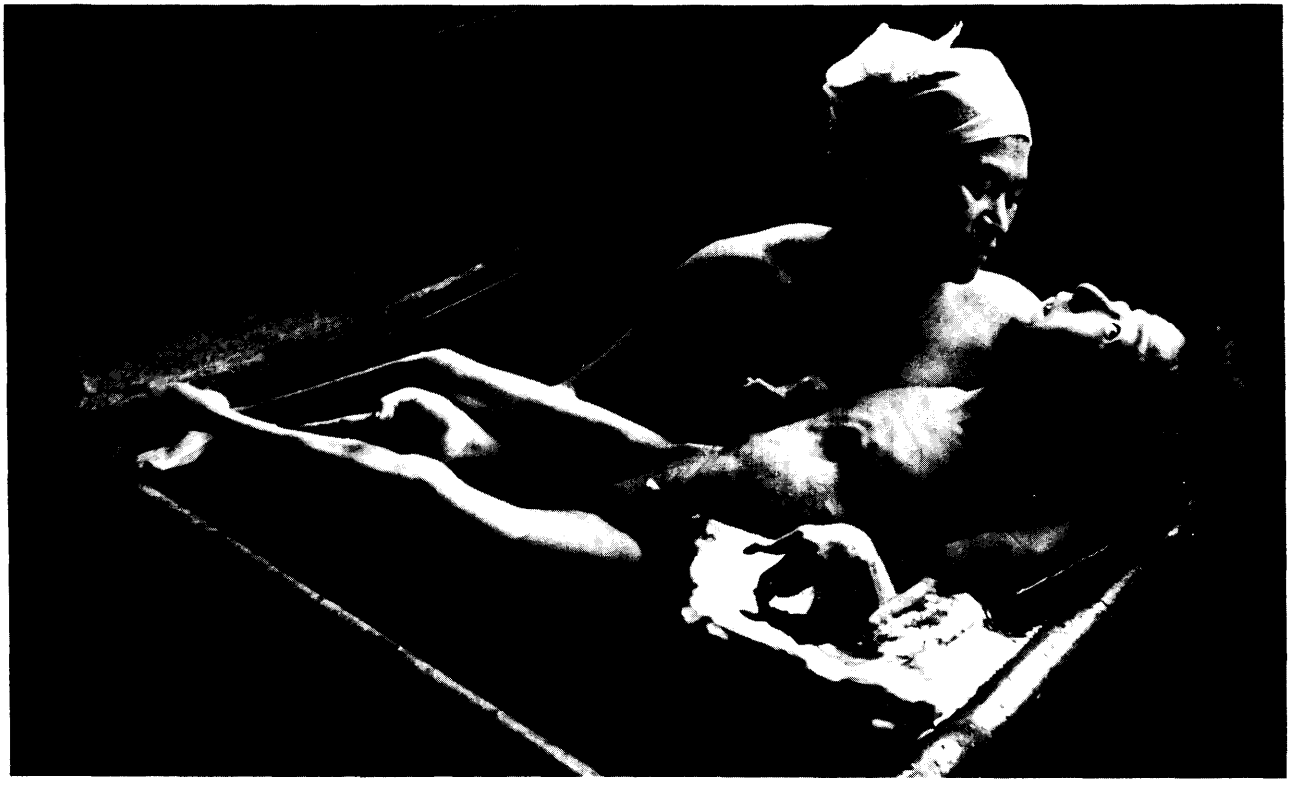
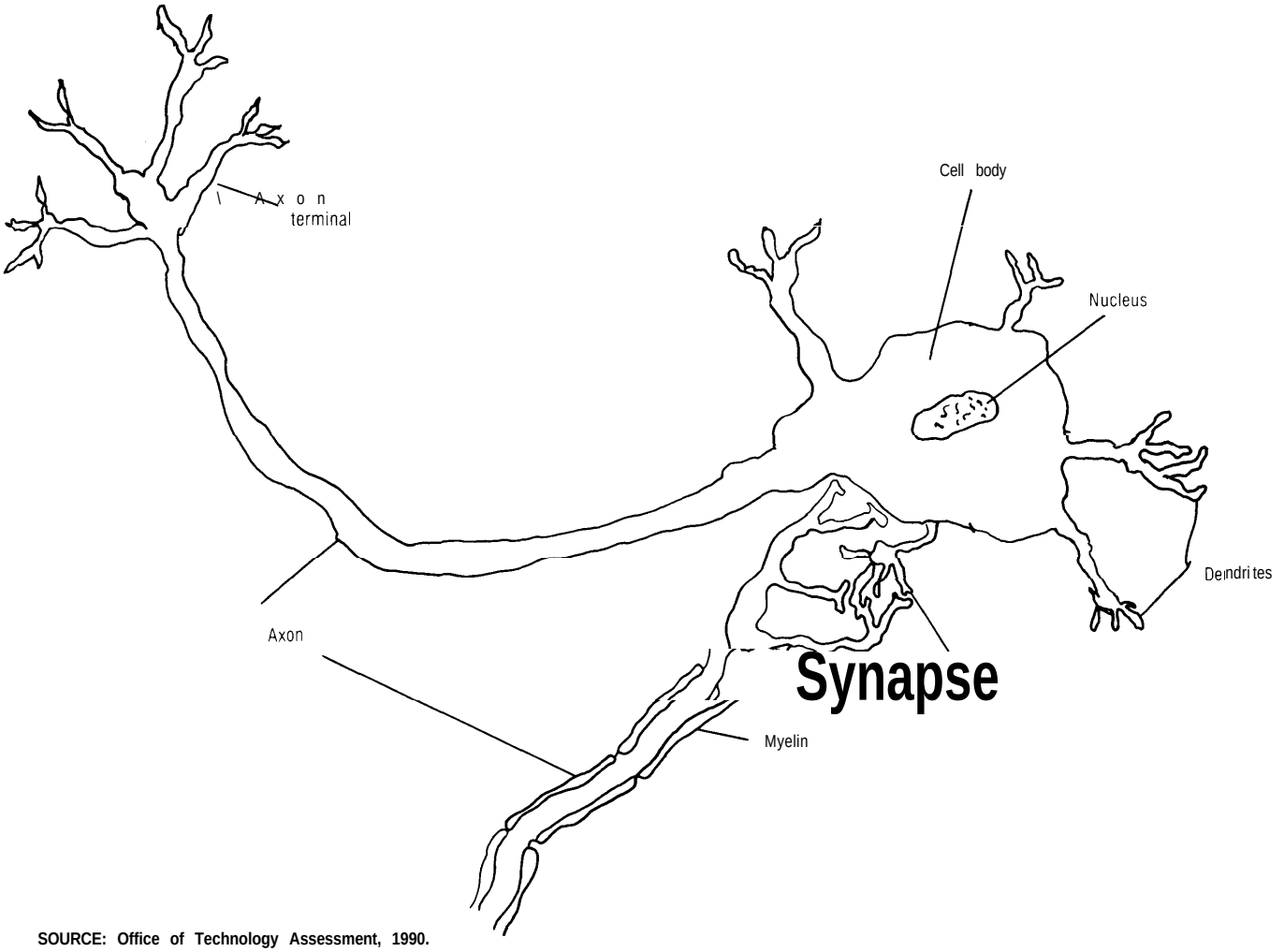


Photo credit: W Eugene Smith and Aileen Smith

A child victimized by mercury poisoning during the Minamata Bay, Japan, incident in the 1950s is bathed by his mother. This is one of the most dramatic poisoning incidents involving a neurotoxic substance.

Figure 1-2—The Fundamental Structure of the Nerve Cell



SOURCE: Office of Technology Assessment, 1990.

Box l-A—Vulnerability of the Nervous System to Toxic Substances

The nervous system is particularly vulnerable to toxic substances because:

. Unlike other cells that make up the body, nerve cells, or neurons, normally cannot regenerate once lost—toxic damage to the brain or spinal cord, therefore, is usually permanent.
- Nerve cell loss and other regressive changes in the nervous system occur progressively in the second half of life—toxic damage may therefore progress with aging.
- Certain regions of the brain and nerves are directly exposed to chemicals in the blood, and many neurotoxic chemicals cross the blood-brain barrier with ease.
- The peculiar architectural features of nerve cells, with their long processes, provide a vast surface area for chemical attack and are therefore inherently susceptible to chemical interference,
- The dependence of the nervous system on a delicate electrochemical balance for proper communication of information throughout the body provides numerous opportunities for foreign chemicals to interfere with normal function.
- Even minor changes in the structure or function of the nervous system may have profound consequences for neurological, behavioral, and related body functions.

SOURCE: P.S. Spencer, personal communication, 1989.

fumes of a solvent in the workplace or eating food or drinking water contaminated with lead. Some substances can permanently damage the nervous system after a single exposure-certain organophosphorous pesticides and metal compounds such as trimethyl tin are examples (box l-B). Other substances, including abused drugs such as heroin and cocaine, may lead to addiction, a long-term adverse alteration of nervous system function. Many neurotoxic substances can cause death when absorbed, inhaled, or ingested in sufficiently large quantities. **Neurotoxic substances play a significant causal role in the development of some neurological and psychiatric disorders; however the precise extent of the contribution is unclear.**

Care must be taken in labeling a substance neurotoxic because factors such as dose and intended effects must be taken into consideration. A substance may be safe and beneficial at one concentration, but neurotoxic at another. For example, vitamins A and B_6 are required in the diet in trace amounts, yet both cause neurotoxic effects in large doses. In other cases, a substance that is known to be neurotoxic may confer benefits that are viewed as outweighing the risk of adverse side-effects. For example, thousands of individuals suffering from schizophrenia have been able to live relatively normal lives because of the beneficial effects of antipsychotic drugs. However, chronic use of prescribed doses of some of these drugs may give rise to tardive dyskinesia—involuntary movements of the face, tongue, and limbs—side-effects so severe that they may incapacitate a patient.

Box 1-B—MPTP and Parkinson's Disease

In recent years, the hypothesis that Parkinson's disease and other neurological disorders might be triggered by environmental factors has become more widely accepted. Although toxic substances have long been considered possible contributors to the cause of some disorders of the nervous system, the MPTP incident has focused more attention on this environmental hypothesis.

MPTP is the abbreviation for l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine, a compound that can be created during the production of synthetic heroin. Remarkably, in just 5 to 15 days, this highly neurotoxic substance can induce a syndrome virtually identical to Parkinson's disease—a disease that usually occurs late in life and develops slowly over a period of years. Both Parkinson's disease and the MPTP-induced syndrome are characterized by tremors and lack of muscular control that stem from degeneration of neurons in the substantial nigra, a region deep in the central area of the brain. Neurons in the substantial nigra synthesize and secrete the neurotransmitter dopamine, hence Parkinson's patients are treated with levodopa, a precursor of this neurotransmitter.

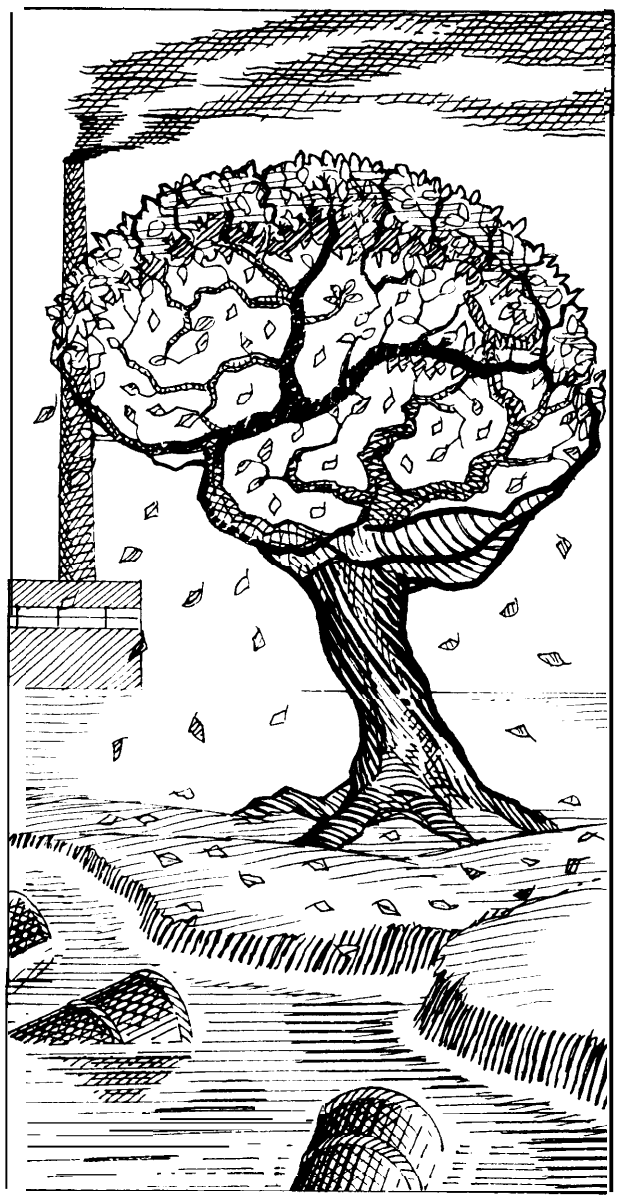
The discovery of the link between MPTP and Parkinson's disease has dramatically changed the nature of research on this disease. Much work has focused on MPP^+, a metabolize of MPTP that is responsible for the adverse effects on the brain. Recently, researchers discovered that a monoamine oxidase inhibitor, a type of drug sometimes used to treat depression, blocks the conversion of MPTP to MPP^+. Other researchers have shown that the monoamine oxidase inhibitor Deprenyl, administered to Parkinson's patients in combination with levodopa, reduces the symptoms of the disease and extends their lives. It was found that Deprenyl slows the rate of degeneration of neurons in the substantial nigra, perhaps making it useful in the treatment of Parkinson's disease.

The MPTP story illustrates how a neurotoxic substance might cause or contribute to the development of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. The relative contributions of environmental and genetic factors to the causes of these diseases are not understood and are the subject of considerable research and debate within the scientific community. Although the extent to which a neurotoxic substance contributes to the cause of Parkinson's disease is unclear, the MPTP story serves as an example of how neurotoxicological research can lead to abetter understanding of the causes of neurological disease and ways to treat it.

SOURCES: I.J. Kopin and S.P. Markey, ''MPTP Toxicity: Implications for Research in Parkinson's Disease,' *Annual Review of Neuroscience* 11:81-96, 1988; J.W. Langston, P. Ballard, J.W. Tetrud, et al., "Chronic Parkinsonism in Humans Due to a Product of Meperidine-Analog Synthesis," *Science* 219:979-980, 1983; R. Lewin, "Big First Scored With Nerve Diseases," *Science* 245:467-468, 1989.

Broadly defined, a substance is considered to have neurotoxic potential if it adversely affects any of the structural or functional components of the nervous system. At the molecular level, a substance might interfere with protein synthesis in certain nerve cells, leading to reduced production of a neurotransmitter and brain dysfunction. At the cellular level, a substance might alter the flow of ions (charged molecules, e.g., sodium and potassium) across the cell membrane, thereby perturbing the transmission of information between nerve cells. Substances that adversely affect sensory or motor function, disrupt learning and memory processes, or cause detrimental behavioral effects are neurotoxic, even if the underlying molecular and cellular effects on the nervous system have not been identified. Exposure of children to lead, for example, leads to deficits in I.Q. and poor academic achievement; however, the mechanisms by which this occurs are not understood. In addition, researchers recently found evidence that phenobarbital, a drug prescribed to children to prevent seizures associated with fevers, reduces intellectual ability. But as is the case for lead, the underlying mechanism is unknown.

For the purposes of this study, the Office of Technology Assessment (OTA) defines neurotoxicity or a neurotoxic effect as **an adverse change in the structure or function of the nervous system following exposure to a chemical agent. This** is the definition currently used by EPA. However, as the preceding discussion illustrates, **this definition should be used in conjunction with information on the intended use of the substance, the degree of toxicity, and the dose or extent of exposure of humans or other organisms. The definition hinges on interpretation of the word "adverse," and there is disagreement among scientists as to what constitutes "adverse change." Determining whether a particular neurological or behavioral effect is adverse requires a comprehensive analysis of all available data.** Although certain effects are clearly adverse (e.g., hallucinations, convulsions, loss of memory, permanent neurological damage, death) others are more difficult to define (e.g., temporary drowsiness, a brief headache). The circumstances of exposure and a variety of other factors must be taken into account in borderline cases. For example, drowsiness in the evening at home may be of little consequence, but drowsiness during the day while operating machinery in the workplace may be detrimental or even life-threatening.



Illustrated by: Ray Driver

Who Is At Risk?

Everyone is at risk of being adversely affected by neurotoxic substances, but individuals in certain age groups, states of health, and occupations face a greater probability of adverse effects. **Fetuses, children, the elderly, workers in occupations involving exposure to relatively high levels of toxic chemicals, and persons who abuse drugs are among those in high-risk groups.**

The developing nervous system is particularly vulnerable to some neurotoxic substances, for several reasons. It is actively growing and establishing cellular networks, the blood-brain barrier that protects much of the adult brain and spinal cord from some toxic substances has not been completely formed, and detoxification systems are not completely developed. Lead is a potent neurotoxic substance that is particularly harmful to children (box l-C). Toxic substances can contribute to neuropsychiatric disorders in children. The National Academy of Sciences recently reported that 12 percent of the *63* million children under the age of 18 in the United States suffer from one or more mental disorders, and it identified exposure to toxic substances before or after birth as one of the several risk factors that appear to make certain children vulnerable to these disorders.

The elderly are more susceptible to certain neurotoxic substances because decline in the structure and function of the nervous system with age limits its ability to respond to or compensate for toxic effects. In addition, decreased liver and kidney function increases susceptibility to toxic substances. Aging may also reveal adverse effects masked at a younger age. Persons who are chronically ill, especially those suffering from neurological or psychiatric disorders, are at risk because neurotoxic substances may exacerbate existing problems. Also, many elderly Americans take multiple drugs that may interact to adversely affect nervous system function. According to the Department

Box l-C—Lead: A Continuing Threat to the Nation's Children

Lead is an especially troublesome neurotoxic substance because it occurs naturally in the environment and therefore may be found in food, water, and air, as well as in the byproduct.. of manufacturing and industry. Environmental Protection Agency (EPA) and Food and Drug Administration (FDA) measures to reduce lead in gasoline and food have been largely successful, but some sources of exposure remain, and some sources that are not major contributors now may become so in the future.

Despite lead reduction in a number of areas, lead poisoning remains a major public health problem, particularly among children, who are both more sensitive to lead's neurotoxic effects and more likely to be exposed to certain sources, such as paint chips from older houses, school water coolers containing lead-lined tanks, and home water supplies contaminated with lead from old piping. According to the Department of Health and Human Services, 17 percent of the Nation's children (in standard metropolitan statistical areas) have levels of lead in their blood that may be adversely affecting their nervous systems. The percentage is much higher for urban children from poor families. As tests become more sensitive, neurotoxic effects become apparent at progressively lower levels of lead in children's blood. In addition, relatively low exposures to lead in early years appear to have developmental and neurobehavioral effects that persist into young adulthood. Because of the widespread nature of the problem, it would be prudent to consider a nationwide screening program of lead poisoning in children.

There is some concern that existing EPA regulations cannot adequately remove lead from drinking water, and it is unclear whether water suppliers or property owners bear the responsibility for removing lead plumbing. The same problem of responsibility exists for the removal of lead-based paint from older houses. Without any central reporting system, it is difficult to ascertain the extent of lead poisoning in individual States; and since funding for lead poisoning prevention was placed under the block grant umbrella, it is difficult to determine the extent to which Federal funds are being spent on lead poisoning prevention.

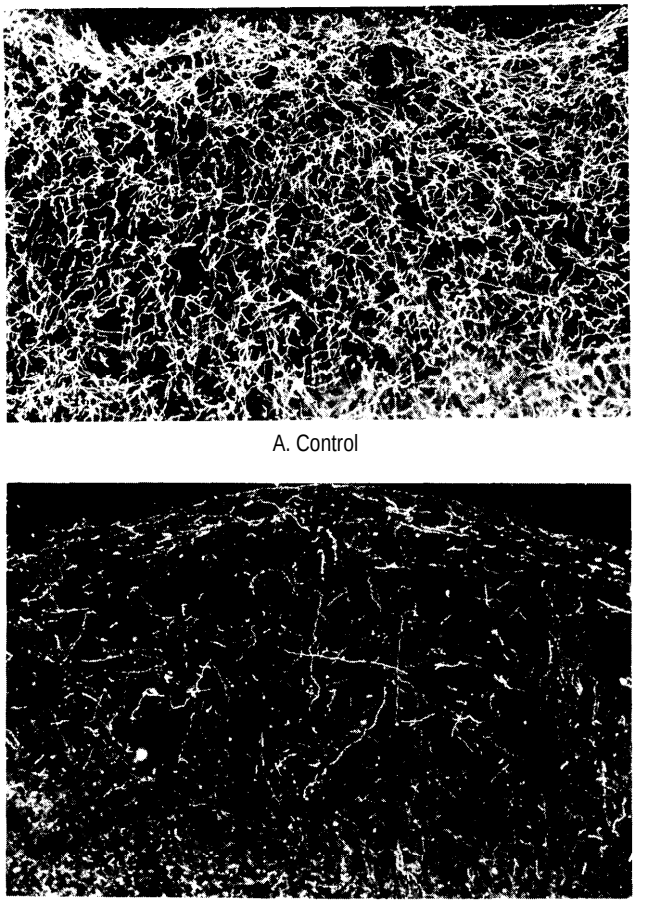
SOURCES: H.L. Needleman, A. Schell, D. Bellinger, et al., "The Long Term Effects of Exposure to Low Doses of Lead in Childhood," New *England Journal of Medicine* 322:83-88, 1990. K.L. Florini, G.D. Krumbhaar, Jr., and E.K. Silbergeld, "Legacy of Lead: America's Continuing Epidemic of Childhood Lead Poisoning," Environmental Defense Fund, Washington, DC, 1990.

of Health and Human Services (DHHS), **people age 60 and older represent 17 percent of the** U.S. **population but account for nearly *40* percent of drug-related hospitalizations and more than half the deaths from drug reactions. Common adverse effects include depression, confusion, loss of memory, shaking and twitching, dizziness, and impaired thought processes.**

Workers in industry and agriculture often experience substantially greater exposures to certain toxic substances than the general population does. Neurotoxic pesticides and solvents are common sources of exposure in the workplace. The National Institute for Occupational Safety and Health (NIOSH) has identified neurotoxic disorders as one of the Nation's 10 leading causes of work-related disease and injury. Other leading causes of work-related disease and injury include noise-induced hearing loss and psychological disorders, both of which are mediated by the nervous system. NIOSH has estimated that several million workers are exposed to neurotoxic substances on a regular basis.

Persons who abuse psychoactive drugs may face particularly severe neurotoxic effects. The National Institute on Drug Abuse (NIDA) reported that in 1986 drug abuse led to more than 119,000 emergency room visits and 4,138 deaths. **Some drugs can permanently damage the nervous system. Damage may be so severe as to cause personality changes, neurological disease, mental illness, or death.** Persons who abuse drugs are often not aware of, or do not take seriously, the threat these substances pose to their health. Drugs such as cocaine, heroin, MDMA (ecstasy), and phencyclidine (PCP) are neurotoxic and threaten the health of many Americans. Figure 1-3 illustrates how one abused drug, MDMA, can destroy nerve fibers in the brain. **Abuse of psychoactive drugs by pregnant women poses a major risk to the developing nervous system of the fetus (see box l-D).**

Figure 1 -3--Neurotoxic Effect of MDMA on Serotonin Nerve Fibers in the Cerebral Cortex of the Monkey



A. Control

B. MDMA

Repeated administration of MDMA (5mg/kg, 8 doses) to a Cynomolgus monkey produced degeneration of most serotonin nerve fibers in this region of the cortex, which is involved in the perception of touch and position sense. Similar toxic effects are seen in most areas of the cerebral cortex.

SOURCE: M.A. Wilson and M.E. Molliver, Department of Neuroscience, Johns Hopkins University School of Medicine.

Research and Education Programs

Federal research related to neurotoxic substances is conducted primarily at the National Institutes of Health (NIH), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), and EPA. Limited research programs are under way at the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), the Department of Energy, the Department of Agriculture, and other agencies.

Box l-D-Cocaine and the Developing Fetus

When a pregnant women abuses a psychoactive drug, she alters not only the activity of her nervous system, but that of her unborn child as well. Depending on the abused substance, the frequency of use, the dose, and other factors, the mother's quest for a high can lead to permanent damage of the rapidly developing fetal nervous system. According to a recent survey by the National Association for Perinatal Addiction Research and Education, each year as many as 375,000 infants may be adversely affected by substance abuse, Maternal substance abuse is frequently not recognized by health-care professionals during pregnancy. Consequently, treatment or prevention programs often come too late. According to the National Institute on Drug Abuse, approximately 6 million women of childbearing age (15 to 44) are current users of an illicit drug, about 44 percent have tried marijuana, and 14 percent have used cocaine at least once.

A recent study of 50 women who used cocaine during pregnancy revealed a 31 percent incidence of preterm delivery, a 25 percent incidence of low birthweight, and a 15 percent incidence of sudden infant death syndrome. These types of parameters are easy to quantify. The biochemical and neurobehavioral effects are more difficult to document, but they are just as real. Early research indicates that cocaine babies suffer abnormal development of the nervous system, impaired motor skills and reflexes, seizures, and abnormal electrical activity in the brain.

Cocaine is so addictive that it can suppress one of the most powerful human drives-maternal care. As one pregnant crack addict put it: "The lowest point is when I left my children in a park for like 3 or 4 days. I had left my kids with a girl that I know and told her. . . 'watch them. . . I'll be back' and I didn't come back. So that was like—when I finally came down off of that high, I realized that I needed help. " Sick and abandoned children of cocaine mothers have placed a heavy burden on a number of the Nation's hospitals. During a l-week period at one hospital, 1 in 5 black infants and 1 in 10 white infants were born on cocaine. Taxpayers usually end up paying the health-care bill—a bill that can exceed $100,000 per infant.

SOURCES: National Association for Perinatal Addiction Research and Education, News, Aug. 28, 1988; J.H. Khalsa, "Epidemiology of Maternal Drug Abuse and Its Health Consequences: Recent Finding,' National Institute on Drug Abuse, in preparation; CBS News, "Cocaine Mothers: Suffer the Children," *West 57th Street*, July 15, 1989.

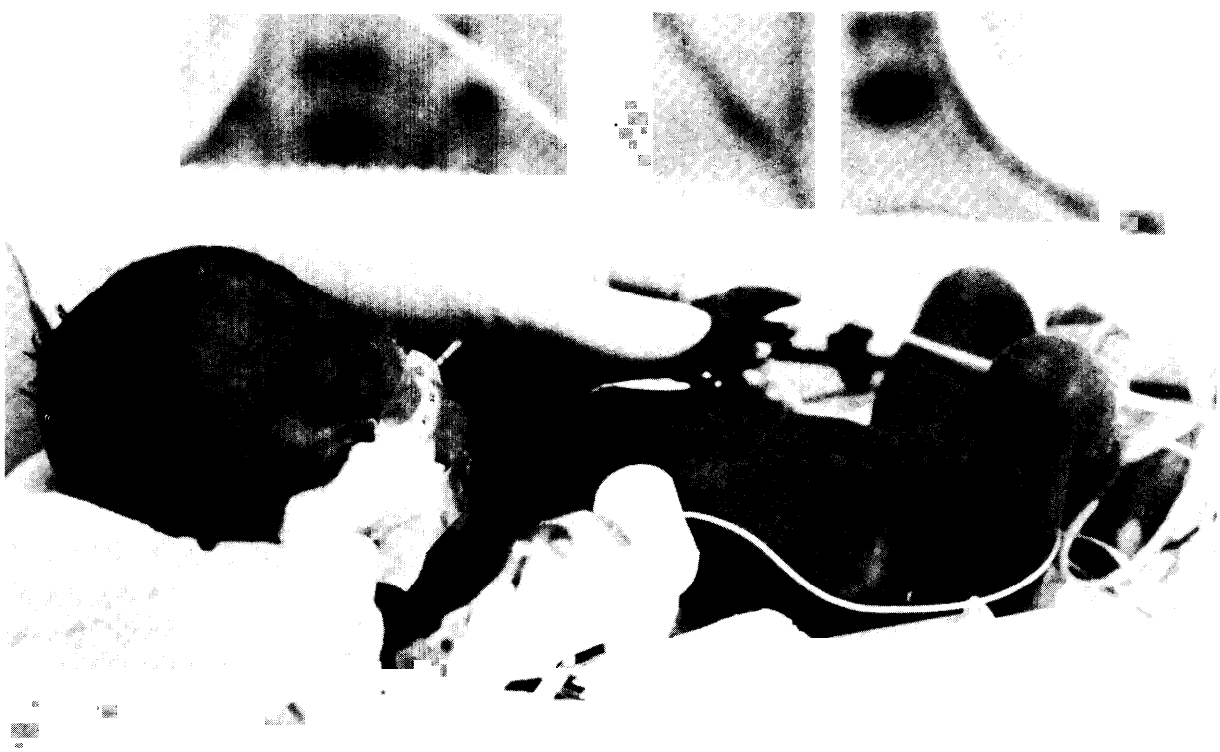


Photo credit: Courtesy of Dr. Emmaiee S. Bandstra, M. D., Division of Neonatology, University of Miami/Jackson Memorial Medical Canter

Table I-I-Federal Funding for Civilian Neurotoxicity-Related Research

Agency	Research[a] ($ millions)
National Institutes of Health[b]	32.6
Alcohol, Drug Abuse, and Mental Health Administration[c]	26.6
Environmental Protection Agency	3.9
National Institute for Occupational Safety and Health	0.7
Food and Drug Administration	1.8
Department of Energy[d]	0.5
Department of Agriculture	0.4
Total	66.5

[a]Totals are based primarily on fiscal year 1988 data.
[b]Excludes research related to nicotine and smoking.
[c]Excludes research related to alcohol and alcoholism.
[d]Excludes research related to radiation.

SOURCE: Office of Technology Assessment, 1990.

As indicated in table 1-1, total Federal funding for civilian neurotoxicology -related research (excluding research related to nicotine and smoking, alcohol and alcoholism, and radiation) is about $67 million. The bulk of this funding (89 percent) is through ADAMHA and NIH and tends to focus on the toxicity of drugs and the biochemical mechanisms underlying neurological and psychiatric disorders. A number of other Federal agencies and organizations provide limited funding for research related to neurotoxicity as well. **Given the threat that neurotoxic substances pose to public health and the lack of knowledge of the mechanisms by which these substances exert adverse effects, OTA found that, in general, Federal research programs are not adequately addressing neurotoxicity concerns.**

Research related to environmental neurotoxicology is confined primarily to the intramural program at EPA and the extramural program at the National Institute of Environmental Health Sciences (NIEHS) within NIH. The NIEHS extramural grants program supports a substantial number of research projects in academia. However, OTA found that, with the exception of the neurobehavioral section of the Laboratory of Molecular and Integrative Neuroscience within NIEHS, NIEHS intramural research programs are focused on the basic neuroscience rather than on environmental neurotoxicology, resulting in a prominent *intramural* research gap at NIH in the environmental neurotoxicology field. Of the approximately $3 million NIEHS spent on intramural research in the neuroscience in fiscal year 1988, OTA found that only about one-fourth was devoted to studies in which neurotoxicology was the primary focus.

Academic research in neurotoxicology is supported almost exclusively by NIH and ADAMHA. Most extramural research funded by NIH is through NIEHS and the National Institute of Neurological Disorders and Stroke (formerly the National Institute of Neurological and Communicative Disorders and Stroke), although several other Institutes have substantial programs. The extramural grants program at NIEHS has been particularly effective in funding research grants in the neurotoxicity field. ADAMHA funds grant programs through NIDA and the National Institute of Mental Health.

EPA has a relatively large intramural research program in neurotoxicology which has been limited in recent years by lack of funding for supplies and equipment. EPA lacks an extramural grants program in neurotoxicology. The Agency has only a small grants program that has rarely funded neurotoxicology-related projects. Traditionally, Federal agencies have supported both intramural and extramural efforts to ensure a balanced, comprehensive, and cost-effective program.

In recognition of the need to expand its research programs in the neurotoxicology area, EPA recently submitted to the Office of Management and Budget (OMB) a request to expand its research budget by $1.5 million. Approximately $1.0 million was requested for the development of in vitro neurotoxicology tests; another $0.5 million was requested to examine adverse effects associated with cholinesterase inhibition and the utility of cholinesterase inhibition as a biomarker for exposure. However, OMB allowed no funding for either research effort. In vitro test development is often cited as a high-priority research need because of the requirement to rapidly screen toxic chemicals

and to try to minimize the use of animals in research. A technical EPA panel recently recommended that the Agency initiate studies to examine the relationship between cholinesterase inhibition and other adverse effects on the nervous system.

FDA funds a small number of research projects related to neurotoxicology, primarily through its intramural research programs. The National Center for Toxicological Research is conducting a number of intramural research projects related primarily to developmental neurotoxicology. The Center for Food Safety and Applied Nutrition has a small in-house program and is supporting three extramural research projects.

Within CDC, NIOSH has small intramural and extramural programs devoted to the identification and control of neurotoxic substances in the workplace. CDC's Center for Environmental Health and Injury Control conducts epidemiological investigations of human exposure to environmental hazards, but few studies focus on neurotoxic effects.

Industry supports neurotoxicology -related research through several mechanisms, including in-house scientists, contract laboratories, consortia, contracts with universities, and grants to universities. Toxicity evaluations conducted as part of internal applied research are necessary to develop safe and effective products, to protect employees, to protect the environment, and to control liability costs. Research programs vary considerably depending on the types of products manufactured and various economic considerations.

OTA found that education of research scientists in the neurotoxicology field is limited, in part, by inadequate Federal support for training programs. Part of the difficulty in obtaining funding is due to the nature of neurotoxicology-the intersection of neuroscience and toxicology. Few academic departments devote significant resources to neurotoxicology, and few Federal research organizations devote major efforts to it. NIEHS supports training in the neurotoxicology field; however, funding limitations allow for support of only a relatively small number of trainees.

Millions of American workers are exposed to neurotoxic substances in the workplace, but illness stemming from these exposures often goes undetected and untreated. The subtlety of neurotoxic responses is one reason for this situation; for example, complaints of headache and nervousness are often ascribed to other causes. Another reason is the lack of adequately trained health-care professionals to diagnose and treat neurotoxic disorders. Medical schools, in general, devote little of their curricula to occupational health issues. After medical school, physicians may undertake residency training in occupational medicine, but in 1987 only about 1 in every 1,000 residents was specializing in occupational medicine. Nurses are also needed in the occupational health field to provide emergency services, to monitor employee health, and to provide counseling and referral to physicians. In addition, industrial hygienists are needed to evaluate and control health hazards in the workplace.

Testing and Monitoring

Controlling toxic substances is a two-part process. The first step is to identify existing substances that adversely affect the nervous system and take action to minimize human exposure to them. The second step is to identify new neurotoxic substances in use and either prevent their manufacture (if they cause serious neurotoxic effects) or limit human exposure to them and release of them into the environment. **Very few new and existing chemicals have been evaluated specifically for neurotoxicity.**

The effects of toxic substances on the nervous system may be evaluated through animal tests, cell and tissue culture (in vitro) tests, and human tests. Each approach has advantages as well as limitations. The best way of predicting adverse effects on human health is to test potentially toxic substances directly on human subjects. However, this approach is often difficult and in many situations is unethical. Therefore, it is

usually necessary to rely on animal and in vitro tests to predict effects on human health. In some cases, in vitro tests can be used to detect neurotoxic effects; at present, however, animal testing is used to obtain a neurotoxicological and behavioral evaluation. As more in vitro testing techniques become available and are validated, they may be used in the initial screening process or to complement animal tests.

Several industrial and Federal organizations have developed animal tests to evaluate the effects of known and potential neurotoxic substances. In industry, several testing methods are currently used on a limited basis to assess the neurotoxic potential of some toxic substances. In the Federal arena, EPA recently developed guidelines for a series of neurotoxicity tests to supplement its general toxicological tests. Core neurotoxicological tests used in initial screening for toxicity include the functional observational battery (a series of rapid neurological tests to evaluate toxic effects on animals), tests of motor activity, and neuropathological examinations. Additional tests that may be used include schedule-controlled operant behavior tests, acute and subchronic delayed neurotoxicity tests for organophosphorous substances, and developmental examinations. Neurophysiological evaluations are also useful in identifying neurotoxic substances and in evaluating their adverse effects.

Several human tests are in use to determine the neurotoxic potential of suspected and known toxic substances. These include neurobehavioral evaluations and various neurophysiological tests. In addition, computer monitoring devices are rapidly advancing to aid in studies of neurotoxicity.

Monitoring the release of toxic substances is critical to regulatory programs. In 1986, Congress enacted the Federal Emergency Planning and Community Right-to-Know Act, which mandated that EPA develop a Toxics Release Inventory of more than 300 toxic chemicals released by industry into the environment. The first data were published in 1989, and the inventory will be updated annually. Such a database will undoubtedly prove to be very useful in monitoring releases of neurotoxic substances. As indicated in figure 1-4, 17 of the top ***25*** toxic substances released into the environment have neurotoxic potential.

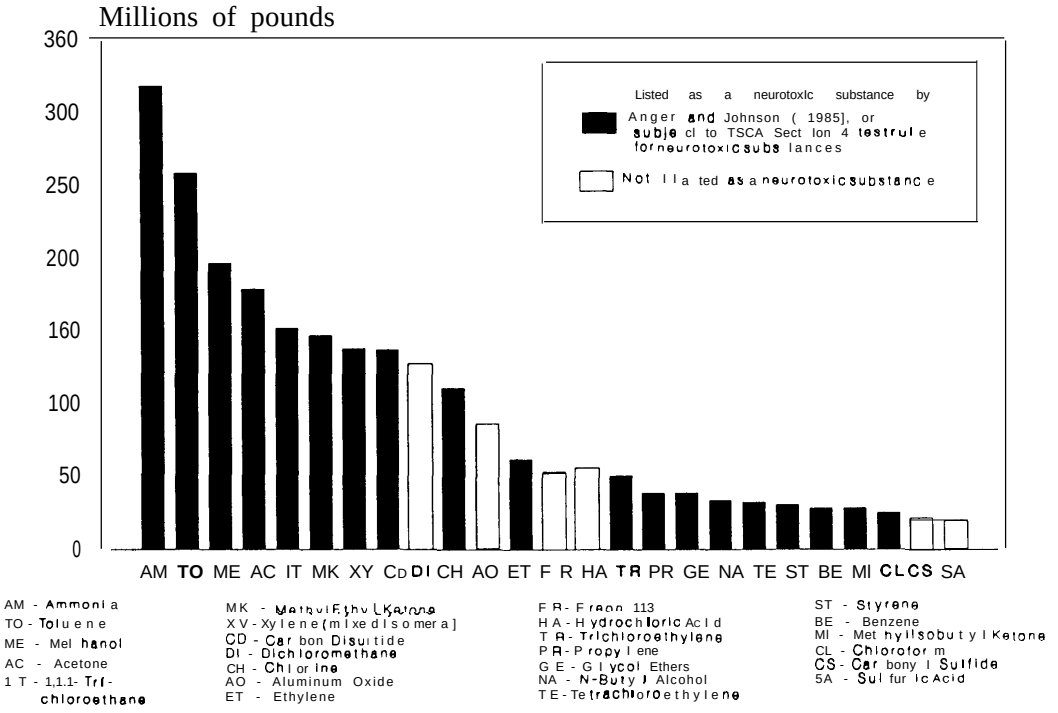
Monitoring exposure to neurotoxic substances is a critical component of public health and environmental protection efforts. Monitoring may be conducted by regularly surveying contaminants in the food supply, banking animal specimens, and collecting biological data on humans. Biological specimens can be used to measure contamination levels over periods of many years and to document adverse effects. Human biological monitoring programs can be undertaken to detect exposure to toxic substances and to aid in making decisions about health risks. Such programs may be particularly useful in monitoring exposures in the workplace.

Risk Assessment

Risk assessment is the analytical process by which the nature and magnitude of risks are identified. Risk, as it pertains to the health effects of toxic substances, is the probability of injury, disease, or death for individuals or populations undertaking certain activities or exposed to hazardous substances. It is sometimes expressed numerically (e.g., 1 in 1 million); however, quantification is not always possible, and risk may sometimes be expressed in qualitative terms such as high, medium, or low risk. Risk management, a process guided by risk assessment, and by political, social, ethical, economic, and technological factors as well, involves developing and evaluating possible regulatory actions and choosing among them.

Some degree of risk is associated with almost every aspect of modern living. For example, traveling in an automobile involves a risk of accidental death of 1 in 4,000, a relatively high risk. In contrast, the risk of being killed by lightning is 1 in 2 million. Whether a risk is acceptable or not depends on many factors, including benefits. Defining acceptable risk is the task not only of scientists and regulatory

Figure I-4-neurotoxic Substances Are Prominent Among the Toxics Release inventory's Top 25 Chemicals Emitted Into the Air in 1987

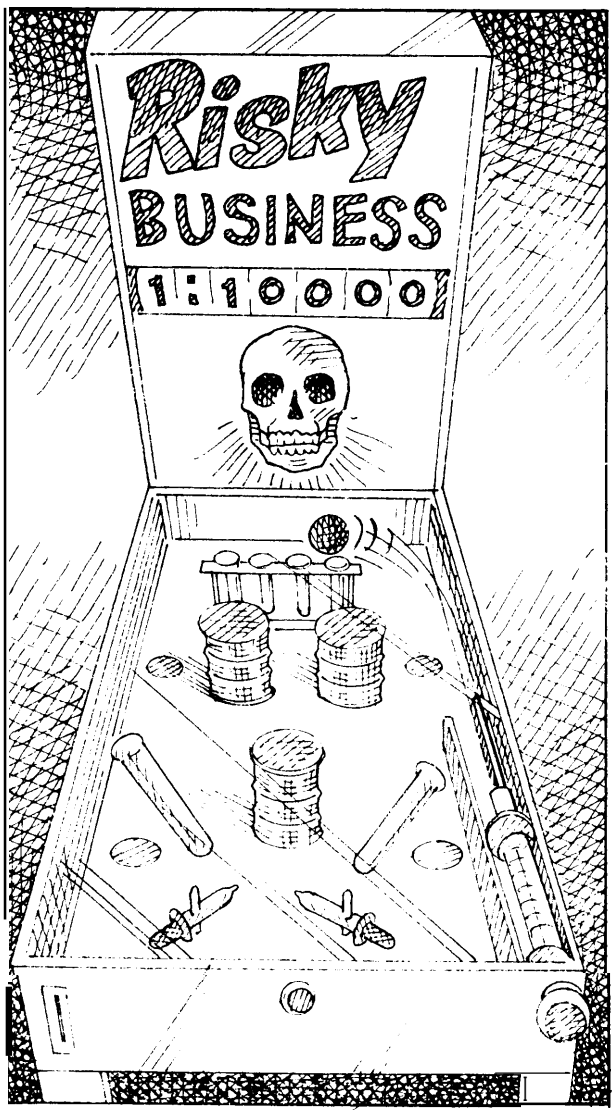


SOURCES: Data obtained from W.K. Anger and B.L. Johnson, "Chemicals Affecting Behavior," *neurotoxicity of Industrial* and Commercial Chemicals, vol. 1, J.L. O'Donoghue (cd.) (Boca Raton, FL: CRC Press, 1965), tables 1 and 2, pp. 70-141; TSCAsec. 4,52 FR 31445; TSCAsec. 4,53 FR 5932; 54 FR 13470; 54 FR 13473; U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances, *The Toxics Release Inventory: A National Perspective, 1987,* EPA 560/4-89-006 (Washington, DC: 1989).

officials, but of society in general. Everyone evaluates risks on a daily basis and makes individual choices depending on experience and other factors.

Risk assessment practices are the subject of ongoing debate within the regulatory and scientific communities, and in the last two decades strategies to regulate toxic substances have changed considerably. In the early 1970s, environmental legislation focused on regulating a relatively small number of pollutants of known toxicity. Today, concern is focused on thousands of toxic substances, for many of which little information is available. This change has been forced in part by improved methods of detecting toxic substances in the environment, improved capabilities for identifying the adverse effects of these substances, and the difficulty of determining threshold levels below which no adverse effects occur.

Policies regarding risk assessment have been controversial. Some people believe that Federal agencies overestimate risk by making overly conservative assumptions in developing risk assessments. Others feel that risk assessment practices do not take into account the complex interactions of multiple pollutants that often occur in the environment. Still others point out that risk assessments focus primarily on adverse effects on human health and devote little attention to other organisms and the environment in general. Critics of established risk assessment



Illustrated by: Ray Driver

procedures believe that too little attention is being paid to the potential effects of toxic substances on children, infants, and the unborn. Regardless of the various viewpoints, risk assessment has become an integral component of regulatory strategies, and it is important to appreciate the scientific issues underlying this process in order to understand how toxic substances are controlled.

Concerns about carcinogenicity have dominated discussions about the risks posed by toxic substances. However, the adverse effects on organs and organ systems, particularly the nervous system, may pose an equal or greater threat to public health. Consequently, it is important to devise risk assessment strategies to address noncancer health risks. An important difference between neurotoxicity and carcinogenicity is the extent to which the effects are reversible. The endpoint of carcinogenicity is considered to be irreversible (although some argue that, strictly speaking, a ''cure' would render the effect reversible), whereas the endpoints of neurotoxicity may be either reversible or irreversible, depending on the specific effect, the duration and frequency of exposure, and the toxicity of the substance. Reversibility requires the introduction of a new variable into the risk assessment equation.

Since the nervous system is perhaps the most complex organ system of the body, evaluating the neurotoxic potential of environmental agents is a particular challenge. For example, testing for a toxic effect on one component of the nervous system (e.g., hearing), may or may not reveal a toxic effect on another component (e.g., vision). Furthermore, an effect on one nervous system function is not necessarily predictive of an effect on another nervous system function.

The results of toxicological analyses are strongly influenced by the age of the organism being examined. For example, mice exposed to methylmercury during prenatal development may not exhibit adverse effects until late in their lives. With age, the functional capacity of the brain declines significantly, and chronic exposure to some neurotoxic substances is thought to accelerate this process. Hence, some scientists and regulatory officials believe that risk analyses should consider adverse effects over a range of ages and should take into account latent effects.

Federal Regulatory Response

It is the task of regulatory agencies to limit public exposure to toxic chemicals through programs mandated by law. Because of the great diversity of toxic substances, many statutes exist to control their use. These laws are administered by various Federal agencies, but primarily by

Table 1-2--Major Federal Laws Controlling Toxic **Substances**

Act	Agency primarily responsible
Toxic Substances Control Act	EPA
Federal Insecticide, Fungicide, and Rodenticide Act	EPA
Federal Food, Drug, and Cosmetic Act	FDA
Occupational Safety and Health Act	OSHA
Comprehensive Environmental Response, Compensation, and Liability Act	EPA
Clean Air Act	EPA
Federal Water Pollution Control Act and Clean Water Act	EPA
Safe Drinking Water Act	EPA
Resource Conservation and Recovery Act	EPA
Consumer Product Safety Act	CPSC
Federal Hazardous Substances Act	CPSC
Controlled Substances Act	FDA
Federal Mine Safety and Health Act	MSHA
Marine Protection, Research, and Sanctuaries Act	EPA
Lead-Based Paint Poisoning Prevention Act	CPSC
Lead Contamination Control Act	HHS
Poison Prevention Packaging Act	CPSC

KEY: CPSC-Consumer Product Safety Commission; EPA-Environmental Protection Agency; FDA-Food and Drug Administration; HHS--Department of Health and Human Services; MSHA—Mine Safety and Health Administration; OSHA-Oocupational Safety and Health Administration.

SOURCE: Office of Technology Assessment, 1990.

EPA, FDA, and the Occupational Safety and Health Administration (OSHA) (table 1-2). OTA found that very few substances have been regulated as a result of neurotoxicity concerns.

New and existing industrial chemicals are regulated by the Toxic Substances Control Act (TSCA). Pesticides are controlled by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and toxic substances in the workplace are regulated by the Occupational Safety and Health Act (OSH Act). The Federal Food, Drug, and Cosmetic Act (FFDCA) regulates food and food additives, drugs, and cosmetics. These laws address the vast majority of toxic substances, and more than a dozen other acts focus on other substances and sources of exposure. Although neurotoxicity is generally not explicitly mentioned in legislation mandating the regulation of toxic substances, it is implicitly included as a toxicity concern.

Under the authority of this diverse framework of legislation, regulatory agencies have promulgated equally diverse regulations for protecting human health. Some regulatory programs require substantial testing of chemicals to screen for toxic effects; others are not empowered to require any such testing. Some regulations call for screening substances before they are allowed to enter the marketplace; other regulations are reactive, coming into effect only when evidence indicates that an existing chemical can or does cause harmful effects.

Federal laws governing toxic effects can be divided into three general categories:

1. **licensing and registration** laws for new and existing chemicals, which entail explicit review processes and may include requirements for toxicity testing;
2. **standard-setting** laws for chemicals used in specific situations, under which regulatory agencies determine recommended or required limits on toxic substances in various environmental media (air, water, or soil) or emitted by a given source, or dictate appropriate labeling of products that contain toxic substances; and
3. **control-oriented** measures for dealing with chemicals, groups of chemicals, or chemical processes that are explicitly identified in the laws as targets of concern.

Distinctions among the three categories are not absolute—there is more of a continuum than a discrete grouping in the legislative language—but this classification indicates the basic types of approaches that have been developed to protect the public and the environment from the adverse effects of toxic substances.

Consistency of the Federal Regulatory **Effort**

There are numerous differences in regulatory practice under different laws, even within the group of Incensing laws (TSCA, FIFRA, FFDCA). These differences do not, for the most part, apply specifically y to the regulation of neurotoxic effects, but rather to regulation of all toxic effects. Thus, consistency of regulation for specific neurotoxic effects hinges on consistency of regulation in a more general sense.

Statutory requirements for chemical regulatory programs differ in several important respects, among them the number of chemicals evaluated, the time available for review, the amount and type of data available at the beginning of the review process, the ability of the reviewer to acquire additional data after review has begun, and the burden of proof regarding safety. For example, the Premanufacture Notice (PMN) process under TSCA necessitates review of hundreds of chemicals every year; each review is allotted only 90 days (although an extension is possible), and substantive toxicity data are rarely submitted. EPA can obtain additional data or impose controls on chemicals only if it finds that there may be an unreasonable risk associated with use of the chemical. **Without significant toxicity data, predicting risk is difficult and must rely on hypothetical relations between chemical structure and biological activity. However, little is known about structure-activity relationships with respect to neurotoxicity.** Applicants for registration of a pesticide under FIFRA must submit extensive *general* toxicological data according to specified test protocols, the review process extends over a period of years, the applicant is required to submit additional data if the basic data raise concerns, and the applicant must establish that the pesticide will be both safe *and* effective under the proposed conditions of use. Few data relating to neurotoxicity concerns are presently required. However, the agency is considering expanded testing requirements.

That there are differences in the degree of regulatory scrutiny under the various Federal regulatory programs is widely acknowledged. Often, these disparate regulatory requirements reflect real differences in the potential risks represented by the chemicals each program regulates. It may be that the more intense scrutiny reserved for some types of chemicals is an appropriate reflection of the likelihood that they will threaten human health or the environment.

Current laws are generally based on the premise that chemicals for which there is a greater probability of exposure should meet a higher standard of safety. This is most clearly illustrated by the prohibition of carcinogenic substances as direct food additives and of pesticides that concentrate in foods (the Delaney clause of FFDCA). No such general prohibition applies to general industrial or commercial chemicals under TSCA or the OSH Act.

The stringency of the evaluation process for new chemicals under the various laws generally matches the presumption of risk—the combination of hazard and exposure potential-posed by each class (in the view of regulatory officials) and the number of new class members introduced each year. Thus, drugs are not to be permitted on the market until proven safe and effective in clinical trials. New pesticides and food additives are evaluated nearly as stringently; however, human trials are not performed. Commercial chemicals, whether intended for industrial or consumer use, receive the least scrutiny.

There are two exceptions to these trends, one minor and one significant. Consumer chemicals have not received any procedurally different scrutiny than those intended for industrial use, despite the fact that larger numbers of persons may be exposed as consumers than as industrial workers. Moreover, FFDCA does not require that cosmetics and cosmetic ingredients undergo premarket toxicity testing. Industry voluntarily tests cosmetic ingredients for acute toxic effects, but few are examined for chronic toxicity. Some have been found to have acute and chronic neurotoxic effects on laboratory animals.

While many scientists find some comfort in the observation that the stringency of review of a chemical matches its presumptive risk (except for cosmetics), public interest groups have voiced concerns over such odds playing. For example, the chemicals regulated under TSCA make up the largest classes of chemicals, yet they receive relatively little scrutiny by EPA. TSCA does offer options for selecting high-risk chemicals for further scrutiny, but the vast majority of chemicals receive only a limited

review. **Critics of EPA argue that regulatory resource considerations and a desire not to burden industry, rather than presumptive risk, are in fact driving chemical review criteria. They raise the question of whether the minimal screening given to the majority of chemicals is adequate to deal with high-risk chemicals that are not members of known risk categories.**

Regulation of New v. Existing Chemicals

Existing chemicals are subject to varying degrees of review and reevaluation. In contrast to procedures for reviewing new chemicals, however, procedures for reexamining existing chemicals do not necessarily reflect the inherent risks of the chemical classes involved.

EPA attempts to ensure the adequacy of the data supporting continued pesticide registration through a regular review process. The registration standards program, which examines 25 chemicals per year, has thus far addressed only a small portion of the active ingredients of registered pesticides and has been the subject of considerable concern. At the present rate, active pesticide ingredients would be reviewed on an average of only once every 12 years or more. The 1988 FIFRA amendments mandated that the review schedule be accelerated so that *all* active ingredients are reviewed by 1997. To meet this goal, EPA will need to streamline its existing review process.

Under section 4 of TSCA, existing chemicals are ranked for probable risk or high exposures prior to entering the test rule or consent order regulatory process. **In the period from 1977 to 1988, final rules were issued on only 25 chemicals or related sets of chemicals, consent agreements were reached on three, with nine proposed rules pending. Clearly, these rules address only a very small fraction of the 60,000 chemicals in the TSCA inventory.**

FDA's various procedures for reviewing existing drugs and food and color additives are less formal than those for pesticides or toxic substances. FDA tracks physicians' reports of adverse drug reactions and reports them to the original evaluators of the drugs. Food and color additives have been notable exceptions to the review of existing chemicals. Until recently, once an additive was registered, there was no monitoring of adverse reactions. For aspartame, FDA established voluntary reporting programs, but most food additives are not the subject of formal reporting programs. Although FDA does not require reporting on the use of approved food and color additives, it could track such information and use it to assess the risks associated with approved uses.

Specific neurotoxicological Considerations

Regulatory differences in general strategies for evaluating toxicity entail corresponding differences in the evaluation of neurotoxic effects. Thus for human drugs, preclinical toxicity tests are only used to guide observations on clinical trials and to elucidate possible mechanisms of toxicity, rather than to directly assess toxic potential. For pesticides and food and color additives, in contrast, animal toxicity data are used directly in predicting human risk. However, even within programs that have essentially similar approaches to assessing toxic risks, there are differences with respect to consideration of neurotoxic risks.

Regulatory programs have adopted one of three basic approaches to toxicity evaluation, depending on which of three underlying assumptions they hold. One approach is based on the assumption that general toxicity tests using high doses are adequate to detect neurotoxic potential and that neurotoxicological evaluations are needed only if general tests, data on structural analogues, or other specific knowledge about a chemical indicate a potential for neurotoxicity. Among these are FDA's preclinical testing program for drugs and its current program for approving food additives. The second approach, represented by the pesticide registration program under FIFRA, accepts more general structural information in guiding neurotoxicity testing. All organophosphorous compounds are evaluated for the potential to

induce delayed neuropathy, but nonorganophosphorous compounds are not specifically evaluated for neurotoxic potential. All pesticides undergo a general toxicity screen; however, specific neurotoxicity tests are not presently required. Finally, under section 4 of TSCA, specific neurotoxicity testing is required for any chemical with high exposure potential, as well as for chemicals specifically suspected of being neurotoxic. Such testing presumes that standard toxicity tests are not adequate to evaluate neurotoxic effects.

OTA found that Federal efforts to control neurotoxic substances varied considerably between agencies and between programs within agencies. Improving the Federal response will require increased neurotoxicity testing, improved monitoring programs, and more aggressive regulatory efforts.

Federal Interagency Coordination

Interviews with toxicologists and neurotoxicologists in various Federal agencies indicated that there is little formal coordination among agencies, although neurotoxicologists at different agencies maintain regular informal contacts. There are also several coordinated research efforts mediated by interagency agreements and by personal contact. **In the spring of 1989, OTA and EPA cosponsored a workshop on Federal interagency coordination at which Agency representatives decided to establish an Interagency Working Group on Neurotoxicology to foster increased interaction among Federal agencies responsible for research and regulatory programs.**

neurotoxicologists at different agencies maintain regular informal contact, but this contact has not fostered a consensus on the best approach to regulating neurotoxic hazards. Real differences of scientific opinion remain, and data that would resolve these differences have not been developed by the agencies involved. Restrictions on revealing confidential business information hinder the transfer of potentially useful toxicological information, both to the public and between Federal agencies. Moreover, even within agencies, neurotoxicologists and other toxicologists sometimes disagree on the proper role of neurotoxicity in safety evaluations.

An agency's approach to neurotoxicity evaluation often corresponds to the presence or absence of neurotoxicologists on the staff. Although this presumably reflects personnel considerations—if an agency is not evaluating neurotoxicological data, it does not require people trained to do so-it does raise the question of whether persons who evaluate general toxicological data understand the contributions of directed testing to the prediction of neurotoxic effects. General toxicologists are essential to the review process; however, individuals with specialized expertise are often necessary to ensure a comprehensive evaluation. Variations in the hiring of neurotoxicologists by Federal agencies reflect a more general problem of toxicological assessment, that of determining the appropriate degree of specialization required to evaluate the many organ systems potentially affected by a toxic substance. **OTA found that effectiveness in addressing neurotoxicological concerns at Federal agencies is dependent on the presence of neurotoxicologists in regulatory program offices. Improving Federal programs will require increased employment of neurotoxicologists trained in risk assessment and regulatory procedures.**

The Federal regulatory response to neurotoxicity is fragmented not only by differences in scientific judgment, but also by differences in regulatory responsibility. The decision to evaluate drugs, pesticides, and food additives by stricter standards than are applied to commercial chemicals is based not only on the views of scientists, but also on national consensus. Thus, the perception of risk by the public can strongly influence regulatory policies related to toxic substances.

Economic Considerations in Regulation

Regulating neurotoxic substances involves consideration of both the economic benefits of

using these substances and their actual or potential costs. The problem of balancing benefits, costs, and risks of regulation is not unique to the control of neurotoxic substances; it arises in all forms of health, safety, and environmental regulation. Regulations that are designed to reduce or prevent neurotoxic risks can benefit society through improvements in public health and environmental amenities. In most cases, however, society incurs costs to achieve these regulatory ends. The costs of complying with health and safety regulations may also result in increases in market prices, reductions in industry profits, and declines in new product innovation.

Many of the key Federal laws under which neurotoxic substances are regulated require agencies to ascertain the positive and negative economic consequences of regulation. In implementing these laws, Congress has generally intended that agencies prepare regulatory analyses and document the balancing of benefits, costs, and risks of proposed alternatives.

The Costs and Benefits of neurotoxicity Testing

Experience with neurotoxicity testing is still relatively limited, creating uncertainty regarding the available cost estimates for this type of testing. Because of the uncertainty regarding these costs, OTA obtained estimates of the costs of several types of neurotoxicity tests from a number of individuals in government, industry, and academia.

The median estimates derived from OTA's survey indicate that a complete set of neurotoxicity tests, including a functional observational battery, motor activity, and neuropathology, may add from 40 to 240 percent to the costs of conventional toxicity tests currently required by EPA. By far the largest portion of the added cost comes from the neuropathology evaluations, which are needed to determine whether structural change in the nervous system has occurred and the nature and significance of the change. Based on its survey, OTA found that acute neurotoxicity tests (including EPA's functional observational battery, motor activity test, and neuropathology evaluations) may add a total of about $50,000 to standard toxicity test costs. Subchronic neurotoxicitytests may add $80,000, and chronic tests may add about $113,000. The EPA subchronic schedule-controlled operant behavior test may add about $64,000. However, the functional observational battery alone would add only $2,500 to the cost of a conventional acute toxicity test. A conventional acute test of oral exposure presently costs about $21,000.

Testing costs should be viewed in the context of the health benefits of minimizing public exposure to neurotoxic substances, the total cost to industry of marketing a new product, potential profits resulting from the sale of the product, and the impact high initial costs have on the innovation process.

The benefits of regulating neurotoxic substances can be measured in terms of the human and monetary values placed on reduction of risk. A number of approaches have been used to assign monetary values to reduction of the risks of mortality, morbidity, and disability. Lead has been the subject of an in-depth economic analysis. **A** 1985 **study estimated that the total health benefits of reducing the neurotoxic effects of lead on U.S. children would amount to more than $500 million annually between 1986 and 1988. If adult exposure to lead, including workers' exposure, were included, the benefits would be considerably larger. Although the health and economic benefits of limiting public exposure to neurotoxic substances are more difficult to estimate than the costs of regulation, the example of lead illustrates the importance of considering the potentially large monetary benefits of regulatory actions.** Like other toxicity testing, neurotoxicity testing is conducted to prevent adverse health effects; hence, the benefits of such testing may not be readily apparent and may accrue well into the future. Often, the immediate costs of testing receive considerable attention by regulatory officials, but the sizable potential economic benefits of preventing public exposure to a hazardous substance receive comparatively little attention.

As indicated earlier, neurotoxic substances, in particular abused drugs, play a significant, causal role in the development of neurological and psychiatric disorders; however, the precise extent of the contribution remains unclear. **Mental disorders and diseases of the nervous system contribute substantially to health costs in the United States. In 1980, they ranked as the third and fifth most expensive medical conditions in terms of personal health-care expenditures.** The estimate of nearly $40 billion (1980 dollars) for these two categories of morbidity does not include values for lost productivity, restricted activity, and other social costs (e.g., criminal activity, law enforcement, and rehabilitation for drug and alcohol abuse) that frequently accompany mental illness or other forms of mental impairment.

International Issues

Like most environmental concerns, neurotoxicity is a problem that is not limited by national boundaries. Pollutants readily cross national borders, hazardous chemicals are frequently imported and exported between industrialized and developing nations, and adulterated food and commercial products enter the United States despite current regulatory efforts. Strategies to limit human exposure to neurotoxic substances should be devised in the context of both national and international regulatory and research initiatives.

International Regulatory Activities

Despite numerous regulations governing the export and import of neurotoxic chemicals and products containing them, some countries do not have the regulatory framework and resources to adequately protect human health and the environment from these substances. Many nations, including the United States, have policies and procedures in place, but too often they work only on paper. In practice, they may allow neurotoxic substances to slip through the regulatory cracks. Some developing nations have regulations to protect workers and consumers from the adverse effects of neurotoxic substances, but these nations often lack the resources to enforce them. This lack of effective regulation and enforcement in developing nations has a negative impact not only on public health and environment in the user country, but also in industrialized nations, including the United States, where people process and consume products imported from developing nations.

Both TSCA and FIFRA contain provisions exempting certain U.S. products produced for export from the requirements that apply to products sold for use in the United States. In most instances, the requirements of TSCA do not apply to substances manufactured, processed, or distributed for export. The requirements will, however, apply if it is determined that the mixture or article will present an unreasonable risk of injury to health within the United States or to the environment of the United States. In addition, because pesticides intended solely for export are exempt from the public health protection provisions of FIFRA, pesticide manufacturers can legally export banned, severely restricted, or never-registered substances that have been deemed too hazardous for use in this country. Companies that do so are required to notify the importing country that the pesticides in question have been banned, severely restricted, or never registered for use in the United States. Sometimes such pesticides are used on food crops that are imported back into the United States for consumption. Critics of this practice have termed it the ‘‘circle of poison. ’

On January 15, 1981, several days before the end of his term, President Jimmy Carter issued an Executive Order that set controls on exports of substances that were banned or severely restricted in the United States. Several days after becoming President, Ronald Reagan revoked this order.

International Research Activities

Active interest in neurotoxicity began in the United Kingdom during and after World War II. Since that time, research efforts in the United States have gradually increased. The United

States is now the world leader in environmental legislation and government funding of neurotoxicology research.

International research activities tend to focus on the heavy metals (lead and mercury), organic solvents, and pharmaceutical agents. Scandinavian countries have been active in research on the neurotoxicity of organic solvents. Other European countries have supported research on compounds of particular concern in occupational settings, such as pesticides and heavy metals. Foreign neurotoxicology -related scientific papers published in international journals most often originate from authors in Canada, England, Italy, Australia, and Japan. A number of papers originate from authors in France, India, Sweden, Finland, and Mexico, as well.

neurotoxicology research has been primarily an intranational effort. In recent years, some international cooperation has been initiated by the World Health Organization and the U.S. National Toxicology Program, but thus far cooperation has occurred only in specific areas such as lead toxicity, solvent toxicity, and the development of testing methodologies. The limited scope of international cooperation is largely due to the lack of funds available for such efforts.

In some European countries, notably the Federal Republic of German and Sweden, environmental movements are becoming increasingly influential. It is likely that these nations will play leading roles in supporting research and in developing regulations to control toxic substances. The Federal Republic of Germany has already acted to remove lead from gasoline and to fund studies of lead toxicity in children. All of the Scandinavian countries (Sweden, Denmark, Norway, and Finland) have traditionally supported research on solvents. These patterns are likely to continue and may broaden to include the investigation of other toxic substances as environmental movements grow. Political events in the Soviet Union have led to the emergence of an environmental movement, and it appears that the Soviet government will also take a more active role in these issues. Finally, in the Far East, both the People's Republic of China and Japan are facing major pollution problems and are becoming increasingly involved in toxicological issues.

POLICY ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

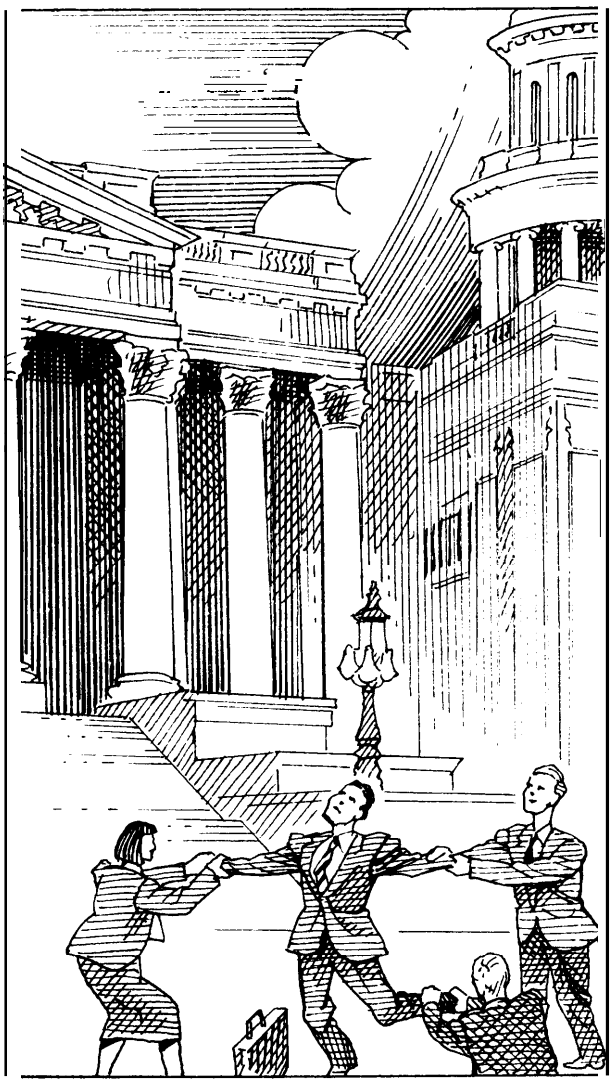
Six broad policy issues related to the identification and regulation of neurotoxic substances were identified during the course of this assessment:

1. adequacy of the Federal regulatory framework,
2. adequacy of Federal and federally sponsored research programs,
3. coordination of Federal regulatory and research programs,
4. availability of adequately trained research and health-care professionals,
5. communication of information to workers and the public, and
6. adequacy of international regulatory and research programs.

Associated with each policy issue are several options for congressional action, ranging in each case from taking no action to making substantial changes. Some of the options involve direct legislative action. Others involve the executive branch, but with congressional oversight or direction. The order in which the options are presented does not imply any priority. Moreover, the options are not, for the most part, mutually exclusive; adopting one does not necessarily disqualify others within the same category or in any other category. A careful combination of options might produce the most desirable effects. It is also important to keep in mind that changes in one area may have repercussions in other areas.

ISSUE 1: Is the current Federal regulatory framework addressing neurotoxicity adequately?

The Federal regulatory framework has been built on the foundation established by four



Illustrated by: Ray Driver

major Acts: 1) Toxic Substances Control Act; 2) Federal Insecticide, Fungicide, and Rodenticide Act; 3) the Federal Food, Drug, and Cosmetic Act; and 4) Occupational Safety and Health Act. At least a dozen other acts address general toxicological concerns. Many of them explicitly or implicitly mandate regulation of neurotoxic substances. Options related to this issue are organized around the Federal agency with lead responsibility for implementing a particular law.

Environmental Protection Agency

EPA is responsible for implementing two of the major acts, TSCA and FIFRA, and several others pertaining to neurotoxic substances, including the Clean Air Act; the Federal Water Pollution Control Act and Clean Water Act; the Safe Drinking Water Act; the Comprehensive Environmental Response, Compensation, and Liability Act; the Marine Protection, Research, and Sanctuaries Act; and the Resource Conservation and Recovery Act.

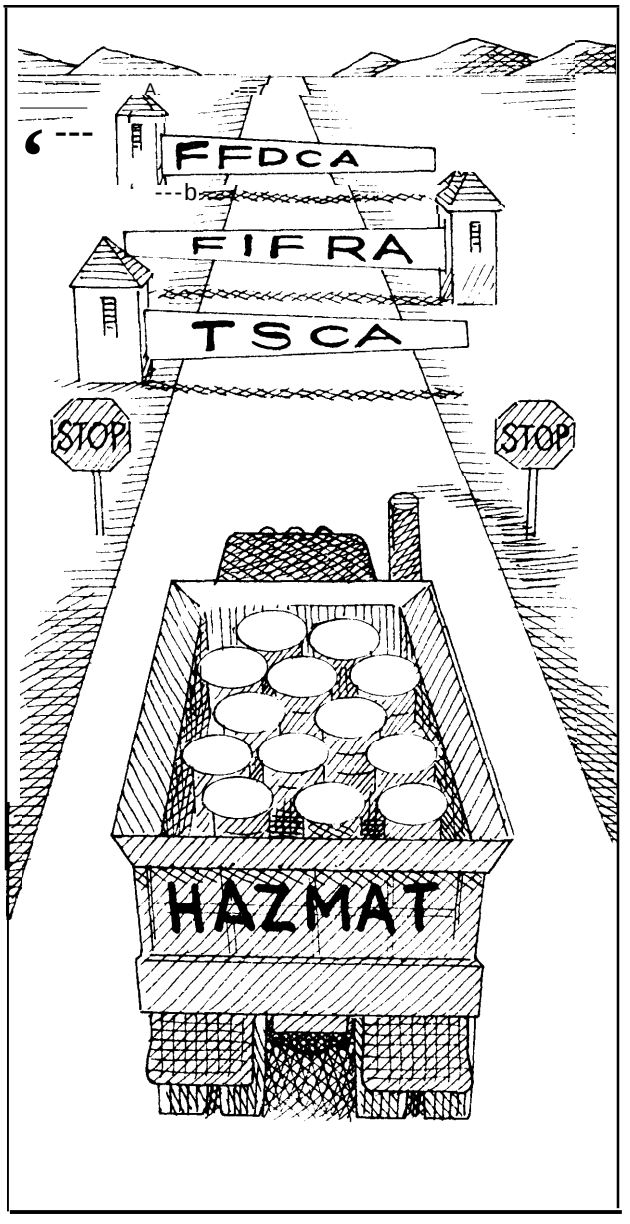
Option 1: Take no action.

If no congressional action is taken, EPA will continue to be responsible for carrying out the provisions of the existing statutes, which implicitly address neurotoxicity in the context of general toxicological concerns. The degree to which neurotoxic substances are regulated will vary according to program priorities, resources, the expertise of Agency personnel, and interpretation of pertinent laws by Agency officials. To date, few toxic substances have been regulated on the basis of known or suspected adverse effects on the nervous system. Even in the absence of congressional action, this situation is likely to change, given greater public and Agency awareness of neurotoxicological concerns and the institution of new neurotoxicity testing guidelines under TSCA and FIFRA. For example, EPA is actively considering requiring functional observational battery, motor activity, and neuropathological tests for all new pesticides and for all existing pesticides undergoing reregistration.

Option 2: Mandate more extensive neurotoxicity " testing under TSCA and FIFRA.

neurotoxicity test guidelines developed by EPA to support regulatory programs mandated by TSCA and FIFRA will allow the Agency to require neurotoxicity testing of a wide range of industrial chemicals and pesticides. The extent and frequency of testing EPA may require is not clear at this time.

If it wishes to mandate additional neurotoxicity testing, Congress could require EPA to test new and existing chemicals if certain production volume and human exposure levels are reached and if structure-activity relationships or other



Illustrated by: Ray Driver

information suggests that the substance may be neurotoxic. Volume and exposure levels can be effective triggers for testing. Production volume is currently being used as a trigger by the Federal Republic of Germany, and this testing approach has been considered by EPA in the past. However, triggered testing does have important limitations-some substances may have potent neurotoxic effects at low doses. Congress may also wish to request that EPA consider novel approaches to obtaining more extensive data from industry under TSCA, perhaps through the use of economic incentives. EPA could work with industry representatives to devise incentives for voluntary neurotoxicity testing. EPA could also work more closely with scientists in industry and academia to develop and validate neurotoxicity tests.

Congress could amend FIFRA, mandating that new and existing pesticides being considered for registration undergo neurotoxicity testing under the newer, more extensive guidelines. This would formalize EPA's pending policy and would underscore congressional concern regarding the potential adverse effects of neurotoxic pesticides on public health. Currently, EPA plans to require the use of three neurotoxicity tests: the functional observational battery, motor activity, and neuropathological evaluations. Congress could also mandate that certain classes of inert ingredients undergo neurotoxicity evaluations as well. Congress may wish to request that EPA consider developmental neurotoxicological and behavioral tests in addition to the three core neurotoxicity tests for certain pesticides. Such tests are considered by some scientists to be particularly important in evaluating the effects of neurotoxic substances on children. Congress could also mandate that risk assessments devote increased attention to the potential adverse effects of pesticides on children.

Option **3:** *Require that EPA and other Federal agencies revise the confidential business information provisions of various toxic substances control laws and regulations to allow greater access to toxicological information.*

Under TSCA, for example, much of the information submitted to EPA by chemical manufacturers or processors can be claimed to be confidential business information. Information covered by such a claim cannot be divulged to anyone outside the small group of EPA employees who have been granted a special clearance, primarily selected EPA staff and contractors. The aim of confidentiality provisions is to prevent commercially valuable infor-

mation from being disclosed to the submitter's competitors. Other environmental statutes contain similar provisions regarding confidential or trade secret information.

Toxicity data per se cannot be claimed as confidential under TSCA, but much of the other information relevant to assessing toxic risks can—including the identity of the chemical for which toxicity data are presented, its physical-chemical properties, and its intended uses. This renders the health and safety data of little use to anyone without a special clearance.

The strong confidentiality provisions in TSCA can present significant barriers to efficient regulation. The requirement for a special clearance prevents the use of confidential data by anyone without a clearance, even if they are EPA officials or officials of other Federal agencies who are attempting to regulate the same chemical or closely related chemicals under different laws. The limited exchange of information can lead to duplication of effort, particularly when several agencies are constrained by confidentiality provisions.

The inability to share information, either inside the government or with outside parties, often interferes with research efforts. For example, much of the information on a chemical's structure-activity relationship is covered by claims that it is confidential business information. Scientists in industry, academia, and other government agencies cannot gain access to this information, even when it might contain valuable data for developing improved methods of predicting neurotoxicity and other toxic effects. At the same time, claims of confidentiality may prevent EPA from obtaining expert advice or consensus opinions from academic or industrial scientists.

Public interest groups and other interested individuals do not have access to information that would allow them to question-or to accept—EPA's actions on many toxic substances. Nor can individuals take action to protect themselves if they do not have access to information regarding the identity of toxic chemicals or the products that might contain them.

Few persons would dispute the need for some form of protection for trade secrets. However, many persons believe that there is good reason to question whether the burden imposed by strong confidentiality provisions and similar statutes on the government, the public, and industry is justifiable.

Congress could disallow certain kinds of information, including the precise chemical identification of a substance and all toxicological data on a substance, from claims of confidentiality. It could mandate that more information about the chemical properties, potential adverse effects, and production and release of toxic substances be made available to the public. It could amend existing laws or write new laws to enable sharing of information between Federal regulatory programs. Congress could also create a centralized confidential database, administered by one designated agency, or a consortium of agencies, and divert all reporting to the designated agency. In addition, it could require more extensive labeling of the contents of chemical products.

Option 4: Take action to provide agricultural workers with greater protection from the adverse effects of pesticides.

Congress could amend FIFRA, giving EPA greater regulatory authority to protect farmworkers and others from the adverse effects of pesticides (see box l-E).

Option 5: Mandate that neurotoxicity concerns be addressed in regulatory activities under various other laws for which EPA has regulatory responsibilities.

Congress could mandate that neurotoxicity receive greater attention under any or all of the following laws: the Clean Air Act; the Clean Water Act; the Safe Drinking Water Act; the Comprehensive Environmental Response, Compensation, and Liability Act; and the Resource Conservation and Recovery Act. Each law addresses toxicological concerns in a different

Box l-E—neurotoxic Pesticides

Organophosphorous and carbamate insecticides are the most neurotoxic classes of pesticides used in the United States and are the most common causes of agricultural poisoning. They pose a significant threat to a substantial portion of the 4 to 5 million Americans who work in agriculture. At the biochemical level, they may affect humans in the same manner that they affect the insects for which they are intended-through inhibition of the enzyme that breaks down the neurotransmitter acetylcholine. The acute health effects of organophosphorous and carbamate insecticides include hyperactivity, neuromuscular paralysis, visual problems, breathing difficulty, restlessness, weakness, dizziness, and possibly convulsions. The organochlorine class of pesticides is also very toxic because these substances accumulate in the body and cause persistent overstimulation of the central nervous system. Acute or subacute intoxication from organochlorines produces excitability, apprehension, dizziness, headache, disorientation, confusion, loss of balance, weakness, muscle twitching, tremors, convulsions, and coma.



Photo credit.' Doug/as Watts/Christopher *Brady*

What scientific and epidemiological data there are suggest pesticide poisoning prevails despite existing protective measures. The Environmental Protection Agency (EPA) is aware of the shortcomings of the protections currently in effect for farmworkers and others who work with pesticides. The Agency has proposed regulations to improve them, but critics have already deemed the proposals inadequate. EPA claims to be restricted by the Federal Insecticide, Fungicide, and Rodenticide Act, which grants the Agency only limited regulatory power. Inadequate funding has also contributed substantially to the weaknesses of Agency programs.

The possible occurrence of neurobehavioral disorders after chronic low-level exposure or acute poisoning deserves further study. Neuropsychological assessments of occupational groups have yielded inconsistent results, perhaps reflecting differences in the type and scope of tests used. Few studies have had an adequate follow-up to assess the length of impairment. Field studies have not provided sufficient data on levels of pesticides in children's blood or duration of exposure to understand dose-response relationships, nor have most studies controlled for age, education, or other potential confounding factors. Few or no studies have examined exposed workers prospectively, subgroups of women or aging workers, interactions between pesticides, or interactions between pesticides and pharmacological agents (including ethanol and common medications).

SOURCE: Office of Technology Assessment, 1990.

reamer. Congress could take action as these laws are amended, as funds are appropriated, and/or through various oversight activities. Such action might include making specific reference to neurotoxic substances or the adverse effects of chemicals on the nervous system, or both, in legislation addressing toxic substances and requiring that neurotoxic potential be considered when conducting risk assessments. With respect to FIFRA specifically, Congress could mandate that neurotoxic potential be carefully considered in setting tolerance levels of pesticide residues in foods. Potential adverse effects of pesticides on the developing nervous system could be cited as a particular concern.

Congress could also request that EPA review the effectiveness of agency programs in regulating neurotoxic substances and examine approaches to improve existing activities.

Food and Drug Administration

The Federal Food, Drug, and Cosmetic Act covers a wide range of substances. It authorizes

FDA to require submission of specific toxicity test data before permitting food additives, drugs, and other substances to be marketed. This authority could be used to incorporate neurotoxicity evaluations in FDA test guidelines or to require neurotoxicity testing during the application process if initial toxicological data indicate potential neurotoxic effects. FDA does not have authority to require premarket toxicity testing of cosmetic ingredients.

Option 1: Take no action.

If Congress chooses to take no action, FDA is likely to continue to address the potential neurotoxicity of food additives, drugs, and other substances in the context of general toxicological concerns. FDA does not routinely require specific neurotoxicity testing for food additives and drugs; instead, it evaluates the potential for neurotoxic effects in the context of a broad toxicological profile. Some scientists, including most FDA officials, believe that specific neurotoxicity testing of drugs and food additives is not necessary and that existing general toxicological testing approaches adequately detect adverse effects on the nervous system. Other scientists believe that existing general toxicological approaches are not sensitive enough to detect many neurotoxic effects and that specific neurotoxicity tests are essential for a complete toxicological evaluation.

Option 2: Commission an independent study by the National Academy of Sciences to determine whether specific neurotoxicity tests should be routinely required by FDA in evaluating the safety of drugs, food additives, and other substances regulated under FFDCA.

This option would address the issue of the adequacy of existing testing approaches. Such a study could include a retrospective analysis to determine whether conventional toxicological tests have failed to detect neurotoxic effects. It could also include a symposium at which scientists from academia, industry, government, and elsewhere could present varying views on this subject and attempt to reach a consensus on the proper course of action.

Option 3: Mandate more extensive neurotoxicity testing under FFDCA for drugs, food additives, and other substances.

Congress could mandate that FDA revise its ‘‘Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food,” commonly referred to as the ‘Red Book, ’ to require routine neurotoxicological screening of new food additives and to formulate improved processes for postmarked surveillance of new and existing additives. Congress could also require that some generally regarded as safe (GRAS) compounds undergo neurotoxicity testing. It could require that new drugs, particularly psychoactive drugs, undergo increased neurotoxicity testing through the use of specific neurotoxicological tests. In particular, Congress could mandate that FDA require complete neurotoxicity testing of psychoactive drugs that may be prescribed to children and pregnant women. Choosing this option would involve agreeing with scientists who believe that present toxicological testing practices at FDA do not adequately address potential adverse effects on the nervous system and that specific neurotoxicological tests are necessary to establish the safety of food additives and drugs.

Option 4: Amend FFDCA to require premarket toxicity testing of cosmetics and cosmetic ingredients.

FDA does not have the statutory authority to require premarket toxicity testing of cosmetics and cosmetic ingredients. Industry voluntarily conducts general testing of many products. If FDA finds that a cosmetic product has not been adequately tested, it can require that it be packaged with a warning label stating that ‘the safety of this product has not been determined. ’ In addition, FDA can take regulatory action against any poisonous or deleterious substance in cosmetics. Congress could amend FFDCA to require that cosmetics and cosmetic ingredients undergo premarket toxicity tests consistent with those required of drugs. Testing requirements could include a screen for neurotoxicological effects. A general toxicological evaluation, at

least, would ensure a degree of safety comparable to that of other products regulated under FFDCA.

Option 5: Mandate more extensive postmarked surveillance and monitoring of the adverse effects of drugs, food additives, cosmetics, and other substances and require that such information be made more readily available to the public.

Congress could mandate that FDA substantially expand postmarked surveillance and monitoring of the adverse effects, particularly neurotoxic effects, of drugs, food additives, cosmetics, and other substances. Congress could mandate that health-care professionals report adverse effects directly to FDA. Congress could mandate that surveillance and monitoring data be made more readily available to the public. It could also mandate expanded patient packaging information in drug products. Additional information could be provided to patients on potential adverse neurotoxic effects of drugs, particularly at higher than recommended doses, and on adverse effects that should be reported to a health-care professional (box l-F).

Occupational Safety and Health Administration

OSHA is authorized under the OSH Act to regulate toxic substances in the workplace in order to ensure that no employee suffers material impairment of health or functional capacity. Recently, OSHA promulgated a far-reaching revision and update of existing standards. The new standards affect 428 chemicals, lowering existing permissible exposure limits for 212 substances and establishing new exposure limits for 164 others. However, in devising the new standards, OSHA relied to a large extent on the recommendations of the American Conference of Governmental Industrial Hygienists, a private organization, instead of NIOSH, the Federal scientific advisory organization on occupational health issues. The advisability of this approach is likely to be a subject of continuing controversy in the occupational health field (box l-G). The adequacy of OSHA's efforts to protect the Nation's workers from toxic substances in general and neurotoxic substances in particular is a controversial issue. There are varying views on the extent to which OSHA regulatory actions take into account neurotoxicological concerns and the adequacy of industrial programs to monitor worker exposure to neurotoxic substances. There is also the question of why farmworkers, a segment of the work force that regularly comes into contact with pesticides with neurotoxic properties, are not afforded the same legal protections as most other U.S. workers.

Option 1: Take no action.

If no congressional action is taken, OSHA will continue to be responsible for carrying out the existing provisions of the OSH Act, which assure that no employee suffers "material impairment of health or functional capacity." Under these provisions, neurotoxic effects are implicitly, but not explicitly, covered. Therefore, the limited attention given to neurotoxicity will continue to be determined by agency priorities, resource considerations, public concerns, and the expertise of regulatory officials.

Option 2: Mandate that neurotoxicity concerns receive greater attention under the OSH Act.

Congress could use the authorization and appropriations process to communicate to OSHA its concern regarding neurotoxicity. The current law could be strengthened by incorporating an explicit reference to neurotoxic substances or the adverse effects of chemicals on the nervous system, or both. Congress could mandate that Material Safety Data Sheets clearly describe potential adverse affects on the nervous system. Congress could encourage industry to assure that health-care professionals, safety officers, and employee supervisors are aware of the neurotoxic potential of the chemicals to which employees are exposed. In addition, Congress could request that the General Accounting Office evaluate the effectiveness of OSHA's enforcement program with respect to neurotoxic substances.

Box l-F—Limitations *of FDA's Postmarked Monitoring System for Adverse Drug Reactions: Halcion, A Case Study*

Halcion, the most widely prescribed sleeping medication in the United States, was first approved for use in late 1982 with a recommended usual adult dose of 0.25 to 0.50 mg. Its package insert included mentions of amnesia, confusion, agitation, and hallucinations as possible side-effects. Over the next few years, FDA's adverse reaction monitoring system recorded an excess of adverse reports for Halcion in comparison to other benzodiazepine hypnotics--even after correcting for market share of the drug. In 1987, as a result of the reports and the apparent dose-relatedness of some adverse effects, several labeling and marketing changes were made. The usual adult dose was changed to 0.25 mg, two paragraphs mentioning the apparent dose-relatedness of some side-effects were added to the package insert, and a "Dear Doctor" letter was issued detailing the labeling changes. In early 1988, Upjohn, the manufacturer, discontinued the 0.50 mg tablet.

Following these changes, public concern about possible problems associated with Halcion use increased, largely because of a September 1988 article in *California Magazine* and a story on the ABC television program 20/20 in February 1989. The number of adverse reports received, which was expected to decline as a result of the labeling changes and Halcion's status as an "older" drug (the number of adverse reports associated with a drug normally decreases over time), rose. In September 1989, FDA convened an expert panel to review the reporting data on Halcion and to discuss whether further changes should be made in the labeling or marketing of the drug.

Discussion at that meeting illustrates the difficulties of drawing conclusions from the spontaneous adverse reporting process. In a comparison of adverse reports for Halcion (45 million prescriptions written since 1982) with adverse reports for Restoril (35 million prescriptions written since 1980), a drug prescribed to patients with similar sleeping problems, the following data were presented:

	Total number of reports received by FDA	
Adverse event	*Halcion*	*Restoril*
Amnestic events	267	4
Hallucinations, paranoid behavior	241	12
Confusion and delirium	304	17
Hostility and intentional injury	48	2

Overall, an average of 38 adverse reports per million prescriptions was received for Halcion, while 7.5 adverse reports per million prescriptions were received for Restoril.

These seemingly dramatic results, however, were tempered by myriad complicating variables. The influence of publicity, differences in reporting rates by manufacturers, lack of dosage information in about one-half of the adverse reports for Halcion, and ''new drug' v. ''older drug' effects all obscured the significance of differences between the sets of data. The 4-week period following the 20/20 episode, for example, produced twice as many adverse reports for Halcion as the 4-week period preceding the show. The FDA panel finally concurred that the data were too unreliable to warrant action, except possibly in the case of amnesia.

The unreliable data generated by the postmarketing monitoring system now in place effectively limit FDA review to premarket trials. Unexpected interactions with other medications or long-term side-effects may easily be missed. This is particularly disturbing from the standpoint of neurotoxicity, since drugs not expected to have neuropharmacological effects are not necessarily subjected to specific neurotoxicity testing. Changes which could improve the present system might include a requirement that all adverse report forms be sent directly to FDA as well as a requirement that physicians submit reports for all ''serious" adverse reactions observed.

Because of the inherent limitations in FDA's drug approval and adverse reaction monitoring systems, it is important that physicians and patients be aware of the possible adverse effects of the medications they prescribe and consume. Drugs are approved for use under certain conditions and at certain doses, and complicating factors such as age, other medications, or illness may significant y alter the effects of these drugs. In most cases, the decision to take any medication is a personal choice for the patient; an individual cannot make an informed decision without access to information about potential adverse effects.

SOURCES: U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, ***Transcript of Proceedings, Thirty-First Meeting*** (Rockville, MD: September 1989); "When Sleep Becomes a Nightmare, " 20/20, ABC, Feb. 17, 1989; Pharmaceutical Data Services, ''Top 200 Drugs of 1989,' ***American Druggist***, in press.

Box 1-G-Organic Solvents in the Workplace

Organic solvents and mixtures of solvents with other organic solvents or other toxic substances are widely used in the workplace. Millions of workers come into contact with solvents every day through inhalation or contact with the skin, Some solvents profoundly affect the nervous system. Acute exposure to organic solvents can affect an individual's manual dexterity, response speed, coordination, and balance. Chronic exposure of workers may lead to reduced function of the peripheral nerves and such adverse neurobehavioral effects as fatigue, irritability, loss of memory, sustained changes in personality or mood, and decreased ability to learn and concentrate.

The National Institute for Occupational Safety and Health (NIOSH) recommends that employers inform and educate workers about the materials to which they are exposed, potential health risks involved, and work practices designed to minimize exposure to these substances. NIOSH also recommends that employers assess the conditions under which workers may be exposed to solvents, develop monitoring programs to evaluate the extent of exposure, establish medical surveillance for adverse health effects resulting from exposure, and routinely examine the effectiveness of control methods being employed.

The Occupational Safety and Health Administration has recently updated the permissible exposure limits for approximately 428 substances, including many solvents. The new ruling established lower exposure limits for approximately 212 substances already regulated by the agency. Permissible exposure limits are established for the first time for another 168 substances, while existing limits for 25 substances are reaffirmed. This marks the first time in 17 years that a new set of exposure standards has been established. For many companies, meeting the new standards may require stricter engineering controls or more frequent use of respirators and other personal protective devices, or both. Continued education of workers, improved methods of preventing exposure, and plans or procedures to maintain compliance with the new ruling are required.

SOURCE: Office of Technology Assessment, 1990.

Option 3: Mandate increased efforts to monitor adverse neurological and behavioral effects of substances in the workplace.

Congress could mandate increased monitoring of adverse neurological and behavioral effects of toxic substances in the workplace. This would include enhanced efforts to detect toxic chemicals and improved reporting of known or potential adverse effects of chemicals on the nervous system, including the incidence of neurological or psychiatric disorders or diseases. Congress could mandate improved postmarketing surveillance of new products.

Congress could also mandate that OSHA conduct a review of its regulatory programs and examine ways to more effectively protect workers from neurotoxic substances.

Option 4: Mandate the extension to farmworkers of legal rights under the OSH Act.

Congress could mandate the OSH Act to include farmworkers under its provisions. This would give workers the right to know about the toxicity of pesticides and other chemicals to which they are exposed, access to exposure and medical records, and protection against retaliation by employers for taking steps to protect their health. Congress could consider extending these rights without preempting the more extensive standards that now exist in some States.

Consumer Product Safety Commission

The Consumer Product Safety Commission (CPSC) is an independent regulatory commission charged with protecting the public from "unreasonable risks of injury associated with consumer products.' Risk of injury is defined as ''risk of death, personal injury, or serious or frequent illness.' The Federal Hazardous Substances Act provides for the protection of public health by requiring that hazardous substances be labeled with various warnings, depending on the nature of the hazard. The Poison Prevention Packaging Act requires that CPSC prevent inadvertent poisoning of small children by specially packaging hazardous substances to make it "significantly difficult for children under 5 years of age to open or obtain a toxic or

harmful amount of the substance therein within a reasonable time. '

Option 1: Take no action.

Present laws treat neurotoxic substances in the context of general toxicological concerns. Therefore, the degree to which CPSC specifically addresses neurotoxic substances depends on program priorities, resources, and the expertise of regulatory officials. Views regarding CPSC's current degree of concern about neurotoxic effects vary.

Option 2: Mandate that neurotoxicity concerns receive greater attention under various Federal laws for which CPSC has regulatory responsibilities.

Congress could mandate that a private commission or organization examine the effectiveness of CPSC's present regulatory activities in protecting the public, especially high-risk groups such as children, from neurotoxic and other toxic substances. In addition, congressional authorization and appropriations committees could request that CPSC programs place a higher priority on concerns related to the adverse effects of toxic substances on the nervous system, including a requirement that the Commission ensure that products with neurotoxic potential be clearly labeled.

Department of Housing and Urban Development

The Lead-Based Paint Poisoning Prevention Act of 1971 required that the Department of Housing and Urban Development (HUD) eliminate as far as practicable the hazards of lead paint in existing houses, and mandated that the Department promulgate necessary regulations. However, the General Accounting Office reported in 1981 that HUD had not fulfilled its responsibility to eliminate lead-based paint in Federal housing. Following litigation and a court order, HUD revised its regulations in 1986 and 1987, and in 1988 Congress amended that Act requiring that HUD promulgate additional regulations to address the problem.

Option 1: Take no action.

HUD is making progress in meeting congressional mandates to address lead-based paint in housing, however, the pace of progress is slow. In the absence of congressional action, HUD will continue to move forward, but large numbers of children will continue to be exposed to lead-based paint in older homes.

Option 2: Amend the Lead-Based Paint Poisoning Prevention Act to better address the problem of lead paint in older homes.

If Congress wished to take action to expedite removal of lead-based paint from older homes, it could amend the had-Based Paint Poisoning Prevention Act establishing new programs to address the problem and providing funds to support paint removal efforts.

Option 3: Establish a major new program to provide finding for the removal of lead-based paint from older homes.

Congress may wish to enact a new law to facilitate removal of lead-based paint from older homes. One proposal recently developed by the Environmental Defense Fund (EDF) recommends establishment of a trust fund financed by an excise fee on the production and importation of lead. The EDF proposal calls for a program jointly administered by EPA and the Department of Health and Human Services.

ISSUE 2: Is the current Federal research framework addressing neurotoxicity adequately?

The current Federal research framework for addressing neurotoxicity is composed of major extramural programs sponsored by NIH and ADAMHA. A sizable intramural program is located at EPA, and more limited intramural programs are under way at ADAMHA and NIH. FDA has a substantial developmental neurotoxicology program at its National Center for Toxicological Research, but research efforts elsewhere are very limited in scope. OTA found that, in general, Federal research programs are not adequately addressing neurotoxicological concerns.

Environmental Protection Agency

EPA has a large intramural research program devoted to environmental neurotoxicology. Although the Agency has a small extramural grants program, it is not currently supporting any projects in which neurotoxicology is a major focus. EPA supports intramural program initiatives through a small number of contracts and cooperative agreements.

Option 1: Take no action.

Without congressional action, EPA intramural programs will continue at moderate levels. However, in the absence of an Agency policy change, lack of funding for supplies and equipment may continue to hamper some research efforts. Failure to expand EPA's intramural program will make it difficult to move into new, priority areas such as the development of in vitro neurotoxicity testing approaches and the analysis of structure-activity relationships of chemicals.

Option 2: Provide funding for expansion of intramural research programs.

Congress could choose to provide greater support to EPA's Office of Research and Development to fund additional research in the environmental neurotoxicology field. Budget increases would also alleviate problems associated with the lack of funds for supplies and equipment. Substantial increases would allow EPA to move into new areas of research that would strengthen its regulatory capabilities, including its efforts to understand the relationship between chemical structure and neurotoxic effects and further development and validation of neurotoxicity testing protocols, particularly in vitro and developmental tests.

Option 3: Provide funding for extramural grant programs to support neurotoxicological and neuroepidemiological research.

EPA's total extramural grants program for environmental issues is small; fiscal year 1989 funding for the entire program (addressing all environmental concerns) was $8.2 million to support individual academic investigators and $4.5 million to support eight Environmental Research Centers (in addition, the Superfund program provides $2.5 million in grants to investigators and $5.0 million to support five hazardous substances research centers). Currently, EPA is funding no neurotoxicology-related research grants to individual investigators through its extramural program. Federal research programs are normally composed of both intramural and extramural efforts: extramural programs enable talented investigators in academia and elsewhere to carry out research of interest to the sponsoring agency. They also allow an agency to complement its short-term intramural efforts, required to meet regulatory needs, with long-term studies that will help guide future research.

EPA is considering substantial expansion of its extramural programs. Congress could support such expansion or mandate programs that go beyond EPA's plans, or both. A grants program in neurotoxicology would greatly improve the scientific foundation of the Agency's regulatory decisionmaking. Areas that would particularly benefit from increased support are monitoring and neuroepidemiology, which aid in tracking the contribution of environmental contaminants to adverse human effects, including neurological and psychiatric disorders. In addition, extramural research designed to improve the Agency's ability to predict neurotoxic effects (e.g., through a better understanding of chemical structure-activity relationships) would greatly benefit regulatory programs. Research on the neurotoxicological properties of specific substances would aid in regulatory decisionmaking, and would enhance the Agency's ability to understand and predict the neurotoxicity of other substances.

National Institutes of Health

NIH supported more than 200 neurotoxicology-related research projects in fiscal year 1988. Most of the projects were extramural competitive grants to investigators in public and private

institutions. A few intramural projects were conducted.

Option 1: Take no action.

In the absence of congressional action, NIH will continue to conduct limited *intramural* research related to neurotoxicology, primarily at the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Deafness and Other Communication Disorders (NIDCD). The very small intramural research effort in environmental neurotoxicology at NIEHS might be enhanced. Institute managers could require that existing basic neuroscience research efforts change their focus to neurotoxicological concerns.

Extramural programs that fund neurotoxicological research projects are sponsored by several Institutes, particularly the three mentioned above. Without congressional action, these programs will continue to fund a core group of neurotoxicologists in academia at moderate levels. It is unlikely that the number of individual research projects funded would increase significantly.

Option 2: Enhance National Institutes of Health research efforts related to neurotoxicology,

If Congress wishes to enhance the NIH effort, it could mandate development of a 5-year plan to address neurotoxicological concerns. Such a plan could include an analysis of current NIH intramural and extramural programs, as well as development of an integrated and comprehensive approach to neurotoxicological research in the years ahead. NIH would also benefit from an outside review of the missions of individual Institutes and the current intramural and extramural programs supporting those missions. Increased interaction among Institutes and between Institutes and other Federal agencies would improve NIH's response to neurotoxicity concerns. Congress could expand the 5-year plan to include all relevant programs in the Department of Health and Human Services. This would include NIH, ADAMHA, FDA, NIOSH, the Agency for Toxic Substances and Disease Control, and other organizations. Development of such a plan would lead to a coordinated Federal effort to address the neurotoxicity issue.

Congress could provide additional funding to NIH to expand extramural grant programs, allowing various Institutes to enhance research efforts on such subjects as the mechanisms by which drugs cause adverse neurotoxic effects, the mechanisms by which environmental contaminants adversely affect the nervous system, and the extent to which toxic substances contribute to neurological and psychiatric disorders. High-priority research goals might include the structure-activity relationships of toxic chemicals, the vulnerability of developing and aging nervous systems to toxic substances, and the variation in sensitivity of individuals to these substances.

Congress could fund additional intramural research into high-priority areas of neurotoxicology research. It could also mandate reestablishment of an intramural neurobehavioral toxicology program at the National Institute of Environmental Health Sciences and request that the National Toxicology Program give a higher priority to neurotoxicity concerns.

Alcohol, Drug Abuse, and Mental Health Administration

ADAMHA funds extensive neurotoxicity research at all three of its Institutes (OTA has excluded research on alcohol and alcoholism from this study). The National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH) both fund a substantial number of extramural research grants. Intramural research programs related to neurotoxicology are somewhat limited in size and scope.

Option 1: Take no action.

If Congress chooses to take no action, ADAMHA programs will continue at moderate levels. However, without budget increases or significant reprogramming of funds, it will be difficult for these institutes to expand research efforts in the neurotoxicology field.

Option 2: Encourage greater research emphasis on the impact of abused drugs on the nervous system and on the potential contributions of toxic substances to neuropsychiatric disorders.

Congress may wish to encourage ADAMHA to devote increased resources to the potential long-term and permanent adverse effects of drug abuse, particularly the effects of maternal drug abuse on the developing nervous system of the fetus. Congress could also encourage greater emphasis on research to understand the mechanism by which psychoactive drugs and other therapeutic drugs act on the central nervous system, and particularly on how to prevent moderate to severe adverse side-effects of these drugs. ADAMHA could also focus more attention on neurotoxicity issues associated with the use of multiple psychoactive drugs for long periods of time by the elderly. Research advances in these areas would promote the development of safer, more effective drugs. Congress could support expanded research on the biochemical processes underlying addiction to abused drugs at NIDA's Addiction Research Center.

Food and Drug Administration

Research programs within FDA are conducted at the National Center for Toxicological Research (NCTR) in Jefferson, Arkansas, and at the Center for Food Safety and Applied Nutrition in Washington, D.C. Research programs related to neurotoxicology are very small, with the exception of the intramural developmental neurotoxicology research program at NCTR.

Option 1: Take no action.

Without congressional action, neurotoxicology research programs within FDA will remain very limited in scope. Relatively little research is currently devoted to neurotoxicological concerns. This is of particular significance because so many substances regulated under the Food, Drug, and Cosmetic Act have neurotoxic potential. Although some funds, particularly at NCTR, could be redirected to this area, present fiscal limitations on FDA research leave little room for flexibility.

Option 2: Provide funding to expand or initiate intramural and extramural research programs related to the adverse effects on the nervous system of drugs, cosmetics, food additives, naturally occurring toxic substances in food, and other substances.

Congress could choose to provide FDA with funds to support both intramural and extramural research related to the potential neurotoxic effects of substances regulated under FFDCA. A sizable research effort in this area would substantially improve FDA's ability to protect public health through an improved understanding of the effects of toxic substances on the nervous system. To promote substantive research efforts in critical areas, Congress could consider establishing research centers at academic institutions to focus on specific neurotoxicological concerns (e.g., structure-activity relationships, development of neurotoxicological tests, epidemiological studies, mechanisms of action). Congress could also provide funds to support a major neurotoxicology research unit within FDA.

National Institute for Occupational Safety and Health

NIOSH, located within CDC, has identified neurotoxic disorders as one of the Nation's 10 leading causes of work-related disease and injury. To aid in understanding the extent and nature of this problem, NIOSH supports a small number of intramural and extramural research activities. The intramural program is devoted primarily to evaluation of testing approaches and to analysis of selected neurotoxic substances found in the workplace. The NIOSH extramural program funds a very small number of grants devoted to understanding the mechanisms by which toxic substances adversely affect the nervous system.

Option 1: Take no action.

If no action is taken, NIOSH research programs related to neurotoxicity will continue at a

low level. Given the magnitude of the problem of exposure to neurotoxic substances in the workplace, the present level of effort will not ensure an adequate database to support the anticipated needs of the Occupational Safety and Health Administration.

Option 2: Expand intramural and extramural neurobehavioral research programs at NIOSH.

This option would lead to improvements in understanding the extent to which workers are exposed to neurotoxic substances, the mechanisms by which these substances exert adverse effects, and means of preventing exposures in the workplace. Substantive increases in funding for research would provide a better foundation for OSHA's regulatory activities related to neurotoxicity. Priority research needs include a better understanding of dose-response relationships, mechanisms of action, and structure-activity relationships. Methods for evaluating worker exposures need to be developed, improved, and validated. Epidemiological studies are needed to reveal the extent of workplace exposure to neurotoxic substances and the contribution of such exposure to neurological, psychiatric, and other disorders and injuries. More research is needed on latent neurological disorders that may result from chronic, low-level exposure to neurotoxic substances.

Substantially increased NIOSH funding of extramural neurotoxicology and neurobehavioral research would improve scientific understanding of workers' exposure to toxic chemicals. Such an increase would encourage research scientists to enter the field of environmental neurotoxicology by supporting laboratories that focus on occupational health issues. It would also be an important source of training for physicians.

Other Federal **Agencies and Organizations**

Other Federal agencies and organizations that undertake neurotoxicity-related research include the Center for Environmental Health and Injury Control and the National Center for Health Statistics within CDC, the Agency for Toxic Substances and Disease Registry, the Department of Energy, the Department of Agriculture, the Department of Veterans Affairs, and the National Aeronautics and Space Administration. The Department of Defense conducts neurotoxicology -related research, particularly as it relates to chemical warfare; however, defense-related research is not included in this report. The National Science Foundation presently supports very little research in this area.

Option 1: Take no action.

If Congress chooses to take no action, small research programs in these organizations are likely to continue. In some of them, limited efforts may be appropriate; in others, particularly those within DHHS, small efforts may hamper the ability of other agencies and individuals to address neurotoxicity-related issues. For example, the National Center for Health Statistics provides most of the current information on the prevalence, mortality, and morbidity associated with neurological and other diseases in the United States. Because of budget cuts in recent years, neuroepidemiologists have had difficulty in obtaining the statistical information necessary for studies of how neurotoxic substances contribute to neurological and psychiatric disorders.

Option 2: Mandate that various Federal organizations and agencies undertake or expand research programs addressing neurotoxicity -related concerns.

Several organizations could support research efforts in neurotoxicology that would enhance their own programs and those of others. Congress could mandate that these agencies adjust program priorities to better address neurotoxicity-related concerns, it could selectively provide increased funds for these programs, or it could do both. For example, enhanced efforts at the Center for Environmental Health and Injury Control, National Center for Health Statistics, and Agency for Toxic Substances and Disease Registry would benefit many Federal and State agencies and would provide support to academic investigators. The Department of Energy has

recently reemphasized research on the toxicological effects of chemicals. Its existing programs are focused on nuclear-related health concerns; support of nonnuclear, neurotoxicity-related research is minimal. Studies of the neurotoxic substances generated by energy-producing technologies would be beneficial. The National Science Foundation could spur academic research into the mechanisms by which toxic substances adversely affect the nervous system by providing support for basic research in the neurotoxicology field,

ISSUE 3: **Should Congress take steps to improve interagency coordination of Federal research and regulatory programs related to neurotoxicity?**

Until recently there was little coordination of Federal research and regulatory programs related to neurotoxic substances. At a workshop sponsored by OTA and EPA, representatives of various Federal agencies decided to establish an Interagency Working Group on neurotoxicology[1] to aid in interagency coordination.

Option 1: Take no action.

Without congressional action, the new interagency coordinating group may succeed in enhancing the exchange of regulatory and research information among Federal agencies. The success of an initiative of this kind is largely determined by the willingness of senior agency administrators, program managers, and technical personnel to participate and voluntarily share information. Whether an adequate level of interest will be maintained is not clear. Another important question is whether the group will have sufficient support at the senior management levels to carry out research and regulatory initiatives.

Option 2: Mandate and formalize the establishment of an organization to foster coordination of Federal interagency research and regulatory programs related to neurotoxicology.

Congress could formalize the existing interagency coordinating group by mandating establishment of an organization to ensure maximum use of U.S. research and regulatory resources. Congress could mandate that all significant Federal programs be represented in the organization, and it could require the submission of a report every 5 years on the state of the Federal neurotoxicology research and regulatory effort. This interagency organization would benefit from a board of advisors from academia, industry, and elsewhere who could evaluate existing programs and provide guidance on future directions. Choosing this option would require the redirection of existing agency funds or the appropriation of new funds.

ISSUE 4: Are current Federal educational and research policies and programs ensuring an appropriate number of adequately trained research and health-care professionals to address neurotoxicity concerns?

A significant portion of our current understanding of the effects of toxic substances on the nervous system comes from application of basic research to environmental health problems. However, too few scientists are trained in both neuroscience and toxicology to provide an adequate supply of neurotoxicologists. In addition, other environmental health professionals are needed to address neurotoxicological concerns, including neuroepidemiologists, occupational physicians, and nurses with training in neurotoxicology.

Option 1: Take no action.

Without congressional action, the focus of federally supported training programs will continue to be determined by individual agencies, and funding will continue at low levels. Inadequate Federal support of training is partly responsible for the shortage of adequately

[1]On Oct. 26, 1989, the name was changed t. the "Interagency Committee on Neurotoxicology" (ICON). The committee is administered through the neurotoxicology Division of EPA's Health Effects Research Laboratory in Research Triangle Park, NC.

trained research and health-care professionals in the field of neurotoxicology.

Option 2: Take steps to encourage individuals to establish careers in research and health-care fields that address toxicological, particularly neurotoxicological, concerns.

If Congress wishes to take this approach, it could mandate expansion of pre- and post-doctoral research training programs in neurotoxicology by increasing the number of training grants to individuals and/or research centers. This would primarily involve expansion of existing programs supported by NIH and NIOSH. Congress could encourage training of medical students in occupational medicine, including course work in neurotoxicology. It could promote training of graduate students in neurotoxicology by providing additional funds to NIH, ADAMHA, and NIOSH for this purpose or by funding a new training program that would be administered by EPA. It could also encourage physician residency training in occupational medicine by increasing the funds (through Title VII of the Health Professionals Education Act) for establishing such programs. Finally, it could encourage training of occupational safety and health specialists through continued or increased funding of the NIOSH training grants program, in particular the Educational Resource Centers.



Photo credit: UnitedAutomobik, Aerospace, and Agricultural Implement Workers of America-UAW Public Relations Department

Respirators may be useful in minimizing exposure to solvent vapors when engineering or work practice controls are inadequate.

ISSUE 5: Are workers and the public receiving sufficient information to allow them to make informed decisions about exposure to neurotoxic substances?

Preventing adverse effects of exposure to neurotoxic substances depends largely on understanding the threat that neurotoxic substances pose to human health and knowing how to limit exposure to these substances. In recent years, Congress has taken steps to increase the quantity and quality of information available to the public concerning health risks posed by toxic substances. For example, the Federal Emergency Planning and Community Right-to-Know Act of 1986 has resulted in a large database, accessible to the public, on the release of more than 300 toxic chemicals at facilities throughout the United States. In 1987, the Department of Labor expanded the OSHA hazard communication standard. This standard gives employees the right to know what chemicals they may encounter in the workplace. In general, information is transmitted through hazard communication programs, which use labels on containers and other warning signs; post appropriate safety information, including material safety data sheets; and train and educate employees about the chemical properties and hazardous effects of the toxic substances to which they are or may be exposed.

Option 1: Take no action.

In the absence of congressional action, existing hazard communication and right-to-know laws will provide the public and workers with useful information about the health risks posed by neurotoxic substances. The relevance of this information to neurotoxicity concerns will continue to be determined to a large degree by the perceptions and priorities of officials in the various agencies with regulatory responsibilities. Federally mandated worker information programs tend to focus on the carcinogenic and teratogenic potential of toxic substances; noncancer health risks such as neurotoxicity tend to receive less attention, even though they may pose an equal or greater health threat.

Option 2: Take action to ensure that the risks posed by neurotoxic substances are explicitly described to the public through hazard communication and right-to-know laws.

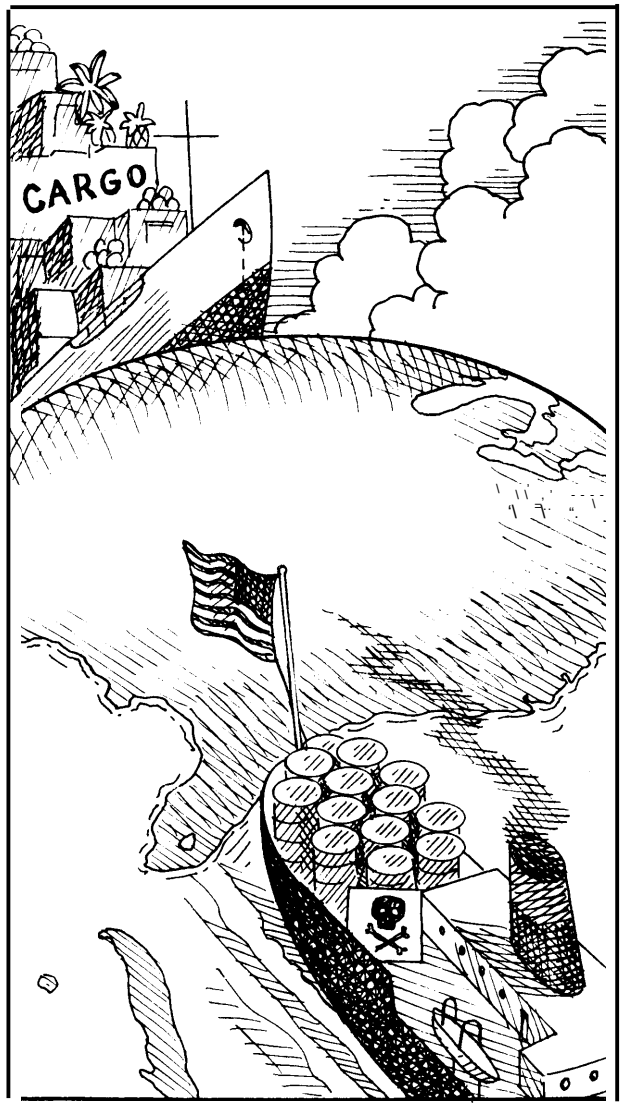
Choosing this option will result in enhanced communication of neurotoxic health risks to the public. Congress could require that information provided to workers under the Hazardous Communication Standards of the Occupational Safety and Health Act include a description of significant hazards posed by neurotoxic substances, and it could mandate improved enforcement of the hazardous communication provisions of this Act. Congress could also require that neurotoxicity concerns be explicitly addressed in information developed and released under the Federal Emergency Planning and Community Right-to-Know Act. Information on trends in annual data would also be useful in monitoring progress, in limiting releases, and in minimizing public exposure.

Option 3: Take additional steps to inform the public of the short- and long-term adverse effects of abuse of psychoactive drugs on the nervous system.

Congress could provide NIDA with funding for an aggressive campaign to inform the public of the potential long-term consequences of drug abuse on the nervous system. Congress could mandate that particular attention be devoted to the abuse of psychoactive drugs by pregnant women and the severe effects these substances may have on the nervous system of the developing fetus.

Option 4: Mandate improved labeling of consumer products with respect to potential neurotoxic effects.

Congress could take steps to assure that substances purchased by consumers that have neurotoxic potential are appropriately labeled and contain appropriate warnings when necessary. Congress could request that agencies devote particular attention to substances that



Illustrated by: Ray Driver

may adversely affect the developing nervous system.

In addition, Congress could mandate that all toxic product ingredients, including those sometimes referred to as 'inert' substances, be listed on product labels. This is particularly important with respect to pesticide products.

ISSUE 6: Should the United States more actively encourage and participate **in international regulatory and research programs related to neurotoxic substances, and should the United States revise its policies with regard to the export of neurotoxic substances?**

The adverse effects on the nervous system of occupational and environmental exposure to toxic chemicals are a major problem in the developing regions of the world. The United States is the leader in the international research effort to understand the health risks posed by neurotoxic substances. Because of this expertise, many persons believe that the United States should participate more actively in cooperative international efforts to address the problem. In addition, many question current U.S. policies regarding the export of neurotoxic substances that have been banned, severely restricted, or never registered for domestic use.

Option 1: Take no action.

At the present time, U.S. scientists actively participate in international conferences pertaining to toxic substances and human health risks. To a more limited extent, public and private agencies in the United States and foreign countries cooperate in research and regulatory activities. In the absence of congressional action, informal international activities will continue, but significant formal arrangements for coordinating research and regulatory efforts are unlikely.

Even though the United States is capable of training individuals from foreign countries in the fields of neurotoxicology and neuroepidemiology, it is very difficult for U.S. academic institutions to obtain funds to support such efforts. In the absence of congressional action, little funding will be available for training of this kind.

Without congressional action, the United States will continue to export neurotoxic substances that are banned, severely restricted, or never registered for use in this country. Persons who support current export policies believe that such practices are appropriate as long as the health risks posed by the chemical are communicated to the receiving country. Persons who oppose these policies believe that, despite efforts at hazard communication, many receiving nations do not have the expertise to judge the nature of the health risks; further, they argue that risk-related information is often not adequately communicated to users. The use of banned, severely restricted, or never-registered pesticides in developing countries is often cited as a particular problem.

Option 2: Encourage Federal agencies to initiate and participate in joint international testing efforts to evaluate the toxicity of new and existing chemicals.

Because so many chemicals have not been adequately tested for neurotoxicity, some persons believe it would be advantageous to test certain chemicals under joint international agreements. If standardized testing procedures could be agreed on, such an approach might result in a more equitable sharing of the chemical testing burden throughout the international community. The International Program on Chemical Safety (a joint venture of the United Nations Environment Program, the International Labor Organization, and the World Health Organization) has sponsored efforts to develop methods for assessing the neurotoxic effects of exposure to chemicals. Congress could encourage and support international programs of this kind. It could also encourage the development of an international toxicity database accessible to developing countries at minimal cost.

Option 3: Provide or redirect finding to encourage neurotoxicological and epidemiological

research and information exchange between public and private U.S. organizations and those offoreign nations.

This option would promote international programs to evaluate the health risks posed by neurotoxic substances and would encourage cooperative efforts to minimize human exposure to chemicals and naturally occurring substances that pose a public health risk. It is currently difficult for U.S. researchers to obtain grant support for projects involving international collaboration. Modest funding to encourage such collaboration would lead to mutually beneficial research efforts. U.S. neurotoxicologists and other scientists have few contacts in Third World countries, where their expertise could promote research and training of foreign personnel. Creation of a grants program to foster these relationships would not only respond to these needs, but also enlarge the perspective of U.S. scientists and promote international cooperation.

This option would encourage Federal agencies to provide grant support to academic institutions for partial sponsorship of international conferences and working groups on neurotoxicological questions. In addition, Congress could encourage continued U.S. participation in international toxicological research and policy planning activities. In particular, it could encourage the design and implementation of educational programs to inform people in developing countries about the risks posed by exposure to neurotoxic substances.

Option 4: Allow academic institutions receiving Federal funds for training grants to use a designated percentage of funds to support non-U.S. residents.

At the present time, NIH can support foreign research fellows through various mechanisms; however, Federal funds are not available to help support foreign students at U.S. academic institutions. Allowing U.S. institutions to use a designated percentage of training funds to support non-U.S. nationals and residents would facilitate the exchange of graduate students and postdoctoral fellows and aid foreign nations in developing their own research and regulatory programs. Congress could also make Federal funds available to encourage public and private institutions to sponsor research and training of persons in developing countries by U.S. personnel working in those countries.

Option 5: Revise existing laws governing the export of hazardous substances.

Congress could take action under various laws to ensure that regulations limiting the exposure of U.S. citizens to toxic substances are extended to individuals in foreign nations. This could involve prohibiting or limiting the export of neurotoxic substances that are banned, severely restricted, or never registered for domestic use. Such action would address the ethical concerns of persons who believe that current policies place the United States in a position of profiting from the export of chemicals that are considered to be too hazardous for domestic use. It would also help to minimize the exposure of U.S. citizens to hazardous chemicals through the import of foods, food products, and other consumer goods containing toxic substances that have been banned, severely restricted, or never registered in the United States.

Specifically with respect to pesticides, Congress could take steps to ban or restrict the export of those products that are not registered in the United States. It could prohibit or restrict the export of particularly hazardous pesticides to countries that do not have adequate regulatory, monitoring, and public and worker health protection programs. Congress could also require proper labeling of all exported pesticide products, including clearly written warnings in appropriate languages. Warning labels could be required to include the use of generally understood poison and health protection symbols. Steps could be taken to prohibit or restrict the import of food products containing the residues of pesticides not registered for use in the United States.

Chapter 2

Introduction

‘‘Chemicals are an everyday fact of life in modern society. They enhance our lives in ways too numerous to count, but progress has its price, and too often the price of the role of chemicals in our society is human illness and disease.

Representative Harold L. Volkmer
Committee on Science and Technology
U.S. House of Representatives
October *8, 1985*

‘‘Nervous system dysfunction during advanced age seems destined to become the dominant disease entity of the twenty-first century. Neither I, nor anyone else, can tell you how much of that dysfunction might be attributable to toxic chemicals in the environment. So far, hardly anyone has looked. ”

Bernard Weiss, Ph.D.
Testimony before the Committee on Science and Technology
U.S. House of Representatives
October 8, 1985

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Chapter 2
Introduction

Chemicals are an integral part of our daily lives and are responsible for substantially improving them. Yet chemicals can also endanger our health, even our survival. This report focuses on neurotoxic substances, those chemicals that adversely affect the nervous system. Included among such substances are industrial chemicals, pesticides, therapeutic drugs, abused drugs, foods, food additives, cosmetic ingredients, and naturally occurring substances. Whether a substance causes an adverse health effect depends on many factors, including the toxicity of the substance, the extent of exposure, and an individual's age and state of health. Minimizing public health risks requires knowledge about the properties and mechanisms of action of potentially toxic substances to which humans may be exposed. This knowledge provides the foundation for safety standards.

More than 65,000 chemicals are in the Environmental Protection Agency's (EPA's) inventory of toxic chemicals, and each year the Agency receives approximately 1,500 notices of intent to manufacture new substances (30). Since few of these chemicals have been tested to determine if they adversely affect the nervous system (or other systems), no precise figures are available on the total number of chemicals in existence that are potentially neurotoxic to humans. Some estimates have been developed, however, based on analyses of certain subsets of chemicals. These estimates vary considerably, depending on the definition of neurotoxicity used and the subset of substances examined. For example, some 600 active pesticide ingredients are registered with EPA (27), a large percentage of which are neurotoxic to varying degrees. One investigator estimated that 3 to 5 percent of industrial chemicals, excluding pesticides, have neurotoxic potential (41). Another investigator found that 28 percent of industrial chemicals for which occupational exposure standards have already been developed demonstrate neurotoxic effects (1). In addition, a substantial number of therapeutic drugs and many abused drugs have neurotoxic potential.

Human *exposure* to most known neurotoxic substances is normally quite limited. Consequently, the number of substances that pose an actual threat to public health is considerably less than the total number of neurotoxic substances in existence. The number of neurotoxic substances that pose a significant public health risk is unknown because the potential neurotoxicity of only a small number of chemicals has been evaluated adequately.

WHAT IS neurotoxicITY?

The nervous system comprises the brain, the spinal cord, and a vast array of nerves that control major body functions. Movement, thought, vision, hearing, speech, heart function, respiration, and numerous other physiological processes are controlled by this complex network of nerve processes, transmitters, hormones, receptors, and channels.

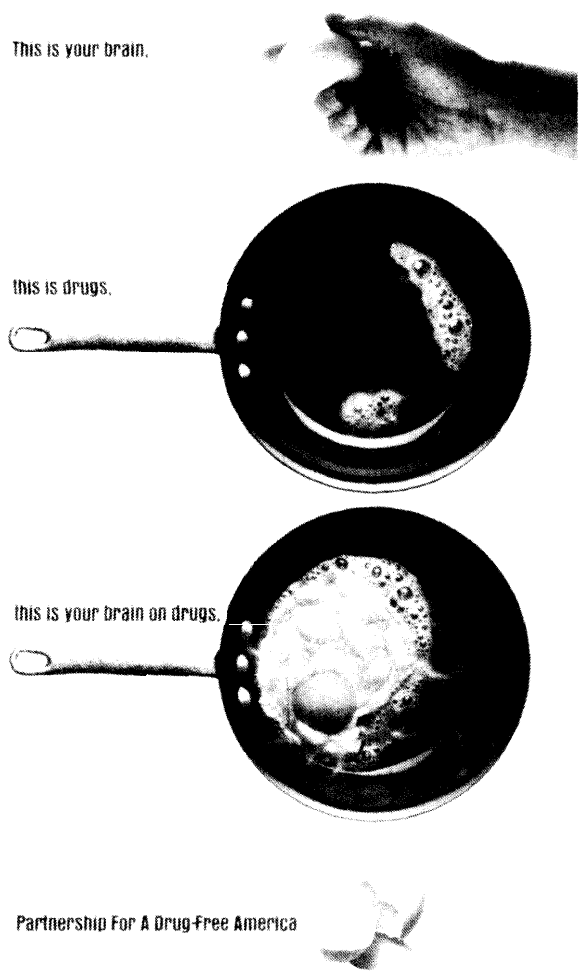


Photo credit: Advertising Partnership for a Drug-Free America, Inc.

Although every major body system can be adversely affected by toxic substances, the nervous system is particularly vulnerable to them. Unlike many other types of cells, nerves have a limited capacity to regenerate. Also, many toxic substances have an affinity for lipids, fat-like substances that make up about 50 percent of the dry weight of the brain, compared to 6 to 20 percent of other organs (8).

Many toxic substances can alter the normal activity of the nervous system. Some produce effects that occur almost immediately and last for a period of several hours: examples include a drug that prevents seizures, an alcoholic beverage, and fumes from a can of paint. The effects of other neurotoxic substances may appear only after repeated exposures over weeks or even years, for example, regularly breathing the fumes of a solvent in the workplace or eating food or drinking water contaminated with lead. Some substances can permanently damage the nervous system after a single exposure: certain organophosphorous pesticides and metal compounds such as trimethyl tin are examples. Other substances, including abused drugs such as heroin and cocaine, may lead to addiction, a long-term adverse alteration of nervous system function. Many neurotoxic substances can cause death when absorbed, inhaled, or ingested in sufficiently large quantities.

Care must be taken in labeling a substance neurotoxic because factors such as dose and intended effects must be taken into consideration. A substance may be safe and beneficial atone concentration but neurotoxic at another. For example, vitamins A and B_6 are required in the diet in trace amounts, yet both cause neurotoxic effects in large doses (50). In other cases, a substance that is known to be neurotoxic may confer benefits that are viewed as outweighing the adverse effects. For example, thousands of individuals suffering from schizophrenia have been able to live relatively normal lives because of the beneficial effects of the antipsychotic drugs. However, chronic use of prescribed doses of some of these drugs may give rise to tardive dyskinesia-involuntary movements of the face, tongue, and limbs—side-effects so severe that they may incapacitate the patient (50).

Another factor that complicates efforts to evaluate neurotoxicity is the potential additive effects of toxic substances. For example, independent exposure to two toxic substances may lead to no observable adverse effects, but simultaneous exposure could result in damage to the nervous system. In addition, the body has an effective but limited capacity for detoxifying many chemical agents. Some chemicals thought to be relatively nontoxic may cause adverse effects if exposure occurs after the body's detoxifying systems have been saturated (17). Such situations might occur following chronic exposure to a complex mixture of chemicals in the workplace or to chemicals at hazardous waste sites.

Broadly defined, any substance is considered to have neurotoxic potential if it adversely affects any of the structural or functional components of the nervous system. At the molecular level, a substance might interfere with protein synthesis in certain nerve cells, leading to reduced production of a neurotransmitter and brain dysfunction. At the cellular level, a substance might alter the flow of ions (charged molecules such as sodium and potassium) across the cell membrane, thereby perturbing the transmission of information between nerve cells. Substances that adversely affect sensory or motor functions, disrupt learning and memory processes, or cause detrimental behavioral effects are neurotoxic, even if the underlying molecular and cellular effects on the nervous system have not been identified. Exposure of children to lead, for example, leads to deficits in I.Q. and poor academic achievement (40). Behavioral effects are sometimes the earliest signs of exposure to neurotoxic substances (56). In addition, there is evidence that the adverse effects of some toxic substance-induced neurodegenerative diseases may not become apparent until years after exposure (49).

For the purposes of this study, the Office of Technology Assessment (OTA) defines neurotoxicity or a neurotoxic effect as an adverse change in the structure or function of the nervous system following exposure to a chemical agent. This is the definition currently used for regulatory purposes by EPA (50 FR 188). However, as the preceding discussion illustrates, this definition should be used in conjunction with information on the intended use of the substance, the degree of toxicity, and the dose or extent of exposure of humans or other organisms. The definition hinges on interpretation of the word "adverse," and there is disagreement among scientists as to what constitutes "adverse change." The nature and degree of impairment, the duration of effects (especially irreversible effects), and the age of onset of effects are among the many

factors taken into account in determining whether or not an effect is adverse. The definition is further complicated by the possibility that adverse effects on the nervous system maybe secondary effects of the action of a toxic substance on other organs. For example, kidney or liver damage may lead to adverse effects on the nervous system (26). Determining whether a particular neurological or behavioral effect is adverse requires a comprehensive analysis of all available data, including consideration of social values (1 1).

SCOPE OF THIS STUDY

This study examines many, but not all, of the classes of toxic substances. The assessment includes discussion of industrial chemicals, pesticides, therapeutic drugs, substance drugs, foods, food additives, cosmetic ingredients, and such naturally occurring substances as lead and mercury. It does not include radioactive chemicals; nicotine (from cigarette smoke); alcohol (ethanol); biological and chemical warfare agents; microbial, plant, and animal toxins; and physical agents such as noise.

WHO IS AT RISK?

Everyone is at risk of being adversely affected by neurotoxic substances, but individuals in certain age groups, states of health, and occupations face a greater probability of adverse effects. The developing nervous system is particularly vulnerable to some neurotoxic substances, for several reasons. It is actively growing and establishing cellular networks, the blood-brain barrier that protects much of the adult brain and spinal cord from some toxicants has not been completely formed, and detoxification systems are not fully developed. Consequently, fetuses and children are more vulnerable to the effects of certain neurotoxic substances than are adults (44). The National Academy of Sciences (NAS) recently reported that 12 percent of the 63 million children under the age of 18 in the United States suffer from one or more mental disorders and identified exposure to toxic substances before or after birth as one of the several risk factors that appear to make certain children vulnerable to these disorders (31).

The elderly are more susceptible to certain neurotoxic substances because decline in structure and function of the nervous system with age limits its ability to respond to or compensate for toxic effects (17). In addition, decreased liver and kidney function increases susceptibility to toxic substances. Aging may also reveal adverse effects masked at a younger age. Persons who are chronically ill, especially those suffering from neurological or psychiatric disorders, are at risk because neurotoxic substances may exacerbate existing problems. Also, many elderly Americans take multiple drugs that may interact to adversely affect nervous system function. According to the Department of Health and Human Services (DHHS), people 60 and older represent 17 percent of the U.S. population but account for nearly 40 percent of drug-related hospitalizations and more than half the deaths resulting from drug reactions (19). Common adverse effects include depression, confusion, loss of memory, shaking and twitching, dizziness, and impaired thought processes.

Workers in industry and agriculture often experience substantially greater exposures to certain toxic substances than the general population. The National Institute for Occupational Safety and Health (NIOSH) has identified neurotoxic disorders as one of the Nation's 10 leading causes of work-related disease and injury. Other leading causes of work-related disease and injury include noise-induced hearing loss and psychological disorders, both of which are mediated by the nervous system. Evaluating the risk posed by neurotoxic substances is critical to the regulatory process. Risk assessment issues are discussed in chapter 6.

EXAMPLES OF neurotoxic SUBSTANCES

neurotoxic substances include naturally occurring elements such as lead and mercury, biological compounds such as botulinum toxin (produced by certain bacteria) and tetrodotoxin (found in the puffer fish, a Japanese delicacy), and synthetic compounds, including many pesticides and industrial solvents. Some commonly encountered substances are neurotoxic but may not be recognized as such. For example, certain antibiotics and hexachlorophene (once frequently used as an antibacterial agent in soaps) are neurotoxic when sufficiently large quantities are ingested or absorbed through the skin; however, exposures to large quantities are rare. Many therapeutic drugs and abused substances also have neurotoxic potential.



Illustrated *by:* Ray Driver

neurotoxic substances can cause a variety of adverse health effects, ranging from impairment of muscular movement to disruption of vision and hearing, to memory loss and hallucinations. Some substances can cause paralysis and death. Often, neurotoxic effects are reversible, that is, the effects diminish with time after exposure ceases and no adverse effects on the nervous system are thought to remain. At times, the effects are irreversible and lead to permanent changes in the nervous system. Table 2-1 summarizes some of the most frequently reported neurobehavioral effects of exposure to toxic substances (2). The adverse effects of neurotoxic substances and the mechanisms through which they occur are discussed in chapter 3.

neurotoxicity has been an important public health concern for many years, and incidents of human poisoning have occurred periodically throughout the world for centuries. Some of the major incidents are

Table 2-l-Neurological and Behavioral Effects of Exposure to Toxic Substances

Motor effects:	*Sensory effects:*
convulsions	equilibrium changes
weakness	vision disorders
tremor, twitching	pain disorders
lack of coordination, unsteadiness	tactile disorders
paralysis	auditory disorders
reflex abnormalities	Cognitive effects:
activity changes	memory problems
Mood and personality effects:	confusion
sleep disturbances	speech impairment
excitability	learning impairment
depression	Genera/ effects:
irritability	loss of appetite
restlessness	depression of neuronal activity
nervousness, tension	narcosis, stupor
delirium	fatigue
hallucinations	nerve damage

SOURCE: Adapted from W.K. Anger, "Workplace Exposures," Neurobe- *havioral Toxicology, Z.* Annau (cd.) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 331-347.

indicated in table 2-2. The neurotoxicity of heavy metals, widely distributed in the soil of the Earth's surface, has been recorded in fable and fact for many centuries. The toxicity of lead, for example, has been a concern since Hippocrates first recognized it in the mining industry (39).

Lead is a widely distributed metal. In its natural state, it is referred to as inorganic lead. Major sources of inorganic lead include industrial emissions, lead-based paints, food, and beverages. Organic lead compounds include the anti-knock gasoline, tetraethyl lead. had has profound effects on the nervous system. At relatively low levels it can cause a variety of neurobehavioral problems, including learning disorders (54). Despite years of research and considerable regulatory action, the extent and consequences of lead poisoning in children remain a major public health problem. In 1988, a Federal agency reported that about 17 percent of American children in metropolitan statistical areas (MSAs) have concentrations of lead in their blood above 15 micrograms per deciliter, a concentration that may adversely affect the nervous system (54). The percentage is much higher for urban children from poor families. Over the years, numerous Federal regulations have been developed to decrease human exposure, but the debate on acceptable levels in children continues. Lead will be discussed in detail in chapter 10.

Table 2-2-Selected Major neurotoxicity Incidents

Year(s)	Location	Substance	Comments
400 B.C.	Rome	lead	Hippocrates recognizes lead toxicity in the mining industry (5)
1930s	United States (Southeast)	TOCP	Compound often added to lubricating oils contaminates "Ginger-Jake," an alcoholic beverage; more than 5,000 paralyzed, 20,000 to 100,000 affected (1)
1930s	Europe	Apiol (w/TOCP)	Abortion-inducing drug containing TOCP causes 60 cases of neuropathy (1)
1932	United States (California)	thallium	Barley laced with thallium sulfate, used as a rodenticide, is stolen and used to make tortillas; 13 family members hospitalized with neurological symptoms; 6 deaths(1)
1937	South Africa	TOCP	60 South Africans develop paralysis after using contaminated cooking oil (1)
1946	—	tetraethyl lead	More than 25 individuals suffer neurological effects after cleaning gasoline tanks (4)
1950s	Japan (Minamata)	mercury	Hundreds ingest fish and shellfish contaminated with mercury from chemical plant; 121 poisoned, 46 deaths, many infants with serious nervous system damage (1)
1950s	France	organotin	Contamination of Stallinon with triethyltin results in more than 100 deaths (1)
1950s	Morocco	manganese	150 ore miners suffer chronic manganese intoxication involving severe neurobehavioral problems (1)
1950s-1970s	United States	AETT	Component of fragrances found to be neurotoxic; withdrawn from market in 1978; human health effects unknown (1)
1956	—	endrin	49 persons become ill after eating bakery foods prepared from flour contaminated with the insecticide endrin; convulsions resulted in some instances (5)
1956	Turkey	HCB	Hexachlorobenzene, a seed grain fungicide, leads to poisoning of 3,000 to 4,000; 10 percent mortality rate (3)
1956-1977	Japan	clioquinol	Drug used to treat travelers' diarrhea found to cause neuropathy; as many as 10,000 affected over two decades (1)
1959	Morocco	TOCP	Cooking oil contaminated with lubricating oil affects some 10,000 individuals (1)
1960	Iraq	mercury	Mercury used as fungicide to treat seed grain used in bread; more than 1,000 people affected (6)
1964	Japan	mercury	Methylmercury affects 646(1 ,6)
1968	Japan	PCBs	Polychlorinated biphenyls leaked into rice oil, 1,665 people affected (9)
1969	Japan	n-hexane	93 cases of neuropathy occur following exposure to n-hexane, used to make vinyl sandals (1)
1971	United States	hexachlorophene	After years of bathing infants in 3 percent hexachlorophene, the disinfectant is found to be toxic to the nervous system and other systems (5)
1971	Iraq	mercury	Mercury used as fungicide to treat seed grain is used in bread; more than 5,000 severe poisonings, 450 hospital deaths, effects on many infants exposed prenatally not documented (3,6)
1973	United States (Ohio)	MnBK	Fabric production plant employees exposed to solvent; more than 80 workers suffer polyneuropathy, 180 have less severe effects (1)
1974-1975	United States (Hopewell, VA)	chlordecone (Kepone)	Chemical plant employees exposed to insecticide; more than 20 suffer severe neurological problems, more than 40 have less severe problems (1)
1976	United States (Texas)	leptophos (Phosvel)	At least 9 employees suffer serious neurological problems following exposure to insecticide during manufacturing process(1)
1977	United States (California)	dichloropropene (Telone II)	24 individuals hospitalized after exposure to pesticide Telone following traffic accident (1 O)
1979-1980	United States (Lancaster, TX)	BHMH (Lucel-7)	Seven employees at plastic bathtub manufacturing plant experience serious neurological problems following exposure to BHMH (8)
1980s	United States	MPTP	impurity in synthesis of illicit drug found to cause symptoms identical to those of Parkinson's disease (11)
1981	Spain	toxic oil	20,000 persons poisoned by toxic substance in oil, resulting in more than 500 deaths; many suffer severe neuropathy (2)
1985	United States and Canada	aldicarb	More than 1,000 individuals in California and other Western States and British Columbia experience neuromuscular and cardiac problems following ingestion of melons contaminated with the pesticide aldicarb (7)
1987	Canada	domoic acid	Ingestion of mussels contaminated with domoic acid causes 129 illnesses and 2 deaths. Symptoms include memory loss, disorientation, and seizures (12)

SOURCES: (1) P.S. Spencer and H.H. Schaumburg, *Experimental and Clinical Neurotoxicity* (Baltimore, MD: Williams & Wilkins, 1980); (2) H. Altenkirch et al., "The neurotoxicologlcal Aspects of the Toxic Oil Syndrome (TOS) in Spare," *Toxicology* 49:25-34, 1968; (3) B. Weiss and T.W. Clarkson, "Toxic Chemical Disasters and the Implications of Bhopal for Technology Transfer," *Milbank Quarterly* 64:216-240, 1986; (4) D.A.K. Cassells and E.C. Dodds, "Tetra-ethyl Lead Poisoning," British *Medical Journal* 2:681, 1946; (5) C.D. Klaassen, M.O. Amdur, and J. Doull (eds.), *Casarett and Doull's Toxicology (New York, NY:* Macmillan Publishing Co., 1986); (6) World Health Organization, *Principles and Methods for the Assessment of neurotoxicity Associated With Exposure to Chemicals,* Environmental Health Criteria 60 (Geneva: 1986); (7) Morbidity and Mortality Weekly Report, "Aldicarb Food Poisoning From Contaminated Melons< alifornia," *Journal of American the Medical Association* 256:1 *75-176, 1986; (8)* J.M. Horan et al., "Neurologic Dysfunction From Exposure to 2-+-Butulazo-2-Hydroxy -5-Methylhexane (BHMH): A New Occupational Neuropathy," *American Journal of Public Health* 75:513-517, 1985; (9) G.G. Goetz, "Pesticides and Other Environmental Toxins, "*Neurotoxins in Clinical Practice (New* York, NY: Spectrum Publications, Inc., 1985) pp. 107-131; (10) U.S. Public Health Service, Centers for Disease Control Morbidity and Mortality Weekly Report, "Acute and Possible Long-Term Effects 1,3-dichloropropene—California," Feb. 17, 1978, pp. 50, 55; (11) J. Kopin and S.P. Maukey, "MPTP Toxicity: Implications for Research in Parkinson's Disease," *Annual Review of Neuroscience 11* :81-96, 1988; (12) J.M. Hungerford and M.M. Wekell, "Control Measures in Shellfish and Finfish Industries: USA, " Bothell, VA, U S. FDA, m press.

Mercury compounds are potent neurotoxic substances and have caused a number of human poisonings worldwide. Common symptoms of exposure include lack of coordination, speech impairment, and vision problems, In the mid-1950s, a chemical plant near Minamata Bay, Japan, discharged methylmercury, a highly toxic organic form of mercury, into the bay as part of waste sludge (17). Fish and shellfish became contaminated and were consumed by local inhabitants, resulting in an epidemic of mercury poisoning and severe neurotoxicological and developmental effects. Mercury used as a fungicide in treating seed grain was the cause of a very serious epidemic in Iraq in 1971, resulting in more than 450 deaths (57) (see box 2-A).

Manganese is required in the diet in trace quantities but is highly toxic when relatively large amounts are inhaled. Hundreds, perhaps thousands, of miners in several countries have suffered from 'manganese madness,' a disorder characterized by hallucinations, unusual behavior, emotional instability, and numerous neurological problems (43). Other metals, including aluminum, cadmium, and thallium, are neurotoxic in varying degrees. It is particularly challenging to limit public exposure to metals because they occur naturally in the environment.

Industrial Chemicals

Thousands of chemicals are produced by industry, and new substances are constantly entering the marketplace. Organic solvents are a class of industrial chemicals that have the potential for significant human exposure. This is due in large part to their volatility; that is, in the presence of air they change rapidly from liquids to gases, which may be readily inhaled. Their fat volubility and other chemical properties make many solvents neurotoxic in varying degrees. Exposures may be accidental, as often occurs in the industrial or household setting, or deliberate, as in glue-sniffing, a common form of inhalant abuse. Many solvents, including ethers, hydrocarbons, ketones, alcohols, and combinations

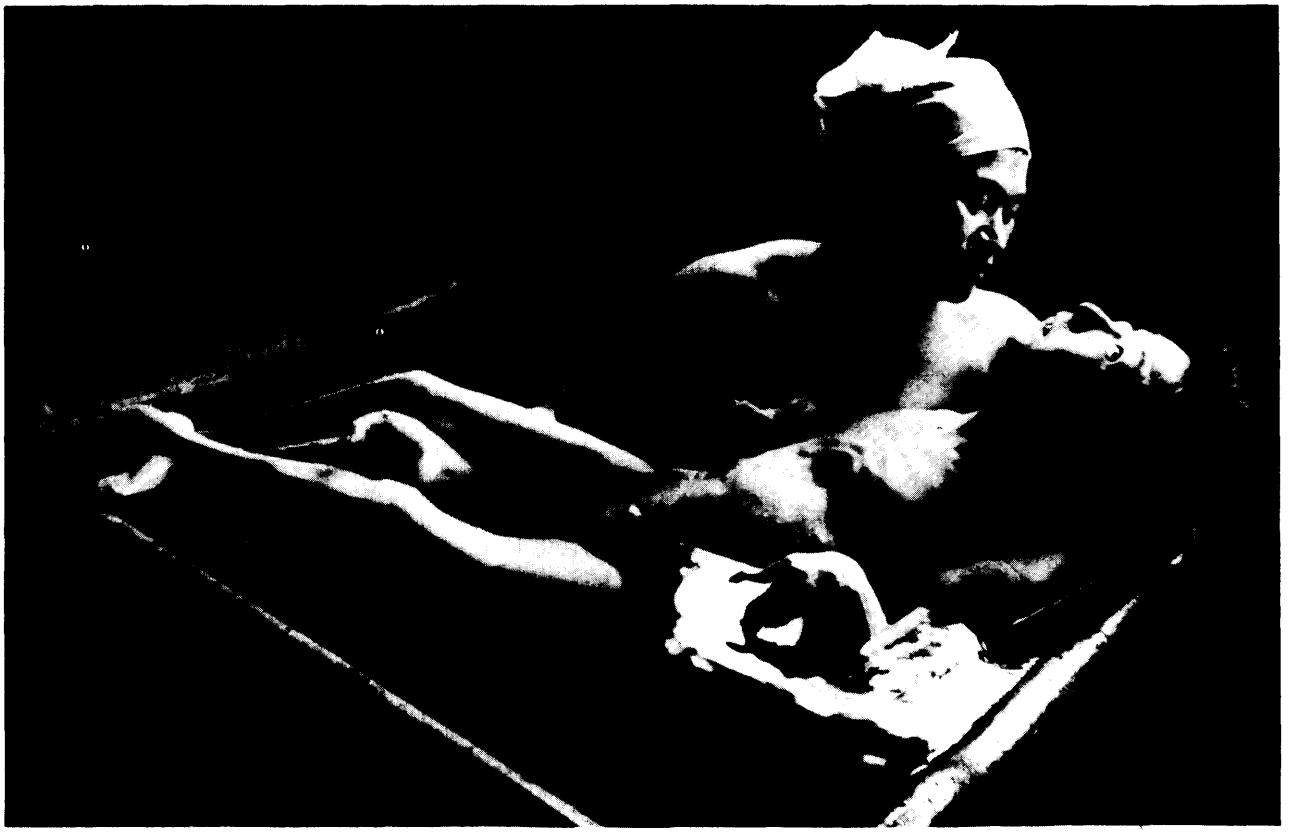


Photo credit: W. Eugene Smith end Aileen Smith

A child victimized by mercury poisoning during the Minamata Bay, Japan, incident in the 1950s is bathed by his mother. This is one of the most dramatic poisoning incidents involving a neurotoxic substance.

Box 2-A—Mass Mercury Poisoning in Iraq, 1971

Wheat is believed to have been domesticated first in the fields of the Fertile Crescent, an area extending from the Persian Gulf to the Palestinian coast, including much of what is now Iraq. Following a major drought in 1971 that ruined the wheat harvest of this region, the Iraqi government decided to switch to a more resilient variety of wheat from Mexico, known as Mexipak. The Iraqis requested that the wheat seed be treated with mercury to protect it from fungal infections. However, in placing the order, a single-letter typographical error was made in the name of the fungicide, resulting in treatment of the grain with highly toxic methylmercury instead of the relatively harmless form of organic mercury normally used.

In the fall of 1971, the largest commercial order of wheat in history (178,000 tons) was delivered to Iraq and distributed throughout the country. In some areas the wheat arrived too late for planting and was used instead to make bread. The sacks contained labels warning against consumption, but the labels were in Spanish. The grain had also been colored by a pink dye to indicate that it was poisonous, but the farmers were not aware of the significance of the color. Some of the sacks still carried the original warning labels from the U.S. manufacturer, with the skull and crossbones poison designation; however, the Iraqi farmers were not familiar with this symbol.

The mercury-treated grain was consumed by thousands of Iraqis over a period of a few weeks. Indeed, the pink color of the bread was thought to be attractive. Weeks later, the effects of mercury poisoning began to appear. At first the symptoms were a burning or prickling sensation of the skin and blurred vision. These symptoms were followed by uncoordinated muscular movements, blindness, deafness, coma, and in some cases death. Tragically, one village was not aware of the delayed effects of mercury poisoning and assumed that the traditional yellow wheat they had just eaten was responsible for the poisoning. Their efforts to obtain the pink variety, which they had recently run out of, were unfortunately successful. The estimated toll of the mass poisoning was 6,000 hospitalizations, 5,000 severe poisonings, and 450 hospital deaths. Since many persons were not admitted to hospitals, the actual totals are not known; however, the number of individuals significantly affected has been placed at more than 50,000 and the number of deaths at 5,000.

The effects on developing fetuses in mothers who ate the bread have not been fully documented, but subsequent analyses indicate that the fetus may be more than 10 times as sensitive to mercury poisoning as the adult. Afterbirth, the exposed child may suffer seizures, abnormal reflexes, and delayed development. Severe cases involve cerebral palsy. The extent and consequences of this tragedy still are not completely documented.

SOURCE: B. Weiss and T.W. Clarkson, "Toxic Chemical Disasters and the Implications of Bhopal for Technology Transfer," Milbank *Quarterly* 64:216-240, 1986.

of these, have caused neurological and behavioral problems in the workplace. For example, in 1973, workers at a fabric production plant in the United States were discovered to have neuropathies, or degeneration of nerve fibers. These workers had been regularly exposed to methyl-n-butyl ketone (MnBK), a dye solvent and cleaning agent introduced to the plant the previous year (25). Subsequent laboratory studies implicated MnBK as the causative agent. neurotoxic solvents in the workplace will be discussed further in a case study in chapter 10.

Solvents are commonly used in glues, cements, and paints. The fumes of toluene-based spray paints, various solvents, and modeling cements are sometimes inhaled as intoxicants. Inhalant abuse, an important public health problem (13,38,45), can cause severe degeneration and permanent loss of nerve cells. About one in five high school students has tried inhalants. Unfortunately, young people are often unaware of the permanent damage that this type of substance abuse can cause (46).

Pesticides

Pesticides are one of the most commonly encountered classes of neurotoxic substances. In this report ''pesticide' is used as a generic term and includes insecticides (used to control insects), fungicides (for blight and mildew), rodenticides (for rodents such as rats, mice, and gophers), and herbicides (to control weeds), among others. More than 1 billion pounds of pesticides are used annually in the United States alone. Some 600 active pesticide ingredients used on crops are registered with EPA. These active ingredients are combined with so-called inert substances to make thousands of different pesticide formulations.

The organophosphorous insecticides, which account for about 40 percent of the pesticides registered in the United States, have neurotoxic proper-

ties (10), as do other classes of pesticides, including the carbamate and organochlorine insecticides. Because of the biochemical similarities between the insect and human nervous systems, insecticides can adversely affect humans as well, Organophosphorous and carbamate insecticides inhibit acetylcholinesterase, an enzyme responsible for inactivating the neurotransmitter acetylcholine (a common chemical messenger in the nervous system) after it has been released by stimulation of a nerve cell. Consequently, these pesticides cause acetylcholine to accumulate in the synapses (or points of contact) between nerves and muscles. This leads to overstimulation of many nerves, including those that control muscle movement, some organ systems, and thought and emotional processes. Indeed, it is this property that led to the development and use of organophosphorous compounds as "nerve gas" weapons. Acute human poisoning from organophosphorous insecticides can cause muscle weakness, paralysis, disorientation, convulsions, and death. Of particular concern are the delayed neurotoxic effects of some of the organophosphorous insecticides. Some of these compounds cause degeneration of nerve processes in the limbs, leading to changes in sensation, muscular weakness, and lack of coordination (29). Because of this property, the EPA requires that organophosphorous insecticides undergo special testing for delayed neurotoxicity.

In the mid-1970s, the American public became acutely aware of the threat to human health posed by neurotoxic substances when a number of workers at a chemical plant in Hopewell, Virginia, were exposed to the insecticide chlordecone (a chlorinated hydrocarbon marketed as Kepone). A previously unidentified neurological disorder resulted, characterized by tremors, muscle weakness, slurred speech, lack of coordination, and other symptoms (24). Of the 62 verified cases, more than a third displayed disabling neurological symptoms. The symptoms appeared from 5 days to 8 months after onset of exposure to large amounts of the insecticide and remained in several of the workers for months after cessation of exposure and closing of the plant (29). This incident illustrates the difficulty physicians face in diagnosing poisoning episodes. Affected workers reported that the overt signs of poisoning were preceded by a feeling of ''nervousness, ' a symptom that might not lead a physician to suspect exposure to a neurotoxic substance.

Because of their widespread use, pesticides are dispersed in low concentrations throughout the environment, including the Nation's food and water supplies. Between 1982 and 1985, the Food and Drug Administration (FDA) detected pesticide residues in 48 percent of more than two dozen frequently consumed fruits and vegetables (28). However, OTA recently found that FDA's analytical methods detect only about one-half of the pesticides that contaminate fruits and vegetables (53). Use of pesticides has been so widespread that measurable levels are frequently found in human tissues. DDT, for example, was banned a number of years ago, yet nearly everyone born since the mid-1940s has measurable levels of this pesticide or its metabolizes in their fatty tissues (29). Some scientists believe that the levels of the persistent pesticides present in humans pose no risk; others think there is cause for concern and that more research is needed to evaluate the public health risk of chronic, low-level exposures. The possible effects on the developing nervous system of chronic exposure to pesticides are of particular concern.

Exposure to agricultural pesticides is highest among mixers, loaders, applicators, farmworkers, and farmers. Some 2 million seasonal and migrant farmworkers harvest the Nation's crops (9). Accurate statistics on the total number of these farmworkers who develop adverse health effects due to pesticides are not available, but in California, where physicians are required by law to report suspected cases of pesticide-related illnesses, 1,093 cases were reported in 1981. Of these, 613 cases were related to agricultural activities, and 235 involved field workers exposed to pesticide residues (60). Reported cases seem to reflect only a fraction of the actual number, however (16). The issue of neurotoxic pesticide use in the agricultural setting is the subject of a case study in chapter 10. Poisonings are a particular problem in developing countries, where the misuse of pesticides is relatively common (see ch. 9).

Therapeutic Drugs

Therapeutic drugs often alter the function, and less often the structure, of the nervous system. Generally, this alteration is desirable, as, for example, in the case of the tranquilizing effects of a drug to treat anxiety or the mood-lifting effects of a drug to treat depression. But such drugs can have undesirable effects on the brain also. As mentioned

earlier, some drugs that effectively control the symptoms of schizophrenia may also severely affect neuromuscular function. Drugs that are used to treat illnesses or health problems unassociated with the nervous system (e.g., some anticancer drugs) may have neurotoxic side-effects. Often, the adverse effects of drugs are poorly documented or may go undetected.

Of particular concern are the effects of therapeutic drugs on the developing fetus. Most prescription drugs given to pregnant women have not been tested for potential effects on the fetus, nor have over-the-counter drugs been evaluated for use during pregnancy (14). Physicians normally exert particular caution in prescribing drugs for pregnant women.

The Federal Food, Drug, and Cosmetic Act requires that drugs be both safe and effective. Some persons assert that FDA does not require adequate neurotoxicity testing of prescription drugs and that neurotoxic concerns are not being adequately addressed in the FDA review and regulatory process. Others suggest that FDA moves too slowly in approving drugs and that regulations are overly burdensome. However, FDA officials believe that current testing and evaluation procedures adequately address neurotoxicological concerns (58).

The reported adverse effects of drugs listed in the *Physicians Desk Reference (42)* and similar publications illustrate that many prescription drugs, especially psychoactive drugs, have neurotoxic side-effects of varying significance. Some adverse effects are an accepted consequence of drug therapy. When a drug has been properly tested for neurotoxic effects, doctor and patient can make informed decisions about using it. However, inadequate testing for neurotoxicity exposes the public to unnecessary risk. There is scientific disagreement regarding whether or not the safety of food additives and drugs can be established in the absence of specific neurotoxicity testing.

Abused Drugs

In 1986, drug abuse in the United States led to more than 119,000 emergency room visits and 4,138 deaths (37). Many more cases go unreported. As users and their families and friends sometimes discover, substance abuse can permanently damage the nervous system. In some cases, damage is so severe as to cause personality changes, neurological disease, mental illness, or death. Persons who abuse drugs are often not aware of, or do not take seriously, the threat these substances pose to their health.



Photo credit: John Boyle, Drug Enforcement Agency

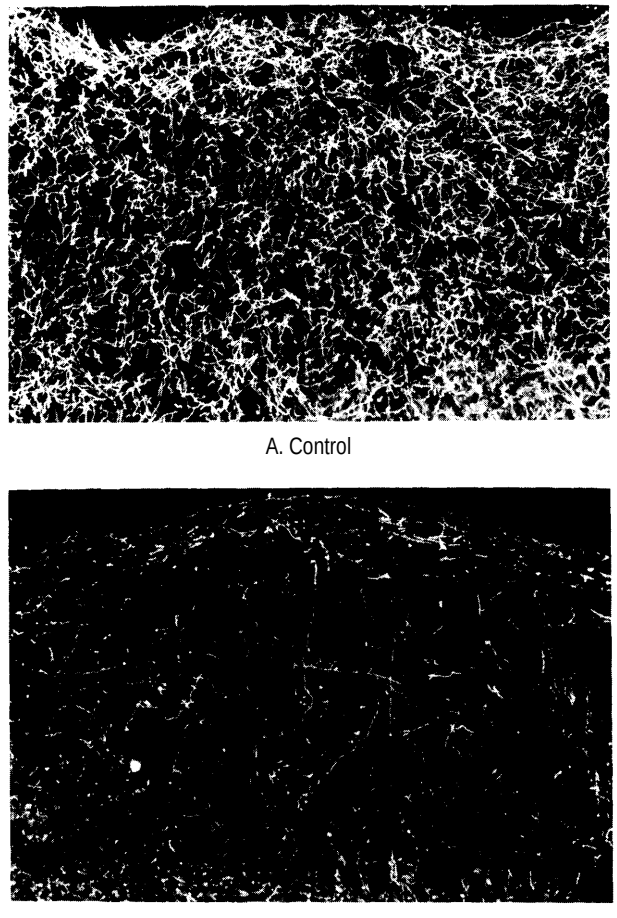
Although the adverse effects of drugs are often short-lived, some effects can be prolonged or permanent. MPTP, an impurity sometimes formed during the illicit synthesis of an analog of the drug meperidine, can cause irreversible brain damage and long-term dysfunction characteristic of Parkinson's disease (18,20,21). LSD, a highly potent hallucinogen, can seriously affect nervous system function (17). Other drugs may have more subtle neurotoxic effects. The chemically sophisticated, illicit "designer drugs" can dramatically alter normal brain functions. MDMA, known on the street as "Adam' or ''ecstasy, ' is a synthetic drug that causes euphoria and hallucinations. It also causes confusion, depression, severe anxiety, blurred vision, and paranoia (3,33). Some of these effects may occur weeks after taking the drug. It was recently discovered that MDMA, at relatively high doses, causes selective degeneration of brain cells producing the neurotransmitter serotonin (4). Figure 2-1 illustrates the degeneration of nerve fibers in a region of the

monkey's cerebral cortex involved in the perception of touch and position sense. Similar degeneration is seen in most areas of the cortex. Until it became illegal, MDMA was occasionally used as an adjunct to psychotherapy because of the belief that it removed barriers to communication between doctor and patient.

Phencyclidine (PCP) is another major abused drug. In 1984, it was responsible for 11,000 hospital emergency room visits and more than 225 deaths. Chronic use of PCP leads to depression, speech difficulties, and memory loss (32,36).

Cocaine (known as 'crack' in its smokable form) is currently the most frequently abused street drug in the United States. More than 22 million Americans have used cocaine at some time in their lives (34). In 1986, approximately 25,000 high school seniors reported that they had used cocaine in the past year and were unable to stop using it (35). Cocaine blocks reabsorption of the neurotransmitter dopamine into nerve cells. Feelings of euphoria are thought to be due to excess dopamine in the synapses between cells. Large concentrations of dopamine cause changes in nerve cells, making them less responsive to normal levels of the transmitter. Consequently, when individuals stop using the drug they experience depression and want to take more to feel "normal." They are then caught in the addiction cycle (35). Recently, it was reported that cocaine use by pregnant women alters the development of the brains of fetuses and infants (59). "Cocaine babies' are a tragic consequence of drug abuse by pregnant women (see box 2-B).

Figure 2-1-neurotoxic Effect of MDMA on Serotonin Nerve Fibers in the Cerebral Cortex of the Monkey



A. Control

B. MDMA

Repeated administration of MDMA (5mg/kg, 8 doses) to a Cynomolgus monkey produced degeneration of most serotonin nerve fibers in this region of the cortex, which is involved in the perception of touch and position sense. Similar toxic effects are seen in most areas of the cerebral cortex.

SOURCE: M.A. **Wilson and M.E. Molliver, Department of Neuroscience, Johns Hopkins University School of Medicine.**

Food Additives

Food additives serve a variety of purposes, such as to prolong shelf-life or to improve flavor, and hundreds of them are used during the preparation, manufacture, and marketing of foods. The use of these substances is regulated by FDA, which maintains a list of additives that are generally recognized as safe and may be used without specific approval. All other food additives must be approved prior to use. However, few additives have undergone neurotoxicity testing. In 1984, the NAS reported that 73 percent of the food additives it examined had not been tested for neurobehavioral toxicity (30). Although animal testing of food additives is required under the Federal Food, Drug, and Cosmetic Act to evaluate their safety, studies in humans are not required. Approval of drugs, however, does require human testing. Many observers believe that food additives should come under the same scrutiny as drugs, particularly because many of them are regularly ingested by millions of people. The food additive approval process is examined in a case study in appendix A.

Cosmetics

Some 3,400 chemicals are used as cosmetics or cosmetic ingredients in U.S. products (30). The

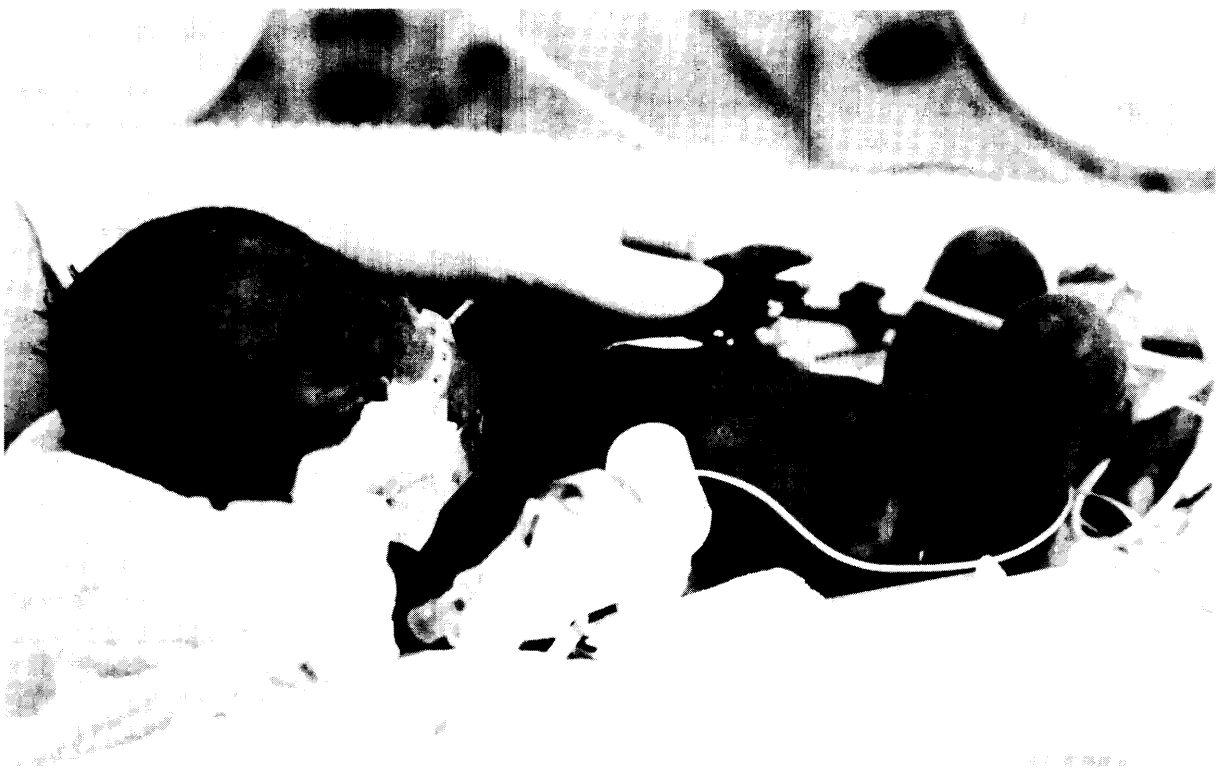
Box 2-B-Cocaine and the Developing Fetus

When a pregnant women abuses a psychoactive drug, she alters not only the activity of her own nervous system, but that of her unborn child as well. Depending on the abused substance, the frequency of use, the dose, and other factors, the mother's quest for a temporary high can lead to permanent damage of the rapidly developing fetal nervous system. According to a recent survey by the National Association for Perinatal Addiction Research and Education (NAPARE), each year as many as 375,000 infants may be adversely affected by substance abuse. Maternal substance abuse is frequently not recognized by health-care professionals during pregnancy. Consequently, prevention and treatment programs are often too late. According to the National Institute on Drug Abuse, approximately 6 million women of childbearing age (15 to 44) use illicit drugs, about 44 percent have tried marijuana, and 14 percent have used cocaine at least once.

A recent study of 50 women who used cocaine during pregnancy revealed a 31 percent incidence of preterm delivery, a 25 percent incidence of low birthweight, and a 15 percent incidence of sudden infant death syndrome. These types of parameters are easy to quantify. The biochemical and neurobehavioral effects are more difficult to document, but they are just as real. Early research indicates that cocaine babies suffer abnormal development of the nervous system, impaired motor skills and reflexes, seizures, and abnormal electrical activity in the brain.

Cocaine is so addictive that it can suppress one of the most powerful human drives-maternal care. As one pregnant crack addict put it: "The lowest point is when I left my children in a park for like 3 or 4 days. I had left my kids with a girl that I know and told her. . . 'watch them . . . I'll be back' and I didn't come back. So that was like—when I finally came down off of that high. I realized that I needed help. " Sick and abandoned children of cocaine mothers have placed a heavy burden on a number of the Nation's hospitals. During a l-week period at one hospital, one in five black infants and one in ten white infants were born on cocaine, Taxpayers usually end up paying the health-care bill—a bill that can easily exceed $100,000 per infant.

SOURCES: National Association for Perinatal Addiction Research and Education, news release, Aug. 28, 1988; J.H. Khalsa, "Epidemiology of Maternal Drug Abuse and Its Health **Consequences:** Recent Finding,' National Institute on Drug Abuse, in preparation; 'Cocaine Mothers: Suffer the Children," *West 57th Street*, CBS, July 15, 1989.



Courtesy of Dr. Emmalee S. Bandstra, M. D., Division of Neonatology, University of Miami/Jackson Memorial Medical Center

neurobehavioral toxicity of only a small percentage of these has been reviewed. Indeed, the National Academy of Sciences evaluated a representative sample of cosmetics in 1984 (focusing on publicly available documents) and found that none had undergone adequate testing to identify potential neurobehavioral effects (30).

The consequences of inadequate toxicity testing are illustrated by the AETT incident. In 1955, AETT (acetylethyl tetramethyl tetralin) was introduced into fragrances; years later it was found to cause degeneration of neurons in the brains of rats and marked behavioral changes in rats, including irritability and aggressiveness. In 1978, it was voluntarily withdrawn from use by the fragrance industry. Its effects on humans through two decades of use will probably never be known (50).

FDA lacks the authority to require premarket testing of cosmetics. The agency may initiate an investigation, however, if a basis is presented for doubting a particular product's safety. The regulation of cosmetics is discussed further in chapter 7.

TOXIC SUBSTANCES AND NEUROLOGICAL AND PSYCHIATRIC DISORDERS

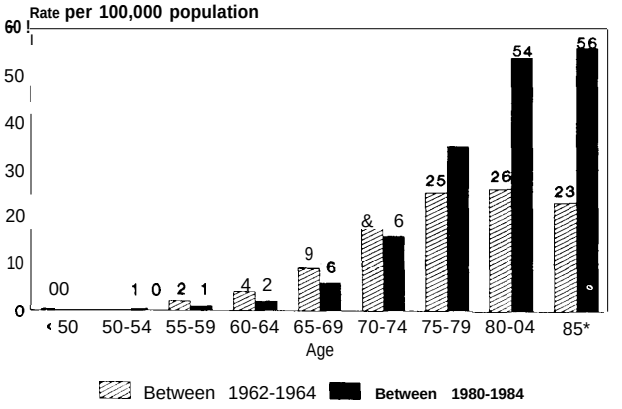
Concerns about the effects of neurotoxic substances on public health have increased recently because of new evidence that some neurological or psychiatric disorders may be caused or exacerbated by toxic agents in the environment. A noted case in point is Parkinson's disease. Researchers recently discovered that exposure to small amounts of the toxic substance MPTP can cause Parkinson-like symptoms (20). Exposure to small quantities over a period of days to a few weeks leads to the muscle weakness and rigidity that is characteristic of Parkinson's disease.

Because of this finding, the possibility that toxic chemicals might be causative agents in some cases of Parkinson's disease is being actively considered by researchers. Some recent findings support this hypothesis. For example, it has been reported that in cases in which Parkinson's disease afflicts several members of a family, the onset of the disease tends to cluster in time (5,21). Normally, if a disorder has a purely genetic basis, onset of symptoms occurs at similar ages, not at similar times. Evidence that Parkinson's disease does not occur more frequently in identical than fraternal twins also argues against a hereditary determinant of the disorder (18). A recent epidemiological study revealed that between 1962 and 1984, U.S. mortality rates for Parkinson's disease substantially increased in individuals over the age of 75 (figure 2-2). Environmental factors appear to have played a significant role in the increase (23). The relative roles of hereditary and environmental factors in triggering Parkinson's disease remain to be determined.

Evidence for a substantial increase in the incidence of motor neuron disease (MND), primarily amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, in the United States has also recently been reported (22). This disease is characterized by the progressive degeneration of certain nerve cells that control muscular movement. MND is a relatively rare disease, and its cause has eluded researchers for more than a century. Recent data indicate that between 1962 and 1984, the MND mortality rate for white men and women in older age groups rose substantially (figure 2-3). The increase is thought to be largely due to environmental factors (22).

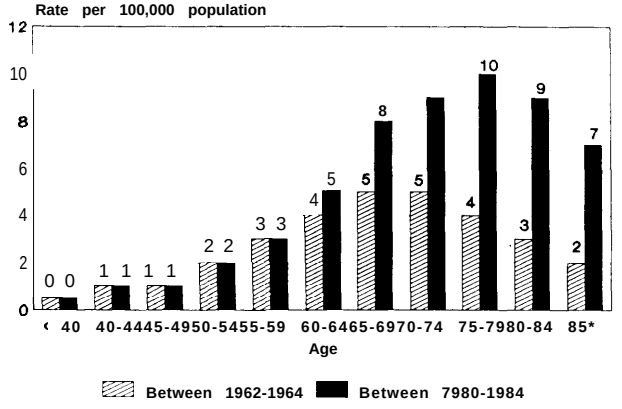
Naturally occurring toxic substances can also affect the nervous system. An unusual combination of the neurodegenerative disorders ALS, Parkinson's disease, and Alzheimer's disease endemic to Guam (known as Guam ALS-Parkinson's dementia) puzzled investigators for many years because of the correlation between incidence of the disease and preference for traditional foods. During food shortages, residents of the island ate flour made from the false sago palm, a member of the neurotoxic cycad family. The cycad contains one or more naturally occurring toxic substances that appear to cause a neuromuscular disease in cattle and trigger slow degeneration of neurons (49), As old age approaches and natural brain cell death accelerates, the effects of the degeneration become apparent and the neurological symptoms appear, This possible link between a naturally occurring compound and a neurodegenerative disease has stimulated the search for other toxic substances that may trigger related neurological and psychiatric disorders. This work and that of others led to the hypothesis that Alzheimer's disease, Parkinson's disease, and ALS could be due in part to damage to specific regions of the central nervous system caused by environmental agents and that the damage may not become apparent until several decades after exposure (6). Aluminum and silicon,

Figure 2-2—Average Annual Parkinson's Disease Mortality in the United States, White Males



SOURCE: Adapted from D.E. Lilienfeld et al., "Two Decades of Increasing Mortality From Parkinson's Disease Among United States Elderly," ***Archives of Neurology,*** **in press.**

Figure 2-3-Average Annual Motor Neuron Disease* Mortality in the United States, White Males



•Most motor neuron disease is diagnosed as amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease.

SOURCE: Adapted from D.E. Lilienfeld, et al., "Increasing Mortality From Motor neuron Disease in the United States During the Past Two Decades," *Lancet,* Apr. 1, 1989, vol. 1, pp. 710-713.

for example, have been hypothesized to be causative agents in Alzheimer's disease; however, numerous other possible causes have been proposed, and no link between a toxic chemical and the disease has been conclusively demonstrated (52).

Several other foods contain known neurotoxic substances and can be responsible for severe neurological disorders. The drought-resistant grass pea causes lathyrism, a disease characterized by weakness in the legs and spasticity and resulting from degeneration of the spinal cord. The disease has been known since ancient times and has been responsible for several epidemics in Europe, Asia, and Africa (48,50). Studies currently under way indicate that the prevalence of lathyrism in an Ethiopian population that consumes the grass pea is 0.6 to 2.9 percent, an unusually high incidence for a neurodegenerative disease. Similarly, a large segment of the African population regularly eats a species of cassava *(Manihot esculenta)* that also damages the nervous system and causes irreversible spasticity (47). Cassava (manioc), one of many cyanide-releasing foodstuffs in the human diet, is found with increasing frequency in U.S. supermarkets.

Understanding the relationship between toxic substances and biochemical and physiological neurological disease requires concerted epidemiological analyses. The extent to which toxic substances contribute to major neurological and psychiatric disorders is not known. Considerable research is needed to define the role of neurotoxic substances as causative agents.

IDENTIFYING neurotoxic SUBSTANCES

Controlling neurotoxic substances is a two-step process. The first step is to identify existing substances that adversely affect the nervous system and take action to minimize human exposure to them. The second step is to identify new neurotoxic substances being generated by industry and take action either to prevent the manufacture of those that cause serious neurotoxic effects or limit the release of the substances into the environment and hence prevent human exposure to them. Testing is the key to both objectives; however, as indicated earlier, relatively few substances are evaluated specifically for neurotoxicity. There are numerous examples of neurotoxic substances that have entered the marketplace because of failure to conduct sufficient tests.

A classic example of testing inadequacy is BHMH (Lucel-7), a catalyst used in the manufacture of reinforced plastics such as bathtubs. The substance had only been used for a few weeks at a plant in Lancaster, Texas, before workers began experiencing neurological symptoms ranging from dizziness and muscle weakness to visual disturbances and memory loss. Two years later, several workers were still experiencing some of these symptoms. Prelimi-

nary animal studies suggested that, BHMH was neurotoxic, however regulatory action had not been taken (15). Animal studies conducted after the exposure demonstrated that rats experienced adverse effects similar to those seen in humans. BHMH might not have been marketed had appropriate neurotoxicological tests been conducted and had the data been properly analyzed and reported.

An important consideration in controlling toxic substances is the need for efficient, economical, and scientifically sound tests to identify substances that should be regulated. Numerous tests are currently available to evaluate neurotoxicity. A number of these tests are described in detail in chapter 5. At the present time, animal tests are an essential component of neurotoxicological evaluations.

In vitro testing, based on tissue and cell culture, is also useful in evaluating the neurotoxic potential of chemicals (12). Two likely advantages are that many substances can be screened in a relatively short period of time and that costs may be considerably less than the costs associated with animal tests (51). In vitro tests may someday prove to be useful as a rapid toxicity screening tool; however, further test development is necessary. Like all tests, in vitro tests have inherent limitations. For example, they are probably of little use in identifying behavioral effects because such evaluations require the intact nervous system. Also, testing drugs or other chemicals in vitro makes it difficult to evaluate active metabolizes that may form or accumulate following administration to the intact animal.

REGULATING neurotoxic SUBSTANCES

Regulatory agencies are responsible for limiting public exposure to toxic chemicals through programs mandated by Congress. Because of the diversity of toxic substances, numerous laws are in place to control their production, use, and disposal. These laws are administered by a variety of Federal agencies, but primarily by EPA, FDA, and the occupational Safety and Health Administration.

New and existing industrial chemicals are regulated under the Toxic Substances Control Act. Pesticides are controlled by the Federal Insecticide, Fungicide, and Rodenticide Act, and exposure to toxic substances in the workplace is regulated by the Occupational Safety and Health Act. In addition, the Federal Food, Drug, and Cosmetic Act regulates food additives, drugs, and cosmetics. Although these laws address most toxic substances, more than a dozen other acts focus on less prevalent but equally important substances. While neurotoxicity is often not explicitly mentioned in laws regulating toxic substances, it is implicit in general toxicity concerns.

Regulating toxic substances on the basis of any single endpoint such as carcinogenicity may not adequately protect the public health. Effects on organ systems and other toxicities may pose an equal or greater threat than carcinogenicity itself. Lead, for example, is both neurotoxic and carcinogenic; however, the neurotoxic concerns have far outweighed the carcinogenic concerns in decisionmaking. Complete characterization of the risk posed by exposure to toxic substances should include an evaluation of both carcinogenic and noncarcinogenic risk, including the potential for neurotoxicity. The Federal framework for regulating toxic substances in general, including neurotoxic substances, is described in detail in chapter 7.

ECONOMIC CONSIDERATIONS

Although it is expensive to evaluate any chemical for its potential toxic effects, these costs may be small relative to the costs associated with development of a new product, care of injured persons, workers' compensation, or litigation resulting from injury. Furthermore, the costs to society of public exposure to toxic substances, measured in terms of medical care and lost productivity, are potentially very high.

Society must weigh carefully the positive health and economic impacts of use of hazardous chemicals against the negative health and economic consequences of human exposure to substances whose toxicity has not been adequately evaluated. If industry is required to do additional testing, regulatory agencies should ensure that the tests are appropriate and cost-effective. Chapter 8 focuses on the challenge of balancing economic costs and benefits.

INTERNATIONAL CONCERNS

neurotoxicity is an international as well as national problem. Of particular concern to many persons is the export of neurotoxic substances from the United States to other nations. Tens of thousands of tons of pesticides, for example, are exported each

year by U.S. manufacturers, even though the use of some of these substances is banned or severely restricted in the United States. Critics of this policy raise questions regarding the ethics of a wealthy, industrialized nation profiting from the export of such substances to developing nations that may not have the resources to ensure protection of the public. In what has been called the 'circle of poison," foods imported into the United States sometimes contain residues of exported pesticides that are unregistered, restricted, or banned for U.S. use (55).

In 1979, a Federal Interagency Hazardous Substances Export Policy Task Force prepared guidelines governing the export of pesticides, drugs, and other materials. Its recommendations led to an Executive Order on Federal Policy Regarding Banned or Significantly Restricted Substances. The order was signed by President Jimmy Carter in January 1981, several days before the end of his term, but it was revoked by President Ronald Reagan shortly thereafter. Consequently, policy regarding the export of banned and restricted hazardous substances, whether pesticides, foods, or other materials, remains a topic of debate. These and other international issues are discussed in more detail in chapter 9.

CHAPTER 2 REFERENCES

1. Anger, W. K., "Neurobehavioral Testing of Chemicals: Impact on Recommended Standards, " *Neurobehavioral Toxicology and Teratology 6:147-143, 1984.*
2. Anger, W. K., "Workplace Exposures, " *Neurobehavioral Toxicology, Z.* Annau (cd,) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 331-347.
3. Barnes, D. B., ''New Data Intensify the Agony Over Ecstasy, " *Science 239:864-866, 1988.*
4. Battaglia, G., Yeh, S. Y., O'Hearn, E., et al., "3,4-Methylenedioxy-Methamphetamine and 3,4-Methylenedioxy-Amphetamine Destroy Serotonin Terminals in Rat Brain: Quantification of Neurodegeneration by Measurement of ^{3}H-Paroxetine-Labelled Serotonin Uptake Sites,' *Journal of Pharmacology and Experimental Therapeutics 242:91 1-916, 1987.*
5. Caine, D. B., "Toxins and Parkinsonism," *Neurologic Consultant 5:1-5, 1988.*
6. Caine, D. B., McGeer, E., Eisen, A., et al., "Alzheimer's Disease, Parkinson's Disease, and Motor-neuron Disease: A Biotrophic Interaction Between Aging and Environment?" *Lancet 2: 1067-1070, 1986.*
7. "Cocaine Mothers: Suffer the Children," West *57th Street,* CBS, July 15, 1989.
8. Cooper, J. R., Bloom, F. E., and Roth, R. H., *The Biochemical Basis of Neuropharmacology (New* York, NY: Oxford University Press, 1982).
9. Coye, M.J., "The Health Effects of Agricultural Production: I, The Health of Agricultural Workers," *Journal of Public Health Policy 6:349-370, 1985.*
10. Ecobichon, D. J., and Joy, R. M., *Pesticides and Neurological Disease* (Boca Raton, FL: CRC Press, 1982).
11. Federation of American Societies for Experimental Biology, *Predicting neurotoxicity and Behavioral Dysfunction From Preclinical Toxicological Data* (Washington, DC: 1986).
12. Goldberg, A. M., "Approaches to the Development of In Vitro neurotoxicological Methods, ' *Model Systems in neurotoxicology: Alternative Approaches to Animal Testing (New* York, NY: Alan R. Liss, 1987).
13. Grasso, P., et al., "Neurophysiological and Psychological Disorders and Occupational Exposure to Organic Solvents, " *Food and Chemical Toxicity 22:819-852, 1984.*
14. Gray, D. B., and Jaffe, S.J., "Prenatal Drugs and Learning Disabilities, " *Learning Disabilities and Prenatal Risk,* M. Lewis (cd.) (Urbana, IL: University of Illinois Press, 1986), p. 3.
15. Horan, J. M., Kurt, TL., Landrigan, P., et al., "Neurologic Dysfunction From Exposure to 2-+-Butyluo-2-Hydroxy-5-Methylhexane (BHMH): A New Occupational Neuropathy, " *American Journal of Public Health 75:513-517, 1985.*
16. Kahn, E., "Pesticide-Related Illness in California Farm Workers, " *Journal of Occupational Medicine 18:693-696, 1976.*
17. Klaassen, C. D., Amdur, M. O., and Doull, J. (eds.), *Casarett and Doull's Toxicology (New* York, NY: Macmillan, 1986).
18. Kopin, I.J., and Markey, S.P., "MDTP Toxicity Implication for Research in Parkinson's Disease, " *Annual Reviews in Neuroscience* 11:81-96, 1988.
19. Kusserow, R. P., "Medicare Drug Utilization Review, " *Office of Inspector General Report* (Washington, DC: U.S. Department of Health and Human Services, 1989).
20. Langston, J. W., Ballard, P., Tetrud, J. W., et al., ''Chronic Parkinsonism in Humans Due to a Product of Meperidine-Analog Synthesis, *Science 219:979-980, 1983.*
21. Levin, R., ''More Clues to the Cause of Parkinson's Disease," *Science 7:978, 1987.*
22. Lilienfeld, D. E., Chan, E., Ehland, J., et al,, 'Increasing Mortality From Motor Neuron Disease in the United States During the Past Two Decades, " *Lancet, vol.* 1, pp. 710-713, Apr. 1, 1989.

23. Lilienfeld, D. E., Chan, E., Ehland, J., et al., "Two Decades of Increasing Mortality From Parkinson's Disease Among United States Elderly,' *Archives of Neurology,* in press.
24. Martinez, A.J., Taylor, J.R., Houff, S. A., et al., "Kepone Poisoning: Cliniconeuropathological Study," *neurotoxicology,* L. Roizin, H. Shiraki, and N. Grcevic (eds.) (New York, NY: Raven Press, 1977).
25. Mendell, J.R., Saida, K., Ganansia, M. F., et al., "Toxic Polyneuropathy Produced by Methyl N-Butyl Ketone," *Science 185:787-789, 1974.*
26. Morell, P., and Mailman, R. B., "Selective and Nonselective Effects of Organometals on Brain Neurochemistry," *neurotoxicants and Neurobiological Function: Effects of Organoheavy Metals,* H.A. Tilson and S.B. Sparber (eds.) (New York, NY: John Wiley & Sons, 1982).
27. Moses, M., "Pesticides,' *Environmental and Occupational Medicine,* W.N. Rom (cd.) (Boston, MA: Little, Brown, 1983).
28. Mott, L., and Snyder, K., "Pesticide Alert" *Amicus Journal 10:20-29, 1988.*
29. Murphy, S. D., "Toxic Effects of Pesticides, " *Casarett and Doull's Toxicology,* C.D. Klaassen, M.O. Amdur, and J. Doull (eds.) (New York, NY: Macmillan, 1986).
30. National Academy of Sciences, *Toxicity Testing: Strategies to Determine Needs and Priorities* (Washington, DC: National Academy Press, 1984).
31. National Academy of Sciences, *Research on Children and Adolescents With* Mental, *Behavioral, and Developmental Disorders* (Washington, DC: National Academy Press, 1989).
32. National Institute on Drug Abuse, "PCB: Update on Abuse," *NIDA Capsules, C-80-13,* rev. April 1986.
33. National Institute on Drug Abuse, 'Designer Drugs,' *NIDA Capsules, C-86-5,* rev. June 1986.
34. National Institute on Drug Abuse, "Use and Consequences of Cocaine, " *NIDA Capsules, C-8444,* October 1986.
35. National Institute on Drug Abuse, *NIDA Notes,* vol. 2, 1987.
36. National Institute on Drug Abuse, "Facts About Teenagers and Drug Abuse," *NIDA Capsules, C-83-*07a, rev. April 1988.
37. National Institute on Drug Abuse, "Frequency of Drug Mentions in Drug-Related Medical Emergencies and Deaths in 1986," NIDA *Capsules,* C-84-1, April 1988.
38, National Institute on Drug Abuse, NIDA *Notes* 4(1):16-17, 1988-89.
39. Needleman, H., and Bellinger, D., "The Developmental Consequences of Childhood Exposure to Lead: Recent Studies and Methodological Issues, " *Advances in Clinical and Child Psychology, vol. 7,* B.B. Lahey and A.E. Kazdin (eds.) (New York, NY: Plenum Publishing Co., 1984).
40. Needleman, H., Gunnoe, C., and Leviton, L., "Deficits in Psychologic and Classroom Performance of Children With Elevated Determined Lead Levels," New *England Journal of Medicine 300:689-695, 1979.*
41, O'Donohue, J., "neurotoxicity Risk Assessment in Industry," paper presented at American Association for the Advancement of Science symposium on Evaluating the neurotoxic Risk Posed by Chemicals in the Workplace and Environment, May 26, 1986.
42. *Physicians Desk Reference* (Oradel, NJ: Medical Economics Co., 1988).
43. Politis, M. J., Schaumberg, H. H., and Spencer, P. S., "neurotoxicity of Selected Chemicals,' *Experimental and Clinical neurotoxicology* (Baltimore, MD: Williams & Wilkins, 1980).
44. Riley, E.P., and Voorhees, C.V. (eds.), *Handbook of Behavioral Teratology (New* York, NY: Plenum Press, 1986),
45. Rosenberg, N., et al., "Toluene Abuse Causes Diffuse Central Nervous System White Matter changes,' ' *Annuls of Neurology 23:61 1-614, 1988.*
46, Sharp, C. W., and Fornazzari, L., "Clinical Syndromes of the Inhalant Abuser," in press.
47. Spencer, P. S., "neurotoxicological Vaccinations," Haninen Lecture, Third International Symposium on Neurobehavioral Methods in Occupational and Environmental Health, Washington, DC, Dec. 12-15, 1988.
48. Spencer, P. S., ''The Grass Pea: Threat and Promise,' speech before the Third World Medical Research Foundation, New York, NY, 1989.
49. Spencer, P. S., Nunn, P. B., Hugon, J., et al., "Guam Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Linked to a Plant Excitant Neurotoxin," *Science 237:517-522, 1987.*
50. Spencer, P. S., and Schaumburg, H.H. (eds.), *Experimental and Clinical neurotoxicology* (Baltimore, MD: Williams & Wilkins, 1980).
51. U.S. Congress, Office of Technology Assessment, *Alternatives to Animal Use in Research, Testing, and Education* (Washington, DC: US. Government Printing Office, 1986),
52. U.S. Congress, Office of Technology Assessment, *Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease and Other Dementias* (Washington, DC: U.S. Government Printing Office, 1987).
53. U.S. Congress, Office of Technology Assessment, *Pesticide Residues in Food* (Washington, DC: U.S. Government Printing Office, 1988).
54. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, *The Nature and Extent of Lead Poisoning in Children in the United States: A Report*

to Congress (Atlanta, GA: Centers for Disease Control, 1988).
55. Weir, D., and Schapiro, M., *Circle of Poison: Pesticides and People in a Hungry World* (San Francisco, CA: Institute for Food and Development Policy, 1981).
56. Weiss, B., "Environmental Contaminants and Behavior Disorders,' *Journal of Developmental Pharmacology and Therapeutics 10:346-353, 1987.*
57. Weiss, B., and Clarkson, T. W., "Toxic Chemical Disasters and the Implications of Bhopal for Technology Transfer, " *Milbank Quarterly 64:216-240, 1986.*
58. Weissinger, J., U.S. Food and Drug Administration, personal communication, 1989.
59. Wiggins, R. C., et al., *neurotoxicology, in* press.
60. Wilk, V. A., *The Occupational Health of Migrant and Seasonal Farmworkers in the United States* (Washington, DC: Farmworker Justice Fund, 1986).

Chapter 3

Fundamentals of neurotoxicology

‘ ‘The upsurge of interest in recent years in academia, industry, and government on the effects of toxic chemicals on the nervous system has created a new discipline of neurotoxicology.”

Peter S. Spencer, Ph.D.
Herbert H. Schaumburg, Ph.D.
Experimental and Clinical neurotoxicology, 1980

. . . the recognition that a chemical component in street heroin [causes] Parkinson’s disease or [a] Parkinsonian disease or [a] Parkinsonian state comes like a lightning bolt to the medical community. . . . Now suddenly, with this new awareness, the neurological community is beginning to ask questions about other disorders, such as Lou Gehrig’s disease, Alzheimer’s disease. Could this possibly be the result of chemical exposure?

Bernard Weiss, Ph.D.
Testimony before the House Committee on Science and Technology
October 8, 1985

« . . . this is not a situation where we get depressed and anxious first and then developed these symptoms in *our* mind. This is a situation where these symptoms came along from exposure to fumes and chemicals and then we got severely depressed and anxious. ’

Aerospace Worker
Testimony before the Senate Committee on Environment and Public Works
July 15, 1989

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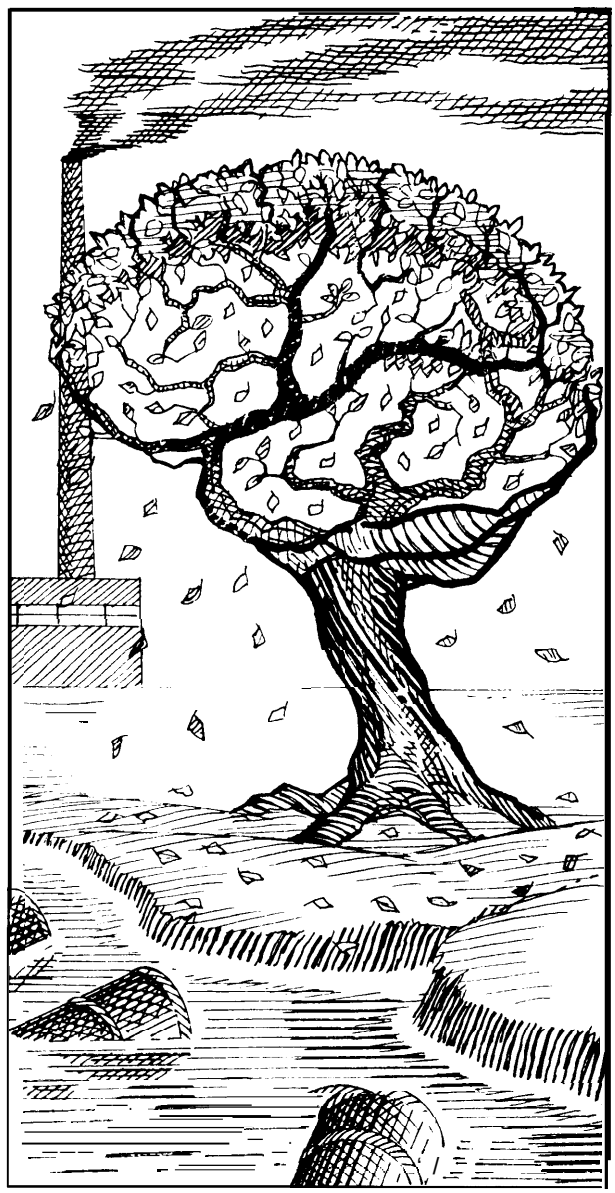
Chapter 3
Fundamentals of neurotoxicology

Toxicology is concerned with the adverse effects of natural or synthetic chemicals on the biochemical, physiological, and behavioral processes of living organisms. Because of the large number of chemicals in commerce and the wide variety of effects they may cause, toxicology is a broad science and toxicologists tend to specialize in one or more areas of the field. Biochemical toxicologists study the effects of toxic chemicals at the molecular and cellular levels. Regulatory toxicologists evaluate the risks posed by these substances and recommend actions that can be taken to reduce human exposure and environmental contamination. Clinical toxicologists examine the effects of drugs and toxic chemicals on human health and develop treatments to mitigate adverse effects. Behavioral toxicologists are concerned with the effects of toxic substances on animal and human behavior. Environmental toxicologists address the effects of pollutants on plants and animals, including humans (10).

neurotoxicology is concerned with the adverse effects of chemicals on the nervous system. Research in this field involves examining the modes by which neurotoxic substances enter the body, the effects of these substances on the various components of the nervous system, the biochemical and physiological mechanisms by which these effects occur, the prevention of damage to the nervous system, and the treatment of neurological and psychiatric disorders associated with exposure to toxic substances. Although scientists have made tremendous progress in understanding the nervous system, there is still much to learn about its function under both normal and abnormal circumstances.

OVERVIEW OF TOXICOLOGICAL PRINCIPLES

In order for a toxic substance to cause adverse health effects, it, or its metabolic products, must enter the body and reach the target organ(s) at a sufficient concentration and for a sufficient length of time to produce a biological response. Chemicals differ in toxicity, with some being toxic in very small quantities and others having little effect at even very high doses. This relationship between exposure to a toxic substance and the extent of injury or illness resulting from it is called the "dose-response" relationship. In addition to dose, other critical variables determining toxicity are the properties of the chemical (e.g., its volubility), the means of exposure (through the lungs, stomach, or skin), the health and age of the exposed individual, and the susceptibility of the target organ or tissues (10).



Illustrated by: Ray Driver

Absorption, Distribution, Biotransformation, and Excretion

Toxic substances normally enter the body through the lungs (inhalation), the skin (absorption), or the gastrointestinal tract (ingestion). In the industrial setting, most exposures occur through inhalation or absorption. After the substance enters the bloodstream, it is partitioned into body tissues, where it may act on target organs or tissues. For various reasons, including insolubility, some substances are not distributed through the body. Ultimately, toxic substances are eliminated from the bloodstream through accumulation in various sites in the body and through biotransformation and excretion.

Sites of accumulation of toxic substances mayor may not be the primary sites of toxic action. Carbon monoxide, for example, reaches its highest concentration in red blood cells, where it competes successfully with oxygen for binding sites in hemoglobin; it then causes widespread brain damage when these red blood cells fail to supply an adequate amount of oxygen to the brain. Lead, a potent neurotoxic substance, is found in highest concentrations in bone but exerts its most serious effects on the brain. The liver and kidney are major sites of accumulation of toxic substances, probably because of their large blood capacities and their roles in eliminating toxic substances from the body. Lipophilic toxic chemicals (i.e., chemicals soluble in fat-like materials; also termed hydrophobic) tend to accumulate in lipid-rich areas such as body fat. The brain may be particularly vulnerable to these toxic substances since 50 percent of the dry weight of the brain is lipid, compared to 6 to 20 percent of other organs of the body (5).

The body has a number of ways to detoxify foreign substances. The liver is the principal organ involved in detoxification, but other organs such as the kidney, the intestine, and the lung also play major roles. In fact, nearly every tissue tested has some capacity for detoxification; these capacities, however, are often limited to particular types of compounds. Adverse effects may occur when the quantity of the substance ingested overwhelms detoxification mechanisms, when an injury or illness has compromised the body's capabilities for detoxification, or when no mechanism is available to modify or remove the particular substance.

Before excretion, a substance may undergo biotransformation, the biochemical process by which it is converted into new chemical compounds which are often more easily excreted. This process usually changes lipophilic compounds to compounds which are more hydrophilic (water soluble) and therefore more easily excreted. Although biotransformation normally aids in the detoxification of substances, it sometimes results in compounds that are more toxic. Therefore, when analyzing neurotoxic substances and the health risks they pose, it is important to remember that the compound originally ingested or absorbed by an organism may not be the toxic substance that eventually acts on the nervous system.

Excretion of toxic chemicals from the body occurs through a variety of routes. Many substances are removed by the kidney and excreted through the urine. The liver is effective in detoxifying and removing substances that enter the body through the gastrointestinal tract. Some toxic substances, such as lead and mercury, are excreted from the liver into the bile and then into the small intestine, bypassing the blood and the kidneys (10).

Toxic substances are more easily removed from the body if they are hydrophilic or if they can be biotransformed into a more hydrophilic compound. Lipophilic toxic substances are removed from the body through a number of mechanisms; these include excretion in feces and bile, excretion of water-soluble metabolizes in the urine, expiration into the air, and excretion through the skin.

Interaction of Multiple Toxic Substances

The health effects of toxic substances are frequently examined with the assumption of a single chemical acting alone on a particular organ or type of tissue. Such an analysis has limitations, however. In some cases, an individual may be exposed to multiple chemicals that act on different organs and tissue types, and one cannot assume that the effect of these substances combined is the same as the combined effects of separate exposures. Chemical interactions may take place between substances. Sometimes the effects are additive (i.e., the combined effects are equal to the sum of the effects of each of the substances individually); at other times, the effects may be synergistic (i.e., the combined adverse effects exceed the sum of the individual effects).

A substance that is not toxic may increase the toxicity of another substance through a process called potentiation. More rarely, two toxic chemicals may result in no adverse effect when present together, a phenomenon called antagonism. Synergism, potentiation, and antagonism must be taken into account when examining exposure to complex mixtures of toxic substances such as those found in contaminated drinking water, smoke from an industrial fire, and fumes from a hazardous waste site (10).

THE NERVOUS SYSTEM

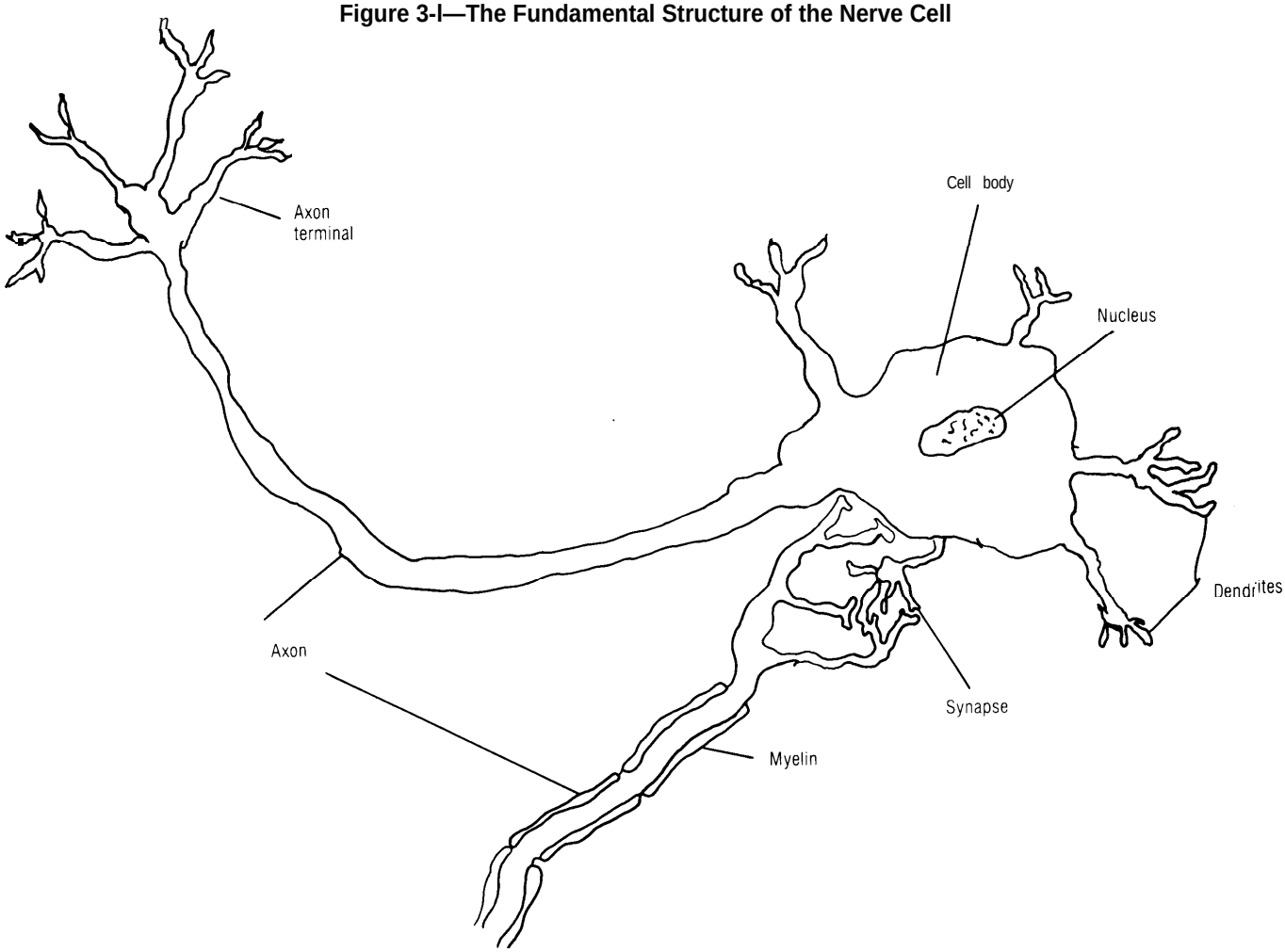
The fundamental unit of the nervous system is the nerve cell, or neuron (figure 3-l). While neurons have many of the same structures found in every cell of the body, they are unique in that they have axons and dendrites, extensions of the neuron along which nerve impulses travel, and in that they synthesize and secrete neurotransmitters, specialized chemical messengers that interact with receptors of other neurons in the communication process.

Certain nerve cells are specialized to respond to particular stimuli. For example, chemoreceptors in the mouth and nose send information about taste and smell to the brain. Cutaneous receptors in the skin are involved in the sensation of heat, cold, and touch. Similarly, the rods and cones of the eye sense light.

Glial cells appear to perform functions which support neurons-i. e., supplying nutrition, structural support, and insulation. Certain glial cells, for example, produce myelin, a fatty substance that covers the axons of many neurons throughout the body and acts as insulation.

Electrical information in the form of nerve impulses travels along the axons and dendrites of

Figure 3-l—The Fundamental Structure of the Nerve Cell



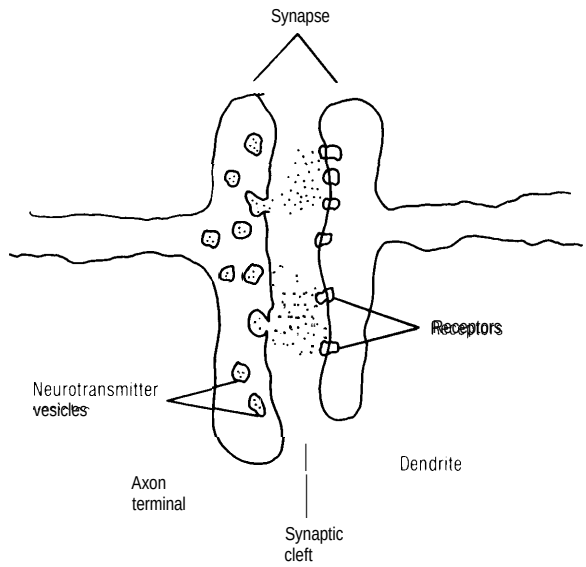
SOURCE: Office of Technology Assessment, 1990.

neurons. The impulses are generated by a rapidly changing flow of charged ions, primarily sodium and potassium, through channels in the nerve cell membrane. The insulating myelin sheath surrounding many nerves allows the electrical impulses (action potentials) to travel farther and faster than they otherwise could. Impulses generally travel away from the cell body of the neuron along axons and interact with the dendrites of other neurons. The point of interaction between adjacent nerve cells is called the synapse (figure 3-2). Here, neurotransmitters stored in vesicles in the axon terminal are released by electrical impulses, travel across the synaptic cleft, and bind to receptors on adjacent nerve cells, triggering biochemical events that lead to electrical excitation or inhibition. Information may also be transmitted from nerves to muscle fibers; in this case the point of interaction is called the neuromuscular junction.

Neurotransmitters are chemical messengers that can be subdivided into two categories: the classical neurotransmitters and the neuropeptides. Classical neurotransmitters include serotonin, dopamine, acetylcholine, and norepinephrine; the neuropeptides include endorphin, enkephalin, substance P, and vasopressin. Classical neurotransmitters are typically secreted by one neuron into the synaptic cleft, where they interact with receptors on the surface of the adjacent cell. Neuropeptides, on the other hand, may act over long distances, traveling through the bloodstream to receptors on other nerve cells or in other tissues. Binding of a transmitter to a receptor triggers a series of biochemical events that ultimately affect the electrical activity, or excitability, of the neuron. Depending on the type of transmitter released and the type of receptors, the effect of the chemical interaction is either to inhibit or to stimulate the electrical activity of the adjacent cell. When multiple neurons impinge on a single neuron, that neuron integrates the inputs, resulting in a net excitation or inhibition.

The nervous system is anatomically separated into two major divisions: the central nervous system and the peripheral nervous system. The central nervous system encompasses the brain and spinal cord, while the peripheral nervous system encompasses the nerves that travel to and from the spinal cord, sense organs, glands, blood vessels, and muscles.

Figure 3-2-Chemical Communication at the Synapse



SOURCE: Office of Technology Assessment, 1990.

The brain is composed of between 10 billion and 100 billion cells organized into vast networks of interacting axons and dendrites which comprise on the order of 10^{15} connections (17). The brain and spinal cord control vital functions of the body (including vision, hearing, speech, learning, memory, and muscular movements) through these complex networks and through a wide variety of neurotransmitters.

Information from sensory receptors is sent to the spinal cord and brain, where it is translated and integrated with other information. Sometimes the sensory information leads to muscular movement—for example, if one touches a hot stove. This reflex circuit involves both sensory neurons, which sense the heat and send the information to the spinal cord, and motor neurons, which send instructions to the muscles.

Most of the central nervous system is partially protected by the blood-brain barrier, a layer of tightly juxtaposed cells in blood vessel walls that allow some substances to pass from blood to neural tissue while keeping others out. This selective barrier protects much of the nervous system from substances that are either not necessary for metabolic functions or that may be damaging. Smaller compounds and compounds that are soluble in lipids tend to cross the barrier more easily, while larger compounds and substances which are soluble in water may be kept out. In addition, some compounds

cross the barrier with the help of carrier proteins which bind specifically to them. Drugs intended to act directly on the nervous system must therefore be designed in such a way as to pass through the blood-brain barrier into the brain. Most tranquilizers, narcotics, and anesthetics readily traverse the barrier.

Development and Aging

The first signs of the nervous system are exhibited around the 10th to 14th day of fetal development, when a flat sheet of around 125,000 cells forms from the outer layer of the ball of undifferentiated embryonic cells. The sheet then rolls into a tube, called the neural tube, which will eventually develop into the spinal cord and brain. Over the next 2 months these cells multiply, migrate, and begin differentiating into specific types of neurons and glia. The mechanism by which the undifferentiated embryo develops is unknown; however, embryologists believe that the cells' chemical environments play large roles in these determinations.

At approximately the 20th week, the neurons begin to extend axons and dendrites, initiating development of the nervous system's complex network of synaptic contacts. The nervous system is not fully developed until sometime during infancy. However, small modifications in the network do appear to take place even in the adult nervous system (7).

The nervous system undergoes major changes with aging. At the tissue and cellular level, the aging process results in nerve cell loss, neurofibrillary tangles (abnormal accumulation of certain filamentous proteins), and neuritic plaques (abnormal clusters of proteins and other substances near synapses). Neurons have a very limited capacity to regenerate; thus, as cells die, the complex neuronal circuitry of the brain becomes impaired. Aging is also accompanied by alterations in neurotransmitter concentration and the enzymes involved in the synthesis of these transmitters. Some neurons gradually lose their insulating myelin sheath, slowing conduction of electrical impulses along the axons.

Some-components of the nervous system appear to age differently than others. In a healthy person, for example, intellectual abilities such as memory, vocabulary retention, and comprehension seem to be maintained at least until the mid-70s, while motor skills, coordination, and sensory functions gradually become impaired (15). Specific areas of the brain may age at different rates. The locus ceruleus and the substantial nigra, two discrete areas of the brain, undergo a period of cell loss between the ages of 30 and 50, with the decline in cell number slowing thereafter (9). Between the ages of 20 and 80, the number of cells in the cerebral cortex may be reduced by half. In contrast, the Purkinje cells of the cerebellum decline in a linear fashion throughout life, while other clusters of cells are maintained at the same levels regardless of age.

EFFECTS OF TOXIC SUBSTANCES ON THE NERVOUS SYSTEM

Structural Changes

Toxic substances can alter both the structure and the function of cells. Structural alterations include changes in the morphology of the cell and the subcellular structures within it, and destruction of groups of cells. The long axons of some neurons, the inability of neurons to regenerate, and the nervous system's dependency on a delicate electrochemical balance for the proper communication of information make the system especially vulnerable to the effects of toxic chemicals.

When a toxic substance enters the human body, it can affect the biochemistry and physiology of neurons and glia in a variety of ways. The cells may swell, their internal contents may become more acidic, and biochemical processes such as protein synthesis and neurotransmitter secretion may be inhibited. Often these changes result from anoxia—i.e., oxygen deprivation. Neurons require relatively large quantities of oxygen because of their high metabolic rate and are therefore more vulnerable than other cells to anoxia.

At the morphological level, toxic substances seem to act selectively on the various components of the nervous system, damaging the neuronal bodies (neuropathy), axons (axonopathy), and myelin sheaths (myelinopathy). A common type of structural change induced by toxic substances on axons is central-peripheral distal axonopathy (CPDA). Degeneration of this type usually begins at the end of the axon and proceeds toward the cell body, hence it is often referred to as the "dying-back" process. Some organophosphorous insecticides can cause this type of damage after a single exposure; however, for the majority of chemicals producing this

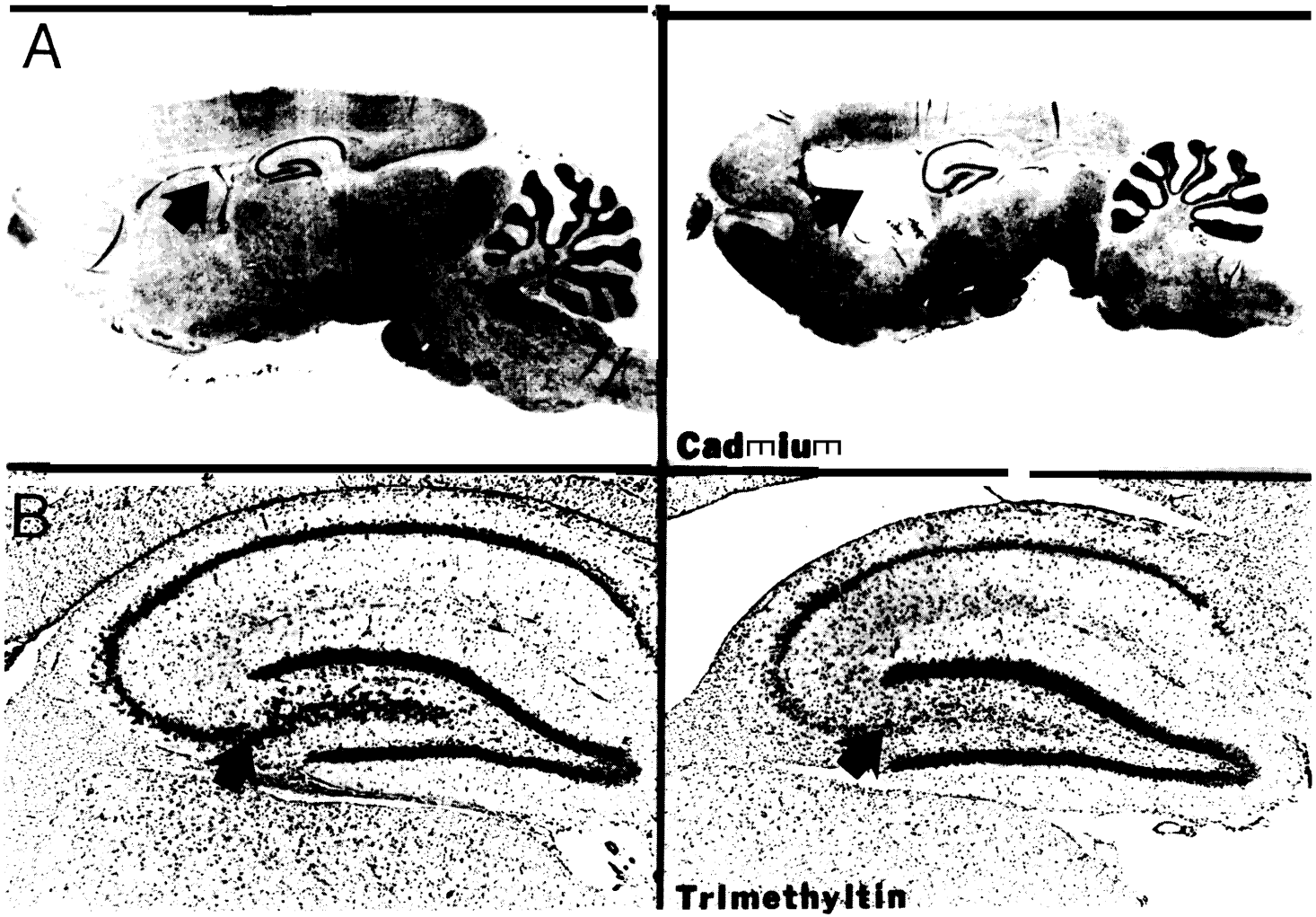


Photo credit: J.P. O'Callaghan, U.S. Environmental Protection Agency

Certain areas of the brain are more sensitive to toxic substances than others. A. Cadmium causes destruction of an entire region of the rat brain (neostriatum). B. Trimethyltin causes loss of a particular type of neuron (pyramidal cells) in the hippocampus, a region of the brain involved in the control of emotion, motivation, learning, and memory.

effect, continuous or prolonged intermittent exposure is necessary. Thousands of people were paralyzed during Prohibition after ingesting a popular alcohol substitute contaminated with an organophosphorous chemical (see box 3-A).

Toxic substances often cause a slow degeneration of the nerve cell body or axon that may result in permanent neuronal damage. Acute carbon monoxide poisoning, for example, can produce a delayed, progressive deterioration of portions of the nervous system that may lead to psychosis and death over a period of weeks (8).

Functional Changes

Toxic chemicals can induce functional changes that involve modifications of motor and sensory activities, emotional states, and integrative capabilities such as learning and memory. Numerous sensory systems can be adversely affected, including sight, hearing, and touch and pain sensation. These effects may be caused by destruction of the myelin sheath that surrounds neurons (a process known as demyelination), damage to the neuron itself, or damage to the neurotransmitter system. Sensory changes are often reported as numbness or a tingling sensation. Methyl mercury is one chemical that is extremely toxic to the visual, sensory, and motor systems. Several episodes of large-scale human intoxication by this organic heavy metal have been described (3). In recent years, tests have been developed to detect sensory changes, particularly in visual and auditory functions resulting from exposure to toxic substances.

Organophosphorous and carbamate insecticides can induce functional changes by inhibiting acetylcholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine. The functionalchanges include hyperactivity, neuromuscular paralysis, weakness, vomiting, diarrhea, and dizziness, with more severe cases exhibiting convulsions, coma, or death. The onset and duration of symptoms depend on the inherent toxicity of the insecticide, the dose, the route of exposure, and preexisting health conditions. Some organophosphorous pesticides can produce delayed and persistent neuropathy by damaging neurons in the spinal cord and peripheral nervous

Box 3-A—The Ginger-Jake Syndrome

During Prohibition, contamination of a popular ginger extract with triorthocresyl phosphate led to an epidemic of partial paralysis that came to be known as the Ginger-Jake syndrome. The case serves as a dramatic example of the neurotoxic potential of organophosphorous substances.

Extract from the Jamaica ginger had been used in the United States since the 1860s as a medicinal tonic. A typical preparation contained 70 to 80 percent alcohol by weight and reputedly aided in digestion, prevented respiratory infections, and promoted menstrual flow. Nicknamed ''Jake," *the* tonic became especially popular in the early 1900s in areas where local legislation outlawed the sale of alcoholic beverages.

During Prohibition, the legal sale of ginger extract was limited to a "fluidextract" which contained 5 grams of ginger per cubic centimeter of alcohol (usually ethanol). Since the high concentration of ginger yielded a solution too irritating to drink, the requirement was supposed to confine its use to medicinal purposes. Department of Agriculture agents would occasionally check for the appropriate ginger content by boiling off the alcohol and weighing the solid residue. However, bootleggers soon saw the possibility of dissolving small amounts of ginger into alcohol and substituting adulterants, such as molasses or castor oil, for the remaining required solid content. The result was a potable alcohol source that could be sold at bargain prices.

In 1930, perhaps in response to an increase in the price of castor oil, one bootlegger tried Lyndol, a heat-resistant oily material used in lacquers and varnishes, as an adulterant. When consumed, the triorthocresyl phosphate in Lyndol caused axonal degeneration in neurons of the central and peripheral nervous systems. Depending on the severity of the case, symptoms ranged from temporary numbness and tingling in the extremities to permanent partial paralysis. Estimates vary widely, but between 20,000 and 100,000 people were permanently affected before all the poisonous shipments were seized.

SOURCES: M.B. Abou-Doniaand D.M. Lapadula, "Mechanisms of Organophosphorus Ester-Induced Delayed neurotoxicity: Type I and Type II, " *Annual Review of Pharmacology and Toxicology* 30:405-440, *1990;* S.D. Davis and R.J. Richardson, ''Organophosphorus Compounds, " *Experimental and Clinical Neurotoxicology*, P.S. Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980); J.P. Morgan, "The Jamaica Ginger Paralysis," *Journal of the American Medical Association* 248: 1864-1867, 1982; J.P. Morgan, City University of New York, personal communication, Jan. 4, 1990.

system; in these cases, the resulting muscle weakness may progress to paralysis (4, 26).

Motor and sensory functions are closely linked within the nervous system. Body movements, for example, involve complex feedback interactions between motor and sensory neurons to allow smooth, controlled movements. Consequently, damage to sensory systems can indirectly affect certain motor functions. Some toxic substances affect motor neurons directly; others damage both sensory and motor neurons (a condition termed mixed neuropathy). Neurophysiological tests are available to monitor the conduction velocity of impulses along nerve axons, and various neurological tests can be used to detect muscle weakness and lack of control of muscular movements.

Toxic substances often affect the higher functions of the nervous system such as learning, memory, and mood. Exposure to inorganic lead can lead to mental retardation in children; at lower levels of exposure, however, it may manifest itself as a shortened attention span or a learning disability (16, 23). Various tests are available to detect impairment of these processes, some of which are described in chapter 5.

Behavioral Effects

Behavioral changes may be the first indications of damage to the nervous system. An individual exposed to a toxic substance may initially experience vague feelings of anxiety or nervousness. These feelings may progress to depression, difficulty in sleeping, memory loss (see box 3-B), confusion, loss of appetite, or speech impairment. In severe cases, a person may exhibit bizarre behavior, delirium, hallucinations, convulsions, or even death. Often, behavioral toxicological testing can detect an impairment for which investigators have not yet found a physiological or biochemical mechanism.

Exposure to neurotoxic chemicals during pregnancy may not produce obvious symptoms of behavioral toxicity until long after the exposure has ceased. This phenomenon has given rise to the field of behavioral teratology (18). An issue of particular concern to neurotoxicologists is the latency of some neurotoxic effects. One explanation for latent, or "silent," damage is that at younger ages the brain may be able to compensate for some adverse effects. With age, this ability to compensate diminishes, and the damage inflicted early in life may become apparent (19, 25). It has been proposed that exposure to toxic substances may trigger biochemical events that may later contribute to the cause of certain neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), or Alzheimer's disease. This hypothesis, sometimes referred to as the environmental hypothesis, has recently been the subject of increased interest following the MPTP incident (see box 3-C) and the Guam-ALS episode (19). (See ch. 2).

Susceptibility to neurotoxic Substances

Everyone is susceptible to the adverse effects of neurotoxic substances, but individuals in certain age groups and persons with certain health problems may be particularly at risk. The developing nervous system is especially vulnerable to certain toxic substances. Its cells are actively growing, dividing, migrating, and making synaptic connections, and the blood-brain barrier is not yet fully developed. During the first weeks of prenatal development, toxic substances may interrupt closure of the neural tube, leading to such birth defects as spina bifida (a defect in which the vertebral column is exposed) and anencephaly (the absence of all or part of the brain). During later development, the risks of exposure have diminished for many components of the nervous system; however, the cerebrum and cerebellum, major portions of the brain responsible for functions such as sight and movement, remain particularly vulnerable (15, 22).

Factors such as dose of the toxic substance and nutritional deficiencies in the mother also influence the extent of damage. Ethanol (alcohol), cocaine, antibiotics, and steroids, for example, can all adversely affect the fetal nervous system (18). Since few drugs have been adequately evaluated for effects on the developing fetus, physicians are advised to exert special care in prescribing drugs to pregnant women.

As the structure and function of the nervous system decline with age, individuals become more susceptible to the effects of many neurotoxic substances. Adverse effects that might have been masked at a younger age by a vital, healthy nervous system may become apparent. Those suffering from neurological disorders are at greater risk because toxic chemicals may exacerbate existing problems. Persons suffering from multiple sclerosis or neuromuscular disorders, for example, are vulnerable

Box 3-B—The Endangered Hippocampus

Deep inside the brain is a crescent-shaped structure that acts as a switching and information storage center. The hippocampus, as it is called, is a site of convergence of many neural pathways and is in a strategic position to modulate chemical information as it is transferred from one region of the brain to another, It is a major component of the limbic system, which, along with the hypothalamus and amygdala, is involved in the control of emotion and motivation. In recent years, evidence has mounted that the hippocampus is important if not critical, to learning and memory processes. These processes are significantly impaired if the hippocampus or certain nerve pathways entering it or leaving it are destroyed.

Learning and memory are often adversely affected by toxic substances, and some researched believe that the hippocampus is an important target site of these substances. A number of toxic chemicals preferentially affect the hippocampus, including many metals, some abused drugs, and certain viruses (including those responsible for rabies and AIDS). The hippocampus is also adversely affected in neurodegenerative disorders such as Alzheimer's disease and in Down's syndrome.

Many of the cells of the hippocampus appear to use the excitatory amino acids glutamate and aspartate as neurotransmitters, Under normal circumstances the synthesis, storage, and release of these transmitters is delicately balanced. However, adverse conditions associated with trauma, stroke, or exposure to toxic chemicals and drugs may upset this balance, sometimes leading to an event known as **excitotoxicity. This is** a process by which excitatory neurotransmitters released from neurons flood neighboring cells and weaken their membranes, leading to cell death. The mechanism of this cascade of events is being examined closely in the case of glutamate because the characteristics of the receptor that binds this transmitter are beginning to be understood. Recently, it was discovered that the drug PCP blocks glutamate receptors and that other compounds that effectively block this receptor are virtually identical to PCP.

There is much to learn about the transmitter systems in the hippocampus and the mechanisms by which toxic substances alter these systems. Clues to how some aspects of learning and memory are altered by toxic substances may ultimately be found in the biochemical machinery of this region of the brain.

SOURCES: S. Blakeslee, 'Pervasive Chemical, Crucial to the Body, Is Indicted as an Agent in Brain Damage," New York *Times, Nov. 29, 1988;* TJ. Walsh and D.F. Emerich, "The Hippocampus as a Common Target of neurotoxic Agents," *Toxicology 49:137-140, 1988.*

because the neural targets of these diseases are the same as those of many neurotoxic substances. Persons suffering from mental disorders may also be more susceptible to neurotoxic substances because of possible augmentation of their symptoms. Toxic chemicals can cause or exacerbate anxiety, depression, mania, and psychosis. Most adverse effects are short-term and reversible; however, long-term effects, including permanent damage to mental health, can occur.

Diseases involving organs such as the kidney or liver can indirectly affect the nervous system. The build-up of waste products in the bloodstream due to kidney failure or diabetes, for example, can cause adverse effects on nervous tissue similar to those caused by environmental exposure to toxic chemicals.

Malnourished individuals are generally at greater risk of harm from neurotoxic substances than are individuals with adequate diets. A person with a thiamine (vitamin B_1) deficiency, for example, is more susceptible to the toxic effects of ethanol on the liver (15). This problem is especially relevant for developing nations-that face regular food shortages.

CLASSES OF neurotoxic SUBSTANCES

neurotoxic substances can be categorized according to the structural or functional changes they cause. The following categorization, which groups neurotoxic substances according to where they appear to act, is a summary of a scheme developed by Spencer and Schaumburg (20). The scheme includes the following targets: neurons, glial cells and myelin, the neurotransmitter system, and blood vessels supplying the nervous system.

Some adverse effects may not be included in this approach. For example, neurotoxic substances may also affect cells of the immune system, which can in turn influence nervous system function at any of these neural sites. Interactions between the immune and nervous systems have become the subject of

Box 3-C-MPTP and Parkinson's Disease

In recent years, the hypothesis that Parkinson's disease and other neurological disorders might be triggered by environmental factors has become more widely accepted. Although toxic substances have long been considered possible contributors to the cause of some disorders of the nervous system, the MPTP incident has focused more attention on this environmental hypothesis.

MPTP is the abbreviation for l-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine, a compound that can be created during the production of synthetic heroin. Remarkably, in just 5 to 15 days, this highly neurotoxic substance can induce a syndrome virtually identical to Parkinson's disease—a disease that usually occurs late in life and develops slowly over a period of years. Both Parkinson's disease and the MPTP-induced syndrome are characterized by tremors and lack of muscular control that stem from degeneration of neurons in the substantial nigra, a region deep in the central area of the brain. Neurons in the substantial nigra synthesize and secrete the neurotransmitter dopamine, hence Parkinson's patients are treated with levodopa, a precursor of this neurotransmitter.

The discovery of the link between MPTP and Parkinson's disease has dramatically changed the nature of research on this disease. Much work has focused on MPP^+, a metabolize of MPTP that is responsible for the adverse effects on the brain. Recently, researchers discovered that a monoamine oxidase inhibitor, a type of drug sometimes used to treat depression, blocks the conversion of MPTP to MPP^+. Other researchers have shown that the monoamine oxidase inhibitor Deprenyl, administered to Parkinson's patients in combination with levodopa, reduces the symptoms of the disease and extends their lives. It was found that Deprenyl slows the rate of degeneration of neurons in the substantial nigra, perhaps making it useful in the treatment of Parkinson's disease.

The MPTP story illustrates how a neurotoxic substance might cause or contribute to the development of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. The relative contributions of environmental and genetic factors to the causes of these diseases are not understood and are the subject of considerable research and debate within the scientific community. Although the extent to which a neurotoxic substance contributes to the cause of Parkinson's disease is unclear, the MPTP story serves as an example of how neurotoxicological research can lead to a better understanding of the causes of neurological disease and ways to treat it.

SOURCES: LJ. Kopin and S.P. Markey, "MPTP Toxicity: Implications for Research in Parkinson's Disease,' *Annual Review of* Neuroscience 11:81-96, 1988; J.W. Langston, P. Batlard, J.W. Tetrud, et al., "Chronic Parkinsonism in Humans Due to a Product of Meperidine-Analog Synthesis," *Science* 219:979-980, 1983; R. Lewin, "Big First Scored With Nerve Diseases," *Science* 245:467-468, *1989.*

considerable interest in recent years, leading to a new field of research known as neuroimmunology.

Actions on the Neuronal Membrane

As described earlier, the neuron consists of the cell body and the dendrites and axons projecting from it. The neuronal membrane contains a complex system of pumps, receptors, and channels through which charged molecules (ions such as sodium, calcium, and potassium) travel into and out of the cell. Toxic substances may act on any of these components. Determining the mechanism of action of neurotoxic substances often requires researchers to investigate possible adverse effects on a variety of receptors and channels.

Naturally occurring toxic substances such as tetrodotoxin (from the puffer fish) and saxitoxin (from the marine alga responsible for paralytic shellfish poisoning) block ion channels, initially causing numbness in the face, neck, and limbs. This is followed by difficulty in speaking and swallowing and by an inability to coordinate muscular movements. In severe cases, respiratory paralysis may result.

Toxic substances can also act to increase the flow of ions across the membrane, resulting in many of the same symptoms as those caused by the channel blockers. Scorpion toxin and the pesticide DDT, for example, act by increasing the flow of sodium ions. Pyrethroid pesticides are an example of widely used commercial compounds that exert toxic effects in this manner.

Actions on Neuronal Structures

Substances such as mercury and lead cause degeneration of the central nervous system. Intoxication by organic mercury, particularly in children, can cause degeneration of neurons in the cerebellum



Photo credit: U.S. Environmental Protection Agency

and can lead to tremors, difficulty in walking, visual impairment, and even blindness. Lead adversely affects the cortex of the immature brain, causing irreversible mental retardation in young children (23).

The peripheral nervous system is particularly vulnerable to the effects of toxic substances because it lies outside the central nervous system which is partially protected by the blood-brain barrier. The antitumor agent doxorubicin, for example, causes degeneration of both central and peripheral nerve axons (21).

Degeneration of the axon is one of the most frequently encountered neurotoxic effects. Many chemicals and drugs will cause axonopathy but will not affect the cell body. In most cases, repeated or chronic exposure is required before adverse effects occur. The precise mechanisms by which axonal degeneration occurs are not understood. Some research suggests that toxic substances block the transport of substances between the cell body and regions of the axon.

Often, degeneration begins at or near the end of the axon and proceeds toward the cell body. As noted earlier, this type of pathological effect is called central-peripheral distal axonopathy (CPDA). An afflicted individual may experience loss of sensation in the hands and feet or muscular weakness. In some cases, the effects gradually worsen, and the loss of sensation progressively ascends to the limbs as shorter nerves become affected. With time and removal from exposure, recovery is often possible.

Numerous toxic substances cause CPDA, including such industrial chemicals as carbon disulfide (discussed further in ch. 10), hexane, acrylamide, and Lucel-7 (discussed in ch. 2). Drugs that cause this axonopathy include thalidomide (whose other tragic side-effects on the developing fetus have been well documented) and vincristine, a drug used to treat cancer. Alcohol abuse, some organophosphorous pesticides, and natural toxins present in buck-

thorn (from the fruit of the shrub *Karwinskia humboldtiana) also* adversely affect the nervous system in this manner.

A less common form of axonal degeneration, central-distal axonopathy, is characterized by adverse effects on the spinal cord but not on the peripheral nervous system. Some 10,000 cases occurred in Japan between 1956 and 1972, when the drug clioquinol was considered a safe and effective nonprescription treatment for diarrhea caused by an amoeba. Affected individuals experienced abdominal discomfort, numbness in the feet, weakness in the legs, blurred vision, and, in cases where large amounts of the drug were consumed, encephalitis (inflammation of the brain).

The most serious form of neurotoxicity involves the complete loss of nerve cells. Sensory nerve cells may be lost in patients treated with megavitamin doses of vitamin B_6; hippocampal neurons undergo degeneration with trimethyltin poisoning; motor nerve cells are affected in cycad toxicity, which has been linked tentatively to Guam-ALS-Parkinsonism dementia (19).

Actions on Glial Cells and Myelin

A large number of neurotoxic substances can cause degeneration of glia1 cells and the myelin that these cells produce. Diphtheria toxin, for example, interferes with the cell bodies of myelin-producing glial cells. Hexachlorophene interferes with the energy-producing mitochondria within glial cells. Perhexilline maleate, a drug used to treat the chest pain of angina pectoris, sometimes causes degeneration of myelin and leads to numbness in the hands and feet and muscle weakness.

Actions on the Neurotransmitter System

Other toxic substances may affect the neurotransmitter systems of neurons. The nicotine in cigarettes and some insecticides, for example, mimic the effects of the neurotransmitter acetylcholine. Organophosphorous compounds, carbamate insecticides, and nerve gases act by inhibiting acetylcholinesterase, the enzyme that inactivates the neurotransmitter acetylcholine. This results in a build-up of acetylcholine and can lead to loss of appetite, anxiety, muscle twitching, and paralysis.

Amphetamines stimulate the nervous system by causing the release of the neurotransmitters norepinephrine and dopamine from nerve cells. Cocaine affects both the release and reuptake (the process by which neurotransmitters and their metabolizes are recycled) of norepinephrine and dopamine. Both amphetamines and cocaine can cause paranoia, hyperactivity, and aggression, as well as high blood pressure and abnormal heart rhythms.

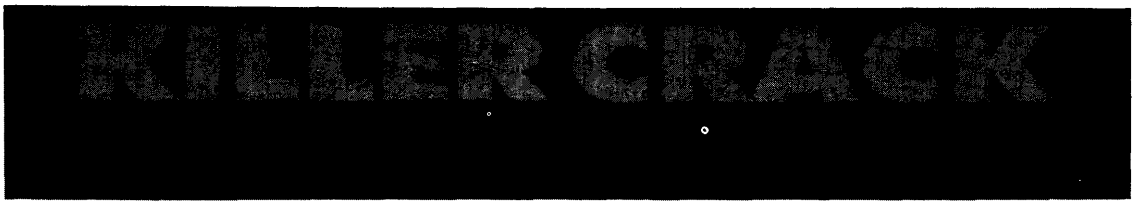
Some drugs act by altering the action of the neurotransmitter serotonin. LSD, a drug widely abused in the United States, especially in the 1960s, is a potent hallucinogen. Although it is not known precisely how LSD functions, it does interfere with the activity of the neurotransmitter serotonin. Mescaline and psilocybin (from the hallucinogenic mushroom Psilocybes) act in a similar fashion.

Opium-related drugs such as morphine and heroin act at specific opioid receptors in the brain. These receptors interact with the endogenous brain neuropeptides, such as the enkephalins and endorphins, which control the perception of pain and give rise to feelings of euphoria. Consequently, drugs acting at opioid receptors cause sedation and euphoria and reduce pain. They also tend to slow the heart rate and may cause nausea, convulsions, and slow breathing patterns. They are highly addictive, leading to as yet unidentified changes in the structure and function of the nervous system. Researchers are actively seeking to understand the mechanisms by which addiction to opiates occurs. Withdrawal from this class of drugs leads to impaired vision, restlessness, and tremors.

A relatively recent phenomenon of increasing concern to health-care workers is the addicted infants born to women who use drugs such as cocaine. These infants suffer from a variety of behavioral abnormalities. Many of the symptoms of withdrawal seen in adults can also be seen in these infants immediately after birth (see box 2-B).

Actions on Blood Vessels Supplying the Nervous System

The nervous system is supplied by an extensive system of blood vessels and capillaries. The brain needs large quantities of oxygen and nutrients and relies on an extensive circulatory system to supply needed substances and to remove toxic waste products. Lead damages capillaries in the brain and leads to the swelling characteristic of encephalopathy. Other metals (e.g., cadmium, thallium, and mercury) and organotins (e.g., trimethyltin) cause



Crack is Cocaine



Crack is not a new drug—it's actually freebase cocaine. It's different because:

- Of the way it's made
- It's pre-packaged for users, and
- It's much stronger and deadlier than other types of cocaine.

Crack is sold in smokable chips or tiny rocks. Sometimes it's in foil or plastic bags or tiny plastic vials—little bottles with colored stoppers like the kind used for perfume.

Dealers love crack—they get rich quickly. Crack is easy to handle and highly addictive. This guarantees steady customers. Crack is a dealer's dream. But it's a user's nightmare because it's quickly and highly addictive, even after a few doses.

Crack Only Looks Harmless

Crack looks like grey or white-colored soap, small rocks or little pellets. Some people say it's odorless, but others think it has the pungent, bitter aroma of burning rubber, where the drug is often used.

Crack appears to be a cheap and easy way to get high. It's usually smoked in water pipes or cigarettes. But the act of smoking doesn't seem as dangerous as injecting something up the nose or inhaling powder into the lungs. But users seriously fool themselves if they think so.

Some heroin addicts have turned to crack because they fear the spread of AIDS among needle users. Crack has not yet been done many of them learn quickly to their sorrow.

Other addicts have turned to crack because they think it is safer than other methods of freebasing, albeit not much safer.

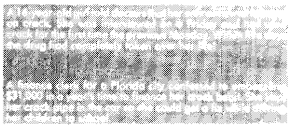
High Cost

The crack high is cheap—at the start. The first dose only costs as little as $5. This makes it especially attractive to young people. They also like crack because it is not bulky or expensive and small sale. The dealer has no need for a white-collar connection. Drug experts say the habit will cost hundreds of dollars a week.

Deadly Cycle

Crack triggers an explosive, short-lasting euphoria. It rushes the brain's supply of several essential neurotransmitters and affects the body in many harmful ways. Many users try to feed the craving by using more and more of the drug, but each dose produces a shorter high. Crack is a powerful addictive drug that can cause seizures, heart failure, respiratory arrest, stroke, and death.

I n s Addiction



Physical Effects

Physical effects [illegible] can be tragic. For younger users as well as older users, crack can cause many dangerous changes in blood pressure, heartbeat, and breathing. It can cripple or kill in many ways.

- [illegible]
- [illegible]
- [illegible]
- [illegible]

Psychological Effects

[illegible]

Tragedy

[illegible]

Users Say:

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The Scope of Use

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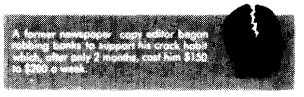

Signs of Use

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Sources of Help

If you believe someone is in trouble with crack, you can get help and information from schools, cities, and local organizations.

Two national toll-free hotlines are:

1-800-COCAINE

This is an around-the-clock information and referral service. Referrals include public employees and private treatment programs, and self-help groups. Callers can request free publications. This hotline is sponsored by the Drug Enforcement Administration (DEA).

1-800-662-HELP

This is a national hotline for information on Drug Abuse (NIDA) of a call operator's referral to the local that directs callers to certified alcohol and drug centers in their local communities. NIDA also publishes [illegible] drug abuse. Write: National Institute of Drug Abuse, 5600 Fishers Lane, Rockville, Md. 20857.

Drug information is available from:

301-984-5700
American Council for Drug Education
5820 Hubbard Drive
Rockville, MD 20852

404-329-5709
Families in Action National Drug Information Center
Suite 300
3845 North Druid Hills Road
Decatur, Ga. 30033

1-800-258-2766
Just Say No Foundation
1777 North California Boulevard
Walnut Creek, Calif. 94596

National Clearinghouse for Alcohol & Drug Information
P.O. Box 2068
Rockville, Md. 20852

1-800-554-KIDS
National Federation of Parents for Drug-Free Youth
Suite 300
8730 Georgia Avenue
Silver Spring, Md. 20910

1-800-241-7946
Regency Recovery Institute for Drug Education (RRIDE)
Suite 1002
100 Edgewood Avenue
Atlanta, Ga. 30303

There are many sources of information and help available in your community. Check with your school district office, physicians, community health groups, clergy, or local law enforcement agencies.

[illegible] Education appreciates information contributed here provided by the U.S. Department of Justice, Drug Enforcement Administration and the National Institute of Justice, the U.S. Department of Health and Human Services, and the Office for Substance Abuse Prevention, National Drug Informa-



Photo credit: U.S. Department of Education

rupturing of vessels that can result in encephalopathy as well.

Further Information

Neurobiology and toxicology are rapidly expanding scientific fields that cut across many disciplines. A brief chapter can only touch on some of the general scientific principles underlying neurotoxicology, which lies at the intersection of these two fields. The interested reader may wish to consult any of several textbooks or nontechnical books for further information.

SUMMARY AND CONCLUSIONS

The complexity of the nervous system has made the field of neurotoxicology one of the most demanding disciplines in toxicology. In the last decade, neurotoxicologists have been able to differentiate the effects of many chemicals in terms of where they act and the symptoms they produce, but in most cases they have not yet been able to determine the mechanisms of action. Very few suspected neurotoxic chemicals have been evaluated in the laboratory and even fewer have been tested thoroughly. These chemicals act at many levels of the nervous system and exert their effects in a variety of ways, with consequences ranging from mild sensations of tingling in the extremities to severe mental retardation, loss of sensory function, and death. The chemicals may be particularly toxic to susceptible populations such as the unborn, the young, the sick, and the elderly. In order to safeguard human populations against the potentially damaging effects of these chemicals, it is necessary to study the consequences of prolonged low-level exposures as well as the effects of neurotoxic chemicals on sensitive populations.

CHAPTER 3 REFERENCES

1. Abou-Donia, M. B., and Lapadula, D. M., "Mechanisms of Organophosphorus Ester-Induced Delayed neurotoxicity: Type I and Type II," *Annual Review of Pharmacology and Toxicology* 30:405-440,1990.
2. Blakeslee, S., "Pervasive Chemical, Crucial to the Body, Is Indicted as an Agent in Brain Damage," New *York Times, Nov. 29, 1988.*
3. Chang, L. W., "Mercury," *Experimental and Clinical neurotoxicology,* P.S. Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980).
4. Cherniak, M. G., "Organophosphorus Esters and Polyneuropathy," *Annals of Internal Medicine* 104: *264-266, 1986.*
5. Cooper, J.R., Bloom, F.E., and Roth, R.H., *The Biochemical Basis of Neuropharmacology (New* York, NY: Oxford University Press, 1982).
6. Davis, S. D., and Richardson, R.J., "Organophosphorus Compounds, *Experimental and Clinical Neurotoxicology,* P.S. Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams& Wilkins, 1980).
7. Ferry, G., "The Nervous System: Getting Wired Up," New *Scientist, Inside Science* 19:1-4, Mar. *4,* 1989.
8. Ginsburg, M.D., "Carbon Monoxide," *Experimental and Clinical neurotoxicology, P.S.* Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980).
9. Katzman, R., and Terry, R. (eds.), *The Neurology of Aging* (Philadelphia, PA: F.A. Davis, 1983).
10. Klaassen, C., "Principles of Toxicology" and "Distribution, Excretion, and Absorption of Toxicants," *Casarett and Doull's Toxicology, C. Il.* Klaassen, M.O. Arndur, and J. Doull (eds.) (New York, NY: Macmillan, 1986).
11. Kopin, I.J., and Markey, S.P., "MPTP Toxicity: Implications for Research in Parkinson's Disease," *Annual Review of Neuroscience* 11:81-%, 1988.
12. Langston, J. W., Ballard, P., Tetrud, J. W., et al., "Chronic Parkinsonism in Humans Due to a Product of Meperidine-Analog Synthesis, ' *Science* 219:979-980, 1983.
13. Lewin, R., "Big First Scored With Nerve Diseases," *Science* 245:467-468, *1989.*
14. Morgan, J. P., "The Jamaica Ginger Paralysis," *Journal of the American Medical Association 248:1864-1867, 1982.*
15. National Research Council, *Drinking Water and Health* (Washington, DC: National Academy Press, 1986).
16. Needleman, H. L., "Epidemiological Studies," *Neurobehavioral Toxicology,* Z. Annau (cd.) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 279-287.
17. Restak, R. M., *The Brain (New* York, NY: Bantam Books, 1984).
18. Riley, E.P., and Vorhees, C.V. (eds), *Handbook of Behavioral Teratology (New* York, NY: Plenum Press, 1986).
19. Spencer, P. S., Nunn, P. B., Hugon, J., et al., "Guam Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Linked to a Plant Excitant Neurotoxin, " *Science* 237:517-522, 1987.
20. Spencer, P. S., and Schaumburg, H. H., "An Expanded Classification of neurotoxic Responses Based on Cellular Targets of Chemical Agents, " *Acta Neurological Scandinavia* 100:9-19(suppl.), *1984.*

21. Spencer, P. S., and Schaurnburg, H.H. (eds.), *Experimental and Clinical neurotoxicology* (Baltimore, MD: Williams & Wilkins, 1980).
22. Suzuki, K., "Special Vulnerabilities of the Developing Nervous System to Toxic Substances, ' *Experimental and Clinical neurotoxicology,* P.S. Spencer and H.H. Schaumberg (eds.) (Baltimore, MD: Williams & Wilkins, 1980).
23. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, *The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress* (Atlanta, GA: Centers for Disease Control, 1988).
24. Walsh, T.J., and Emerich, D.F., "The Hippocampus as a Common Target of neurotoxic Agents," *Toxicology* 49:137-140, *1988.*
25. Weiss, B., "Neurobehavioral Toxicity as a Basis for Risk Assessment," *Trends in Pharmacological Sciences* 9:59-62, *1988.*
26. Young, B. B., ''neurotoxicity of Pesticides,' *Journal of Pesticide Reform* 6:2, *1986.*

Chapter 4

Research and Education Programs

"There is increasing concern that basic research directed towards predicting, detecting, and understanding neurotoxicity is being neglected by government, industry, and academic researchers.

Committee on Science and Technology
U.S. House of Representatives
September 16, 1986

"I would say that the methyl n-butyl ketone outbreak was the key episode in bringing attention to the field of behavioral toxicology. That signaled a shift in thinking about behavioral problems. Before Columbus, many of us thought, 'Well, people who work with some chemicals might have trouble concentrating, or maybe even some temporary or unimportant changes. After Columbus, we could see that even relatively safe chemicals, in concentrations that pose no danger to other systems of the body, can bring serious and sometimes irreversible damage to the nervous system.

W. Kent Anger, Ph.D.
Psychology Today
July 1982

"Much more work on mechanisms of chemical neurotoxicity will be required before structure-toxicology considerations prove generally useful as a screen for neurotoxicity.

Peter Spencer, Ph.D.
"Testimony before the House Committee on Science and Technology
October 8.1985

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Chapter 4
Research and Education Programs

Increasing public concern about the effects of toxic substances on the nervous system has led to some expansion of research programs in government, academia, and industry in recent years. Even so, the research programs are relatively small, and questions are frequently raised as to whether they are capable of addressing the threat that neurotoxic substances pose to public health. The style and purpose of research differs in each of these settings, yet each makes important contributions. An optimal national research program requires effective cooperation among researchers in all sectors and an appropriate balance of effort.

This chapter describes current programs in the United States and future needs for research into the causes, extent, and consequences of exposure to neurotoxic substances. The first half of the chapter describes Federal research programs; the second half addresses research efforts under way in academia and industry. State research programs are not described in this report.

FEDERAL RESEARCH ACTIVITIES

Federal research related to neurotoxic substances is conducted primarily at the National Institutes of Health (NIH), the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), and EPA. Limited research programs are under way at the Food and Drug Administration (FDA), the Centers for Disease Control (CDC), the Department of Energy, the Department of Agriculture, and other agencies. As indicated in table 4-1, total Federal funding for neurotoxicology -related research (excluding research related to nicotine and smoking, alcohol and alcoholism, and radiation) is $67 million. The bulk of this funding (89 percent) is through ADAMHA and NIH and tends to focus on the toxicity of drugs and the biochemical mechanisms underlying neurological and psychiatric disorders. A number of other Federal agencies and organizations provide limited funding for research related to neurotoxicity as well. Given the threat that neurotoxic substances pose to public health and the lack of knowledge of the mechanisms by which these substances exert adverse effects, OTA found that, in general, Federal research programs are not adequately addressing neurotoxicity concerns.

Environmental Protection Agency

The principal research component of EPA is the neurotoxicology Division (NTD) within the Health Effects Research Laboratory at Research Triangle Park, North Carolina. This division was organized in 1978 and has gradually grown into an effective interdisciplinary research program. A committee of EPA's Science Advisory Board recently reviewed NTD's program and described it as "the leading Federal neurotoxicology research organization" (30). NTD research programs range from development of methods to evaluate the neurotoxicity of chemicals to testing of specific substances and determining the mechanisms by which toxic substances adversely affect nervous system structure and function.

The NTD is divided into three branches: the Neurophysiology and Neuropathology Branch, the Behavior and Neurochemistry Branch, and the Systems Development Branch, which provides engineering and technical support services to the first two. Recently, the Science Advisory Board review committee recommended that consideration be given to developing a branch to focus on cellular and molecular toxicology (30)$_0$

EPA has developed a multidisciplinary program to examine how toxic substances adversely affect the nervous system. The overall program strategy stresses the development of test methods and approaches for identifying and characterizing neurotoxicity and for predicting risk to humans. Studies conducted to evaluate the cellular and molecular

Table 4-l-Federal Funding for Civilian neurotoxicity-Reiated Research

Agency	Research[a] ($ millions)
National Institutes of Health[b]	32.6
Alcohol, Drug Abuse, and Mental Health Administration[c]	26.6
Environmental Protection Agency	3.9
National Institute for Occupational Safety and Health	0.7
Food and Drug Administration	1.8
Department of Energy[d]	0.5
Department of Agriculture	0.4
Total	66.5

[a]Totals are based primarily on fiscal year 1988 data.
[b]Excludes research related to nicotine and smoking.
[c]Excludes research related to alcohol and alcoholism.
[d]Excludes research related to radiation.

SOURCE: Office of Technology Assessment, 1990.

basis for chemically induced functional changes in the central and peripheral nervous systems are designed so that effects on laboratory animals can be extrapolated to humans.

Behavioral research is aimed at evaluating autonomic, sensory, motor, and cognitive functions; developing measures to screen chemicals for neurotoxic potential; and evaluating specific behavioral processes that are disrupted by exposure to toxic substances (12). Research to determine the utility of short-term behavioral tests for measuring neurotoxic effects helps EPA regulatory program offices in the development of test guidelines. Long-term research goals include the development of animal models that can be used to predict behavioral toxicity in humans.

Cellular and molecular research focuses on locating biochemical and anatomical sites of toxicant-induced changes in the nervous system. This includes developing biochemical markers to identify the targets of toxic substances within the nervous system and performing morphological studies to determine the structural consequences of exposure to neurotoxic substances. NTD's long-term goals are to develop cellular and molecular approaches that improve neurotoxicity testing and provide a better understanding of the neurobiological basis for risk assessment.

The neurophysiology component of the research program is aimed at attaining a better understanding of how physiological processes are disrupted by neurotoxic chemicals. A primary focus is the electrophy biological evaluation of sensory systems, which allows for direct measurement of nervous system activity. Where possible, the program uses methods that have direct counterparts in human research, in order to make extrapolation easier (9).

EPA regulatory program offices need more methods of evaluating neurotoxicity, largely because of the general requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) (see ch. 7). When EPA requires industry to conduct neurotoxicity testing under TSCA, it must specify the types of tests required and the data it expects from them. At times, industry may request permission to deviate from EPA guidelines (e.g., in the case of test rule development under TSCA), but these alternative test methods must be evaluated by the Agency. NTD provides much of the technical expertise necessary to support EPA program offices in this regard.

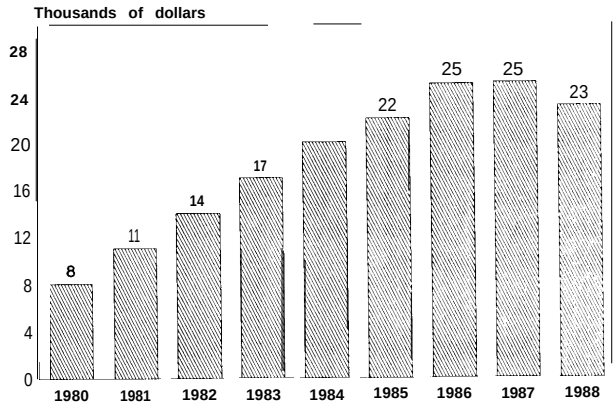
NTD is actively developing and validating two major neurotoxicity screening tests: the functional observational battery and automated testing of motor activity (see ch. 5). These tests are validated by evaluating how well they confirm the neurotoxicity of known, representative toxic substances. In this way, profiles can be developed for classes of neurotoxic chemicals.

Other approaches to neurotoxicity testing are also being developed. Electrophysiological approaches are being refined to enable investigators to monitor the excitability of individual nerve cells or groups of nerve cells or regions of the brain. Behavioral tests are being developed to assess the effects of toxic substances on memory, learning, and muscular coordination. In addition, methods are being devised to evaluate the effects of toxic substances on the developing nervous system. A variety of molecular and cellular approaches are being developed to determine the effects of toxic substances on various proteins in nerve cells (including enzymes) and on several biochemical processes, including the transport of substances along the axons of nerves. Tests designed to evaluate exposures at toxic waste sites and at chemical spills are also being developed and refined:

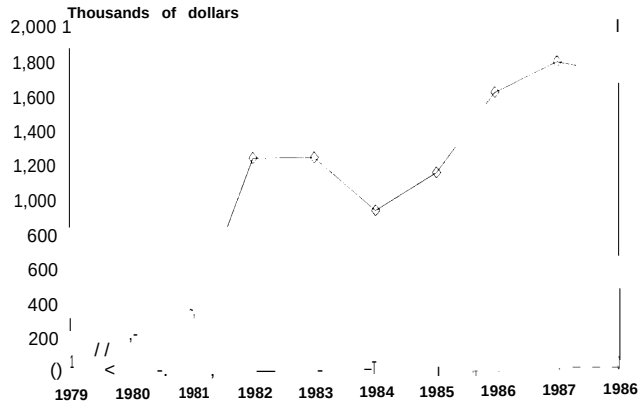
Because EPA's neurotoxicology Division is the principal Federal intramural research organization in the environmental neurotoxicology field, and because resource information on the program has been available since its inception, OTA analyzed the funding of this program in some detail. The total number of principal investigators (including some postdoctoral fellows and on-site contractors) fell to *23* in fiscal year 1988, down from 25 in fiscal years 1986 and 1987 (figure 4-1A). Funds for on-site contract support remained constant over these years at $1.7 million, up from $0.9 million in 1984 (figure 4-l B). Funds for outside contracts and cooperative agreements have fluctuated considerably (figure 4-lC). Budget stability has been a continuing administrative problem. According to the EPA Science Advisory Board committee's analysis, funds for NTD are frequently cut with little prior notice, impeding in particular the development of long-range plans. As indicated in figure 4-lD, NTD's supplies and equipment budget has dropped precipitously in recent years. In 1985, NTD allocated $23,500 in supplies and equipment to each principal investigator. In 1988, only $8,100 could be allocated (figure 4-lE). In its recent review, the Science

Figure 4-l-Resources for EPA's neurotoxicoiogy Division

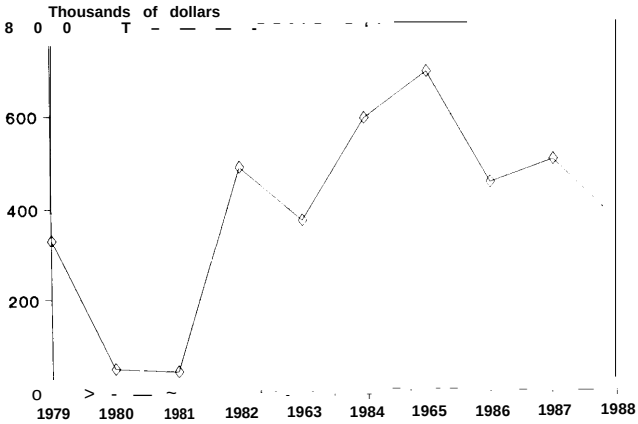
A. Total Principal Investigators



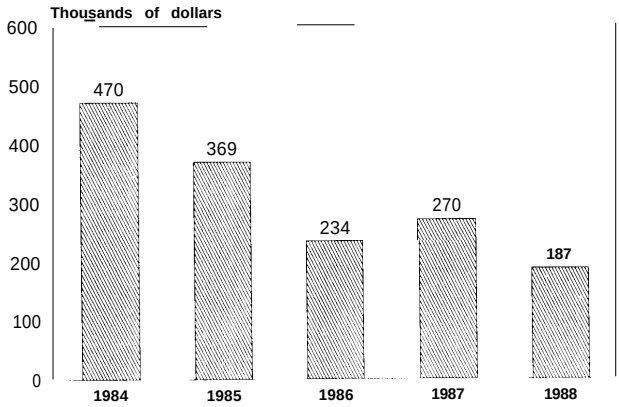
B. R&D Funds: On-site Support Contracts



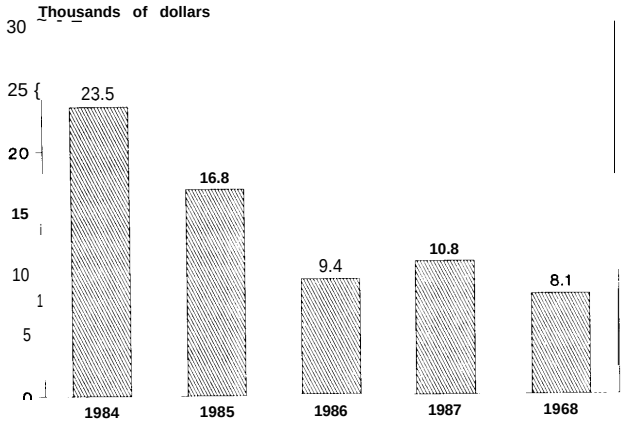
C. R&D Funds: Outside Contracts and Cooperative Agreements



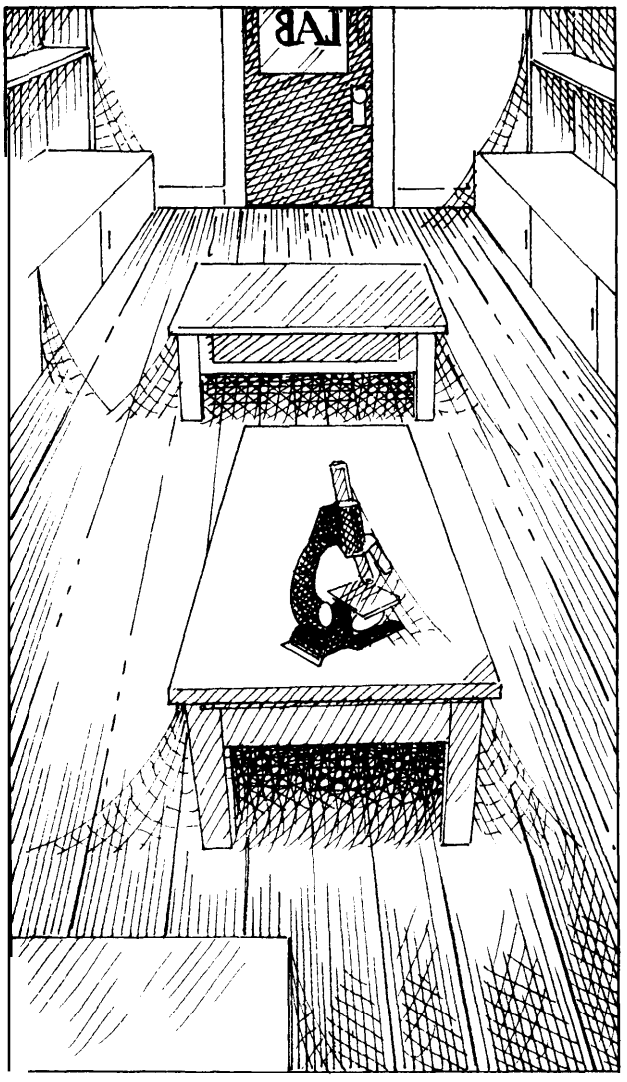
D. Funds: Supplies and Equipment



E. Supplies and Equipment per Principal Investigator



SOURCE: Based on R. Dyer, U.S. Environmental Protection Agency, personal communication, 19aa



Illustrated by: Ray Driver

Advisory Board committee described NTD's supply budget as "totally inadequate" and concluded that "important research is not carried out" because of budgetary restrictions (30).

EPA has rarely funded extramural grants in the neurotoxicology field. A substantial grants program in this area would be a valuable adjunct to its intramural program.

In recognition of the need to expand its research programs in the neurotoxicology area, EPA recently submitted to the Office of Management and Budget (OMB) a request to expand its research budget by $1.5 million. Approximately $1.0 million was requested for the development of in vitro neurotoxicology tests; another $0.5 million was requested to examine adverse effects associated with cholinesterase inhibition and the utility of cholinesterase inhibition as a biomarker for exposure. However OMB allowed no funding for either research effort. In vitro test development is often cited as a high-priority research need because of the requirement to rapidly screen toxic chemicals and to try to minimize the use of animals in research. A technical EPA panel recently recommended that the agency initiate studies to examine the relationship between cholinesterase inhibition and other adverse effects on the nervous system.

National Institutes of Health

Approximately 250 neurotoxicology -related research projects were funded by NIH in fiscal year 1988 (29). Most were funded through competitive grants to investigators in public and private institutions; the rest were conducted at NIH itself. About 80 percent of the neurotoxicology -related research (based on fiscal year 1988 expenditures) is funded through or conducted at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. (NIEHS is the only NH-I institute not located in Bethesda, MD.) Individual research projects averaged about $120,000. NIH expenditures on neurotoxicology -related research (excluding projects at the National Cancer Institute related to nicotine and cigarette smoking) totaled approximately $33 million. This is 0.5 percent of the total $6.5 billion ND-I research budget (44). In comparison, NIH spends approximately $1.5 billion on cancer research (44), which accounts for about 23 percent of the total research budget.

OTA found that NIH supports few programs in the field of neuroepidemiology. NIH supports a relatively large number of research projects designed to elucidate how toxic substances influence the nervous system but devotes few resources to projects examining the extent to which these substances contribute to human neurological disorders. Although the latter studies are often expensive and time-consuming, they are critical to understanding the extent to which toxic substances adversely affect public health and in determining the direction and scope of regulatory programs.

National Institute of Neurological and Communicative Disorders and Stroke[1]

In fiscal year 1988, NINCDS funded 71 research projects related to neurotoxicity. All but three of these were extramural grants to investigators at public and private institutions. Research sponsored by NINCDS covers abroad range of problems, from the level of the gene, to the cell, to the whole organism. Much of the work focuses on the mechanisms by which toxic substances adversely affect the nervous system: for example, how the flow of ions through membrane channels is altered by toxic substances, how these substances cause degeneration of nerves, how they alter other biochemical components of the nerve cell, and how toxic substances cause or contribute to neurological disorders. Several projects focused on how the chemical MPTP affects the nervous system and how it induces symptoms of Parkinson's disease. Other projects examined how therapeutic drugs influence the structure and function of the nervous system. For example, drugs used in cancer chemotherapy may adversely affect the nervous system. It is important to understand how and when this occurs in order to help maximize effects on cancerous cells and minimize damage to healthy cells.

Three intramural projects are under way at NINCDS laboratories. The largest was funded at more than $400,000 and is examining how cells derived from the brain of mammals perceive and respond to signals in their environment. A second project is examining the neurological and behavioral effects of MPTP on the monkey, and the third is devoted to the mechanism by which nerves lose their myelin sheaths.

National Institute of Environmental Health Sciences

NIEHS conducts and supports research related to the effects on human health of chemical, physical, and biological agents in the environment. NIEHS has an extensive extramural program, and it sponsored more than 80 grants related to the neurotoxicity of environmental contaminants and other substances in fiscal year 1988. The NIEHS extramural grants program is the largest source of Federal funds for research grants in the environmental neurotoxicology field. Funding for these projects amounted to nearly $12 million. NIEHS also received nearly $900,000 from EPA's Superfund program (through an interagency agreement) to support four extramural projects. In addition, NIEHS funded three neurotoxicology-related contracts totaling $755,000. The extramural projects focused on a broad range of neurotoxic substances, including metals, pesticides, solvents, natural toxins, PCBs, and other industrial chemicals. NIEHS also funded grants to several academic institutions.

Until 1987, an intramural Laboratory of Behavioral and Neurological Toxicology existed within NIEHS. Following a management change, the laboratory's emphasis shifted to basic neuroscience research (specifically, molecular and cellular neurobiology) and its name was changed to the Laboratory of Molecular and Integrative Neuroscience (LMIN). This laboratory comprises three sections and several smaller working groups, only one of which, the Neurobehavioral Section, focuses primarily on environmental neurotoxicology problems. (The neurotoxicologist who headed that section left the Institute in 1989.) An OTA analysis of fiscal year 1988 research projects found that many LMIN research projects in the neuroscience were only generally related to toxicology. Of the $3 million expended on intramural research in the neuroscience, OTA found that only about one-fourth was devoted to studies in which neurotoxicology was the primary focus. Hence, OTA found that, with the exception of the Neurobehavioral Section of LMIN, there is little distinction between intramural basic neuroscience research programs at NIEHS and those at other NIH and ADAMHA institutes. This has lead to a prominent intramural research gap at NIH in the environmental neurotoxicology field.

National Toxicology Program

The National Toxicology Program (NTP) was established in 1978 by the Secretary of the Department of Health and Human Services (DHHS) to coordinate DHHS activities related to the testing of toxic chemicals. The program was initiated to develop information about the toxicity of selected chemicals, to test selected chemicals for toxicity, to develop and validate tests and protocols, and to set priorities for testing needs and communicate results

[1]In late 1988, the National Institute of Neurological and Communicative Disorders and Stroke became the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Deafness and Other Communication Disorders (NIDCD) was formed. Since OTA's analysis was based on fiscal year 1988 programs, this discussion will refer to NINCDS programs.

to government agencies, the scientific community, and the public. NTP coordinates toxicology-related programs within the NIEHS, the National Institute for Occupational Safety and Health (NIOSH), and the U.S. Food and Drug Administration's (FDA) National Center for Toxicological Research (NCTR). NTP is administered by the Director of NIEHS. Program activities are overseen by an executive committee made up of the senior administrators of Federal health research and regulatory agencies. The quality of technical research programs is ensured by an independent Board of Scientific Counselors. After receiving nominations from participating Federal agencies and other public and private organizations, NTP selects chemicals to be tested. Testing is then performed by outside organizations through contract arrangements. Federal regulatory agencies have rarely requested neurotoxicity studies by NTP. From 1982 to 1988, only one substance had been nominated for neurotoxicity by the multiagency nominating committee (16). Consequently, NTP has sponsored little extramural neurotoxicology research as of fiscal year 1988. One of the few projects funded by NTP resulted in development of an automated assessment of behavior in the home cage (13,14). Intramurally, NTP has developed a neurobehavioral test battery to be used as part of its analysis of target organ toxicity. This battery will be used in a tiered testing approach to determine whether more specialized testing is necessary (43).

Within NIEHS, NTP is located under the Division of Toxicology Research and Testing. The division is composed of four branches: Carcinogenesis and Toxicologic Evaluation, Cellular and Genetic Toxicology, Chemical Pathology, and Systemic Toxicology. Toxicological concerns focus on carcinogens and mutagens (and to a limited degree on teratogens). NTP also evaluates the toxic effects of environmental agents on organ systems, including the nervous system. When health hazards are identified by NTP, additional studies characterizing the hazard are often undertaken by researchers in other government agencies, industry, and academia (16). Although the Division of Toxicology Research and Testing at NIEHS is the primary toxicological testing organization within the Federal Government, in 1988 it employed no neurotoxicologists. As of 1989, expert in-house scientific advice was provided through periodic consultation with the chief of the Neurobehavioral Section of LMIN. NTP is presently restructuring its program to address neurotoxicological concerns more effectively. Representatives of the NTP agencies participating in research efforts are preparing cooperative program plans to address neurotoxicologica.1 concerns specifically (16).

National Cancer Institute

The National Cancer Institute sponsored eight neurotoxicity-related projects in fiscal year 1988. Half of them focused on the adverse effects of cancer chemotherapy agents on the nervous system. The other four examined such problems as the induction of brain tumors by neurotoxic agents and the treatment of pain caused by cancer. Although smoking and nicotine are not included in this report, it should be noted that the Institute sponsored 64 projects related to smoking and nicotine addiction. Total funding for these 64 projects was in excess of $26 million in fiscal year 1988.

National Institute on Aging

The National Institute on Aging (NIA) sponsored 10 neurotoxicology -related research grants in fiscal year 1988. Several of these projects examine the possible role of metals in causing Alzheimer's disease; recent work has suggested that aluminum may contribute to the development of the structural changes in the brain that are characteristic of this disease. Other projects analyze age-related changes in the concentrations of excitatory amino acids (aspartate and glutamate) and the reduction in brain glutamate receptors seen in individuals with Alzheimer's disease, Two projects focus on MPTP, the aging process, and induction of Parkinson's disease-like symptoms. NIA is particularly interested in the question of why certain populations of nerve cells are particularly vulnerable to neurodegenerative diseases. Because the mechanism of cell death may be similar in different diseases, NIA is encouraging research into the molecular events underlying cell death (28). A 1988 workshop, sponsored by NIA, examined issues related to the susceptibility of the aging nervous system to infections and toxic substances.

The NIA has two intramural projects underway to examine the influence of toxic metals on aging processes and their possible role in the onset of dementia. The distribution of metals in the brain is being examined, as are the factors controlling the transport of metals across the blood-brain barrier.

In 1988, NIA sponsored a small workshop on the epidemiology of pesticide exposure and cognitive disorders in aging migrant and seasonal farmworkers. The effects on the human nervous system of long-term, low-level exposure to neurotoxic agricultural pesticides and herbicides are not known. The workship assessed the feasibility of using seasonal and migrant farmworkers, resident farmers, and others as research subjects in epidemiological studies.

National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development sponsored 11 research projects related to neurotoxicity in children in fiscal year 1988, with funding totaling approximately $1.2 million. Six of these projects focus on lead, which adversely affects the developing nervous system (see ch. 10). Two of the projects analyzed the effects of drugs used to treat epilepsy on the fetuses of mothers who must take these drugs. There is evidence that valproic acid, a drug widely used to treat epilepsy, adversely affects the nervous system of the developing fetus. The effects of valproic acid and phenytoin (another antiseizure drug) on the development of the nervous system of rhesus monkeys are being examined.

Another project is evaluating the effects of diets high in sugar or the artificial sweetener aspartame, or both, on the behavior and mental development of children. Other projects are examining mechanisms by which acrylamide, alcohol, and other substances affect the developing brain.

Division of Research Resources

The Division of Research Resources funded a total of 47 neurotoxicity-related research projects at various private and public research institutions. Projects focused on a broad range of toxic substances, including lead, pesticides, chemotherapy agents, ethanol, mercury, MPTP, and natural venoms and toxins. Total funding for these projects in fiscal year 1988 was $788,000.

Other NIH Institutes and Organizations

The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of General Medical Sciences (NIGMS), National Heart, Lung, and Blood Institute (NHLBI), National Center for Nursing Research, Fogerty International Center (FIC), and National Institute of Dental Research sponsored several projects concerned with neurotoxicity. These include projects investigating the actions of a paralytic toxin from a snail (NIGMS), the adverse effects of an antibiotic on hearing (NIGMS), how bacteria degrade and avoid the effects of organophosphates (NIGMS), the possible neurotoxic effects of drugs used to treat Herpes virus infections (NIAID), the side-effects of drugs used to treat high blood pressure (NHLBI), and the effects of antipsychotic drugs on brain dopamine receptors (FIC).

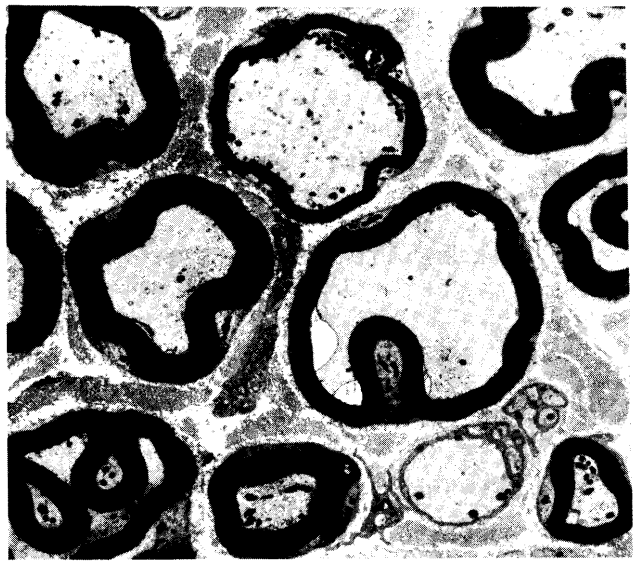


Photo credit: John O'Donoghue

This photograph illustrates the swelling of axons (dark areas) that can occur following exposure to a neurotoxic substance, in this case, 2,5-hexanedione.

National Library of Medicine

The National Library of Medicine (NLM) supports toxicological research by maintaining automated toxicology databanks and providing information services. The Toxicology Information Program was established in 1967 in response to a recommendation made by the President's Science Advisory Committee that efforts to handle toxicological information be enhanced. The NLM maintains several computerized, interactive retrieval services, including Toxline, Toxnet, and Chemline. Toxline provides information on the toxicological effects of drugs and chemicals. Toxnet contains information on potentially toxic or hazardous substances. Chemline is a chemical dictionary providing chemical names, synonyms, registry numbers, molecular formulas, and related information.

Alcohol, Drug Abuse, and Mental Health Administration

ADAMHA is composed of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). As indicated in chapter 2, OTA is excluding research on alcohol and alcoholism from this assessment; consequently, research programs at NIAAA will not be described. Both NIDA and NIMH have extensive research programs to examine the neurotoxic effects of drugs (NIDA) and the influence of neurotoxic substances on mental health (NIMH).

National Institute on Drug Abuse

NIDA sponsors a large research program related to the neurotoxicity of abused drugs. In fiscal year 1988, it funded 110 neurotoxicity-related grants. Total extramural funding was $15.5 million, or approximately $140,000 per grant. The extramural program addresses a broad range of issues from a variety of perspectives, including biochemical, pharmacological, pathological, and behavioral studies (14) and supports studies on all abused drugs. In 1988, it spent $1.5 million on in vitro studies of the neuropathological effects of drugs and on the neurotoxicity of designer drugs, cocaine, and inhaled solvents. An interagency agreement with NCTR supported studies of marijuana neurotoxicity (11).

Intramural research at NIDA is conducted at the Addiction Research Center in Baltimore, Maryland. Scientists at the center are examining the adverse effects of drugs such as MDMA (' 'ecstasy' and the related drug fenfluramine, cocaine, and THC, the active component of marijuana. The center's neurotoxicology-related research is conducted primarily in its neurobiology laboratory, but projects are also being carried out in its molecular pharmacology, preclinical pharmacology, neuropharmacology, neuroendocrinology, immunology, and cognitive sciences laboratories. Through an interagency agreement, FDA has provided the Addiction Research Center with funding to develop and validate methodologies for assessing the neurotoxicity of various drugs currently prescribed or under consideration for treatment of neuropsychiatric disorders. The center has been asked by the Drug Enforcement Administration to assess the neurotoxicity of some substances that are currently under consideration for regulatory scheduling (8). Funding for intramural neurotoxicity-related research in fiscal year 1989 was approximately $256,000 (8).

National Institute of Mental Health

A sizable portion of NIMH's research effort is devoted to neurotoxicity-related concerns. In fiscal year 1988, it funded 65 extramural grants totaling $8.6 million (excluding alcohol-related research), an average of some $132,000 per grant. These grants supported research into such issues as the mechanisms by which psychoactive drugs influence nervous system function, ways of minimizing the adverse effects of psychoactive drugs, and the contribution of toxic substances to neuropsychiatric disorders (14).

NIMH spent $2.2 million on eight major intramural research programs related to neurotoxicity. These programs are examining how toxic substances influence behavior and memory, how toxic substances may contribute to such diseases as Parkinson's disease and dementia, the mechanisms by which toxic substances disrupt biochemical processes within nerve cells, and methods of detecting toxic substances in the brain (14).

Food and Drug Administration

FDA's primary responsibility is to protect "the health of the Nation against impure and unsafe foods, drugs and cosmetics, and other potential hazards" (27). neurotoxicity research at FDA is limited in size and scope. A small research program (within one laboratory) exists in the Center for Food Safety and Applied Nutrition (CFSAN), but there is no significant research program in the Center for Drug Evaluation and Research. Several intramural research projects related to developmental neurotoxicology and one extramural project are underway at the National Center for Toxicological Research.

Center for Food Safety and Applied Nutrition

The General and Molecular Toxicology Branch of CFSAN conducts toxicological research related to food and nutrition and examines approaches to assessing health risks posed by food additives. The Neurobehavioral Toxicology Team (NBT), one of five teams within this branch, conducts neurotoxicological studies in this area. With the recent departure of a principal investigator, NBT currently consists of only the team leader, one laboratory biologist, and several laboratory assistants.

In recent years, FDA has interacted closely with EPA's Health Effects Research Laboratory, and for some time FDA has transferred funds to EPA as part of an interagency agreement (37,38). NBT is currently examining how altered ratios of carbohydrates to proteins affect brain function and how toxic chemicals are distributed in the brain. The team is also developing dog and miniature swine model systems that may eventually prove useful in predicting the effects of toxic substances on the human nervous system. Efforts are being made to assess the reliability and sensitivity of the model through a collaborative effort with investigators at NIMH.

The FDA is sponsoring three extramural projects related to aspartame and the influence of dietary amino acids on brain function (see app. A). One contractor is examining how changes in the relative concentrations of dietary amino acids affect the function of transmitters and receptors at neuronal synapses. Under an interagency agreement with FDA, NIEHS is determining whether an altered amino acid balance affects neuronal excitability or induces behavioral changes, or both, in adult and developing animals. FDA also has an interagency agreement with the Federal Aviation Administration to conduct clinical studies of the effects of aspartame on cognitive functions (39).

National Center for Toxicological Research

Located in Jefferson, Arkansas, NCTR conducts toxicology research programs that:

> . . . study the biological effects of potentially toxic chemical substances found in the" environment, emphasizing the determination of the health effects resulting from the long-term, low-level exposure to toxicants and the basic biological processes for chemical toxicants in animal organisms; develops improved methodologies and test protocols for evaluating the safety of chemical toxicants and the data that will facilitate the extrapolation of toxicological data from laboratory animals to man; and develops Center programs under the National Toxicology Program (27).

neurotoxicity-related research at NCTR currently focuses on developmental issues. NCTR is well qualified to carry out investigations of toxicological problems. Expertise is available in the areas of neurochemistry, neuropathology, neuropharmacology, behavioral pharmacology, primatology, developmental neurotoxicology, and nutritional influence on neurotoxicity.

Approximately one-third of the intramural research conducted within NCTR's Division of Reproductive and Developmental Toxicology is devoted to developmental neurotoxicology and related issues. The approximately $1.3 million intramural neurotoxicology effort includes seven to eight full-time scientists, seven to eight laboratory technicians, and two to three graduate students (32).

From fiscal year 1983 to 1988 NCTR conducted a study of the effects on primates of chronic exposure to marijuana. This project was not funded by FDA, but through an interagency agreement with NIDA. Cumulative fiscal year 1983 to 1987 funding was $1.8 million. The project was then extended for 1 year (through fiscal year 1988) at $748,000.

NCTR has the facilities, equipment, and personnel to expand interdisciplinary research in neurotoxicity and to conduct research related to therapeutic drugs and food additives, but it is currently constrained by lack of funds. NCTR recently decided to consider establishing a formal neurotoxicology unit.

Agency for Toxic Substances and Disease Registry

The Agency for Toxic Substances and Disease Registry (ATSDR) is responsible under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA, or Superfund) and the Superfund Amendments and Reauthorization Act of 1986 to carry out applied research on health effects of exposure to hazardous substances.

Hazardous waste sites contain solvents, pesticides, and metals, all of which are known to be neurotoxic. These chemicals have been released from waste sites into the air, soil, and water however, it is not known what neurotoxic effects, if any, will be caused by long-term exposure to these chemicals in the environment. The neurotoxic effects on sensitive and vulnerable populations, for example, pregnant women, young children, and the elderly, are also not understood.

ATSDR is required by statute to compile a list of the 200 most toxic substances found at Superfund sites. This list contains hazardous substances known to cause neurotoxic effects (e.g., toluene and others). ATSDR is also required to fill in any significant gaps in data on adverse health effects associated with exposure to these chemicals. For many of these chemicals, little is known about their neurotoxic

effects. ATSDR is collecting information on the neurotoxicity of these substances for dissemination to the public (4).

Another way that citizens may come into contact with solvents, pesticides, and metals is when one or more of these chemicals is spilled during transport. The acute and chronic neurotoxic effects in rescue workers and others who respond to spills and in citizens who do not have the time, knowledge, or ability to evacuate an area are not known. These situations can be serious because frequently there is a large concentration of the chemical in one location, the incident occurs suddenly, and the populations exposed may not know how to minimize adverse effects (4). Although ATSDR does not conduct or sponsor laboratory research in this area, it recently supported the National Academy of Sciences study *neurotoxicology and Models for Assessing Risk,* and was a cosponsor of the Third International Symposium on Neurobehavioral Methods in Occupational and Environmental Health.

National Institute for Occupational Safety and Health

NIOSH has identified neurotoxic disorders as one of the 10 leading occupational problems in the United States. NIOSH funds intramural and extramural activities designed to implement a program to identify, characterize, and control exposure to neurotoxic agents.

Intramural activities include an extensive surveillance program directed toward identification of a wide range of possible endpoints that may include, but are not restricted to or focused exclusively on, neurotoxic agents. These activities include the development of a database describing exposures from an extensive sampling of workplaces throughout the Nation, in order to identify patterns of use of known neurotoxicants, and a health hazard evaluation program that responds to requests for workplace assessments throughout the Nation (and which has identified cases of neurotoxic exposure in the past).

The identification and characterization of neurotoxic agents are conducted through both the intramural and extramural programs. Current intramural research includes the evaluation of possible long-latency effects of chronic exposure to ethylene and propylene oxide in primates and the effects of acute exposures to aliphatic carbons on motor activity and physiology of rodents. A human study is also being designed to evaluate the impact of exercise on exposure to combinations of chemicals. Effects of exposure will be assessed by means of behavioral measures and will be correlated with pharmacological information. A study of workers exposed to pesticides is in the early stages of development.

The primary thrust of NIOSH's intramural program is methods assessment. The Institute is participating in the National Health and Nutrition Survey, in which approximately 6,000 people from around the Nation will be given three tests from the Neurobehavioral Evaluation System (NES) in order to develop baseline data for future evaluations of exposure to neurotoxic chemicals. Similarly, NIOSH is one of three organizations conducting the international, cross-cultural assessment of the Neurobehavioral Core Test Battery (NCTB) recommended by the World Health Organization. The NCTB assessment has been conducted jointly with an evaluation of the NES. In this study, people in different age ranges were administered both batteries, thus providing information on the effects of participant age and means of administration. The NES is administered by a computer, and the NCTB is administered by a psychologist or other suitably trained professional (6).

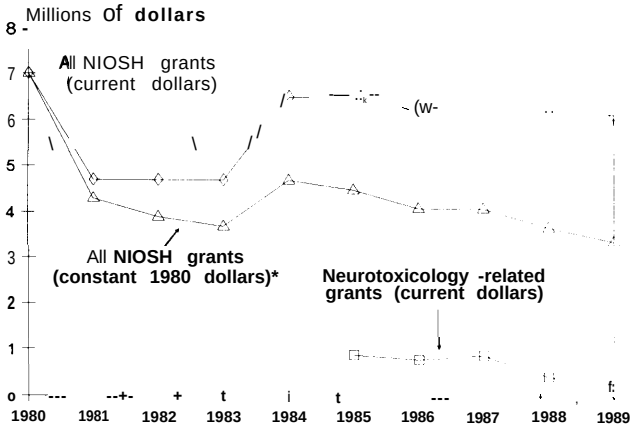
Funding for that portion of the intramural program directed exclusively at assessing neurotoxic disorders includes nine full-time-equivalent staff (including four persons with Ph.D.s) and $90,000 for the four projects currently funded.

Funding for neurotoxicology-related grants makes up a small portion of the total NIOSH extramural budget. In 1989, that total was $6.1 million, with $0.2 million (6), or less than 4 percent, devoted to neurotoxicology -related research. Since 1985, funding for neurotoxicology -related grants has declined, reflecting in part a decline in NIOSH's total extramural grants budget (figure 4-2). The current NIOSH budget has approximately half the buying power it did in 1980, due to inflation and budget cuts (47). NIOSH extramural grant programs are clearly weak in the neurotoxicology area.

Center for Environmental Health

Toxicology research at the Center for Environmental Health (CEH) in Atlanta, Georgia, is conducted under two divisions. The Division of Environmental Hazards and Health Effects is responsible for design, implementation, and analysis of expo-

Figure 4-2—Funding for NIOSH Research Grants



'Based on the Biomedical Research and Development Price Index
SOURCE: Office of Technology Assessment, 1990.

sure assessments and epidemiological studies. The Division of Environmental Health Laboratory Services develops and standardizes laboratory methods.

CEH is designing sensitive laboratory tests to assess the impact of toxic chemicals on public health. A major objective of its program is to develop tests that will enable investigators to evaluate toxic substances under a variety of biological conditions. Another major objective is to conduct tests at sites of environmental hazards to determine the threat to human health.

CEH conducts epidemiological investigations of human exposure to environmental hazards, including man-made and naturally occurring toxic substances, and determines the health effects resulting from exposure. It also provides emergency response to environmental disasters.

Department of Defense

The Department of Defense conducts and supports research related to neurotoxicity, much of which is relevant to the toxicity of chemical warfare agents. Defense-related neurotoxicology research programs were not evaluated by OTA for this report.

Department of Energy

The Department of Energy (DOE) supported only two research projects related to neurotoxicology through grants to public institutions in fiscal year 1988. Total funding of these projects was $487,000 (46). The first project examined the effects of environmental agents (as well as endogenous hormones and neurotransmitters) on cultured brain cells, A major goal of the project was to analyze the sensitivity of three major types of brain cells to environmental agents and to identify chemicals that influence the survival, proliferation, and differentiation of these cells.

The second project focused on the biological effects of magnetic fields. This type of non-ionizing radiation emanates from magnetic resonance imaging devices used in medicine and to a lesser extent from high-voltage power lines. There is considerable debate as to whether magnetic fields in the vicinity of high-voltage power lines adversely affect the nervous system. In this project, researchers have used several techniques to examine a series of physiological parameters, including possible effects on vision and other nervous system functions.

The Department of Energy Organization Act of 1977 mandates that DOE carry out the planning, coordination, support, and management of a balanced and comprehensive energy research and development program. The Act requires that DOE advance the goals of restoring, protecting, and enhancing environmental quality and assuring public health and safety (Public Law *93-577*, Title 42).

For several years, DOE supported applied research on the neurotoxicological and behavioral effects of chemicals. Recently, however, it changed the focus of some of its research programs from energy-related issues to fundamental biological questions, for example, sequencing the human genome. This shift in direction appears to have led to reductions in applied toxicological research, including work in the neurobehavioral field.

DOE research programs are currently not adequately addressing neurotoxicological concerns. DOE could be conducting neurotoxicological research into the health effects of energy-related processes and products including lead and lead substitutes in gasoline, methanol, and other fuels, and heavy metals used in nuclear and nonnuclear processes. It could be examining the effects of combustion products on the nervous system, and it could be working with Federal agencies and other public and private organizations to develop new and better toxicological tests to evaluate these effects.

Department of Agriculture

The U.S. Department of Agriculture (USDA) supports a small number of extramural research projects related to neurotoxicology. These projects are administered through the Cooperative State Research Service and fall into four major categories:

1. USDA competitive research grants,
2. special grants to State Agricultural Experiment Station scientists,
3. animal health funds, and
4. Hatch Act funds (34).

In fiscal year 1988, USDA supported 25 research projects related to neurotoxicology, nearly all of them involving insecticides and their metabolizes. Total funding for these projects was $422,000. Most of the research was supported by Hatch Act funds; the remainder was supported by special grants, animal health funds, and competitive grants. USDA research efforts span a wide range of objectives, from molecular biology and biochemistry, to structure-activity relationships, monitoring of agriculture workers, and the development of poisoning antidotes (21,33).

National Aeronautics and Space Administration

Toxicology research within the National Aeronautics and Space Administration (NASA) is conducted in the Biomedical Laboratories at the Johnson Space Flight Center in Houston, Texas. Space flight involves prolonged confinement in an artificial atmosphere with an array of equipment and materials. The Biomedical Laboratories evaluate spacecraft equipment and materials to ensure that flight crews are not exposed to harmful levels of toxic substances.

In the last several years, NASA has evaluated the neurobehavioral effects of many potentially toxic substances, including polyurethane thermal decomposition products, bromothifluoromethane, and various fire-extinguishing agents. In 1988, NASA completed a study of continuous low-dose exposure to Halon 1301, the active component in fire extinguishers in the space shuttle cabin.

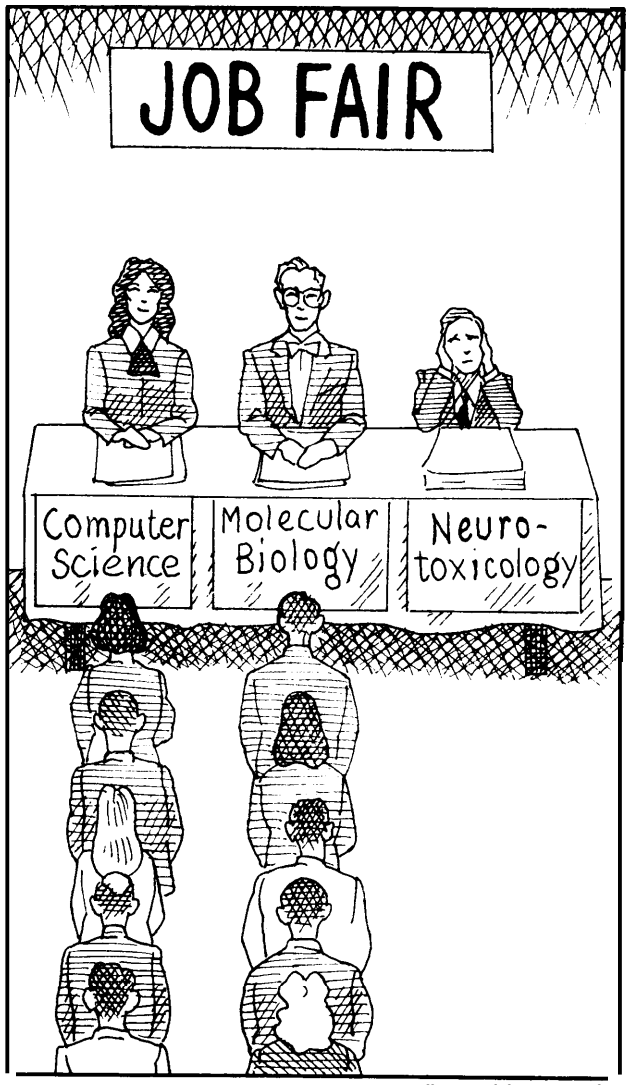
NASA has established maximum allowable concentrations (MACs) of atmospheric contaminants in manned spacecraft for missions of up to 7 days. These criteria are used in the development of all materials that will be used in space vehicles to ensure a nontoxic cabin atmosphere. In 1981, MACs were established or revised for some 200 chemicals that might be used in spacecraft.

ACADEMIC RESEARCH ACTIVITIES

Research interest in the neuroscience has increased rapidly in the last decade, as evidenced by growth in the membership of the Society for Neuroscience. The neurobehavioral sciences have made major advances in recent years, and society can continue to expect new and important discoveries that will not only improve understanding of the brain and behavior, but also make substantial contributions to public health. In the last decade, neurobehavioral toxicology has become an increasingly active field. Scientific papers are published in an array of journals, including two specialty journals *(Neurotoxicology and Neurotoxicology and Teratology).* A neurotoxicology specialty section has been organized within the Society of Toxicology, and two small scientific societies have been formed, the Behavioral Toxicology Society and the Behavioral Teratology Society. Behavioral scientists and neuroscientist have been appointed to the editorial review boards of the journals of the Society of Toxicology and participate in the peer review process of the extramural grants programs sponsored by NIH, ADAMHA, and EPA (48). However, despite recent advances, U.S. neurotoxicology research programs are small relative to the threat neurotoxic substances pose to public health.

Factors Influencing Academic Research Directions

Neurotoxicology will continue to benefit from the rapid advances being made in understanding the structure and function of the nervous system. With the tools of modern molecular biology and pharmacology, investigators are mapping and redefining the brain itself. As researchers learn more about the brain and its molecular components, they gain insights into how chemicals can alter nervous system structure and function. The detailed study of simple neuronal systems in invertebrates or in tissue culture can aid in understanding the mechanisms by which chemicals exert their effects in mammals; such studies should assist in screening for neurotoxicity. Improved understanding of the behavioral determinants of chemical actions will assist in the construction of test systems that will facilitate both



Illustrated by: Ray Driver

the detection and characterization of toxic effects. Increased efforts in academia, as well as in industry and government, are necessary in order to move beyond basic research and to apply basic knowledge to the development and validation of neurotoxicity tests.

The challenge in the years ahead will be to foster basic research and to persuade investigators and students that the field of neurotoxicology offers substantial opportunities for increasing our understanding of the structure and function of the nervous system. The neuroscience could provide novel and beneficial approaches to many important occupational and environmental health problems. These include identifying subtle neurological and psychiatric disorders occurring in exposed populations; exploring why some individuals appear to be particularly sensitive to chemicals; and developing preparations targeted at health problems associated with single chemicals, industries, occupations, modes of transportation, sources of energy, urban environments, and dietary habits. If occupational and environmental chemicals do play a key role in causing neurodegenerative disorders, for example, Parkinson's disease and Alzheimer's disease, prevention becomes an important goal.

The contributions of colleges, universities, and research institutes to neurotoxicology depend on continued grant support for research and graduate education. Neurotoxicology research and training take place in many university and medical center contexts, for example, departments of pharmacology, toxicology, pathology, psychology, neurology, psychiatry, anatomy, obstetrics and gynecology, ophthalmology, pediatrics, epidemiology, and occupational, environmental, preventive, and community medicine. There are only a few laboratories or institutes around the country that focus on neurotoxicology. There are no broadly based centers or departments of neurotoxicology. Thus, there are few environments in academia where neurotoxicology or behavioral toxicology is a major focus. As in any academic research environment, the spatial, financial, and personnel resources available, as well as the professional advancement and remuneration of the investigator, depend on the perceived merits of the research and on the interest and goodwill of the researcher's colleagues (48).

What leads an investigator to study a particular neurotoxic substance? In many cases, a chemical is of interest not because of its impact on human health, but because of its usefulness as a tool to study nervous system structure or function. Such studies provide necessary information about the substrates on which chemicals exert their effects and the mechanisms by which the effects occur. Knowing the mechanism of action of a toxic substance not only advances our knowledge, but aids in predicting what other chemicals will have similar effects. In other cases, a neurotoxic substance is selected for study because it has produced human injuries that have been well described or, if the compound has injured only a few people, because the injuries produced a severe impairment, repeatable in animals, that is of interest to the investigator, a funding agency, or public interest organization. There is also academic interest in understanding the possible role

of toxic chemicals in triggering neurodegenerative diseases.

Universities see basic research as one of their principal missions; routine toxicity evaluations are not usually considered to be an appropriate use of university resources or faculty time. There is little interest in studying either proprietary products or chemicals about which little or nothing is known unless the study offers insight into the mechanisms by which related chemicals exert known effects.

Funding pressures play a substantial role in an investigator's choice of research project. Two factors are at work: 1) the difficulty of finding a sponsoring agency, and 2) the short duration of typical grant awards. Neurotoxicology, like other emerging areas of toxicology, is a discipline that generates relatively small numbers of grant applications. Consequently, for the most part, there are no initial review groups, that is, expert committees appointed by Federal agencies to review the merits of neurotoxicology grant proposals. A study section charged with reviewing occupational or environmental health problems may understand the consequences of human exposure to a compound but not be able to review adequately the scientific methods of a research proposal or to balance its merit and relevance against those of other studies. If the proposal is forwarded to a study section that is competent to review the techniques involved, it may still face difficulties. A proposal deemed an appropriate application of existing techniques to an "applied" problem would not fare well in competition with a proposal that advances "basic" knowledge. One funding strategy that has been productive is to integrate neurotoxicity studies with a larger, multidisciplinary center or program project. In general, the success of any grant application depends largely on both accurate identification of the funding agency and specific tailoring of the proposal to the initial review group (48).

Funding usually extends for 3 to 5 years and takes the form of an individual grantor a multidisciplinary program project or center grant. Progress, as measured by publications, is necessary to maintain a research career. In order to achieve results rapidly, investigators are frequently drawn to compounds that produce easily recognized and reproducible effects after exposing animals for brief periods. Experiments involving agents that require inhalation exposure or chronic administration are more costly and require more effort, hence the number of journal articles produced at the end of the project is correspondingly reduced.

Cooperative Agreements Between Government and Academia

Government agencies sometimes channel intramural funds to 'investigators in universities or research institutes. These negotiated agreements tend to focus on projects of mutual interest and usually address specific problems. They have the advantage of permitting questions to be examined more rapidly and at less expense than would be possible intramurally. As a means of supporting extramural research programs, however, they have drawbacks: they often do not benefit from the intense scrutiny of the peer review process, and they tend to devalue research that does not produce data and conclusions in the short term. In times of tight budgets, this pattern of funding is the frost to be cut, because it is usually derived from the resources available to support intramural programs.

INDUSTRIAL RESEARCH ACTIVITIES

Industrial research falls into several categories and is funded by several mechanisms:

1. internal basic and applied research,
2. research conducted in contract laboratories,
3. research conducted through consortia,
4. contract research through universities, and
5. research grants for universities.

Toxicity evaluations conducted as part of internal applied research are necessary to develop safe and effective products, to protect employees, to protect the environment, and to control cost liability. Research programs vary considerably, depending on the types of products manufactured and economic considerations.

Pesticide Industry

The search for new pesticides begins with screening tests, which are designed to provoke a particular biological response. The toxicity profiles developed from screening tests may be considered to be proprietary information, because disclosure of them could give the competition information useful for product development. There are, however, methods

of giving outside experts data without compromising trade secrets.

Industry is willing to perform tests to obtain or maintain product registration, but it is cautious about devoting funds to the development of test protocols that might not satisfy regulatory authorities. Government and academic scientists may suggest testing strategies that they judge to be appropriate but may find it difficult to defend a specific testing scheme if there is an inadequate history of testing for the class of compounds in question or the extent of the public health hazard and possible economic impacts on society are difficult to predict (48).

Pharmaceutical Industry

Drug development begins with screening and development of structure-activity relationships. Acute and subchronic toxicity information emerges early in the process, but characterization of chronic toxicity usually develops more slowly. The quest for biological activity has produced some compounds that reach the market, but most are important research tools for the neuroscience and have no clinical utility or are too toxic to be used clinically.

Pharmaceutical industry research on toxic substances is directed largely toward therapy for central nervous system impairments and the development of animal models for screening drugs to ameliorate the signs and symptoms of nervous system damage. Examples of such injuries include oxygen starvation, MPTP-induced Parkinsonism, seizures induced by convulsant drugs, and brain injuries produced by excitotoxins (chemicals that produce so much activity in localized areas of the brain that the cells there die). The pharmaceutical industry also evaluates compounds in behaviorally normal animals and in the offspring of mothers exposed to toxic substances. It has promoted the development of a variety of neurotoxicity tests. The research contributions of the pharmaceutical industry emerge as a product nears approval. However, as is true in other sectors, much information generated by industry is never made public, even though it may be important in other contexts (48).

Consumer Product Industry

Information about the toxicity of consumer products typically emerges from premarket testing, human exposures, accidental ingestions by consumers, or in response to regulatory demand. Manufacturers of consumer products frequently maintain vigorous product development research teams. Their work sometimes produces serendipitous findings of wider interest, but it seldom sheds light on the possible neurotoxicity of their products.

Little information on the neurotoxicity of consumer products has been generated as a result of these recommendations. The laws administered by the Consumer Product Safety Commission (CPSC) permit the agency to require some toxicity evaluations as part of compliance with labeling and packaging regulations (15 U.S.C. 1261—Federal Hazardous Substances Act). For several years CPSC has encouraged regulated groups to develop voluntary standards. One such group is the art supplies industry, which developed recommendations for minimizing injuries through product labeling. (Some materials used by artists have neurotoxic potential.) Labeling standards may, in turn, prompt manufacturers to reformulate products in order to minimize toxicity and the need for warnings at the point of purchase. These recommendations were recently given the force of law in the Art Materials Labeling Act (Public Law 100-695).

Specialty and Commodity Chemical Industries

Chemical companies have a mixed record with respect to minimizing the adverse effects of chemicals on the health of their workers. Like other industries, however, they have no interest in marketing chemical products that may become substantial liabilities. Some companies rely on developing information of such high quality that it defines the state of the science—this is no doubt the best defense of a successful and prestigious corporation. To achieve this end, good scientists must be recruited and maintained as vigorous members of a corporate team. A good example is the publication by scientists at one major U.S. corporation of a series of high-quality papers describing the role of diketones in causing peripheral neuropathy (20). Unfortunately, less well capitalized companies cannot afford to invest in research of this kind, instead testing solely to comply with regulatory requirements. Commodity chemicals are produced by a number of different companies, so it is generally not in the interest of any one company to assume responsibility for evaluating the adverse health effects of a particular substance. The companies that manufacture and distribute such chemicals could be compelled to address the chemical's toxicity under

TSCA, or they could avoid such regulation by supporting a testing program under the auspices of a trade association.

INTERACTIONS AMONG GOVERNMENT, ACADEMIA, AND INDUSTRY

Industry and Government Consortia

Industry and government consortia devoted to environmental health are rare. One such consortium is the Health Effects Institute (HEI), an independent, nonprofit corporation ''organized and operated to study the health effects of emissions from motor vehicles . . .' (18). HEI serves as a potential model for other consortia. The institute makes no regulatory or social policy recommendations; its goal is "simply to gain acceptance by all parties of the data that may be. necessary for future regulations" (34). It has joined together the regulator and the regulated industry in mutual support of research activities targeted at joint concerns, and it does so by deriving funding jointly from EPA and the automobile industry.

The institute has recognized the importance of the effects of automobile emissions on the nervous system and on the quality of life in general. It has conducted a review of the topic (48) and has solicited research proposals in this area, The HEI model is a promising one for circumstances in which health concerns are generic and in which proprietary and competitive interests do not interfere with industry's participation.

Industry Research Consortia

The Chemical Industry Institute of Toxicology (CIIT) is a research institute funded by a consortium of chemical companies to study commodity chemicals of concern to members. CIIT has achieved a reputation for conducting excellent toxicological research targeted at a broad range of problems and has generated considerable goodwill in the process. Interest in neurotoxicity issues has recently been evidenced in the publications of the institute. However, in the absence of a significant new initiative, the contributions of this organization to knowledge of neurobehavioral effects may be limited.

CIIT could serve as a model for other industries with common interests, particularly industries meeting similar regulatory challenges. The pesticide industry as a group makes proprietary products, and it is unlikely that a group of competitors would be willing to share the cost of generating information about a single member's profit-making product. The companies are bound together by a common desire to be regulated appropriately and efficiently, however, and they could benefit from a joint research program that would help advance the state of the art in toxicology and risk assessment. This would include advances in the development of in vitro testing, the extrapolation of data from rodents to primates, the validation of screening approaches tailored to the needs of the pesticide industry, and the detailed characterization of identified toxicities and their mechanisms of actions, an important contribution to the risk assessment process.

Other industries with profitable products are challenged periodically by a rule-making activity or judicial finding requiring them to provide toxicity information. Such organizations might find it in their interest also to be part of a larger, standing organization with a governance structure that ensures that its research and testing of products are of the highest quality.

Cooperation in Epidemiological Investigations

Since individuals working in the chemical industry almost invariably experience higher levels of exposure to chemicals than do other groups in society, they are at greater risk of suffering the adverse effects of exposure to toxic substances. Thus, workers also serve as a sentinel population for the detection of neurotoxic disorders that occur in the general population. Often, workers are the first to identify adverse effects and bring them to the attention of their doctors. Epidemiological studies can be initiated by a number of organizations, but they are most often conducted by the CDC, ATSDR, and State health authorities. CERCLA and TSCA require manufacturers to collect and keep information regarding exposure and effects on health. Unions can play an important role in obtaining cooperation and in ensuring compliance with these efforts.

Unions can also help stimulate research activities pertinent to the health of their members. The United Auto Workers recently established jointly administered research programs with Ford, General Motors, and Chrysler in which studies of neurobehavioral

toxicity were identified as a priority. The funding was directed predominantly at human studies (26,49).

Charitable Organizations

The Third World Medical Research Foundation is a small, U.S.-based, nonprofit organization that encourages university and other biomedical scientists worldwide to find innovative solutions to toxic, nutritional, and other disorders of importance to developing countries. Working with university and NIH scientists, it was able to demonstrate the association of African cases of spasticity with infection by the HTLV-1 virus and to disprove a proposed causal association with methylmercury. More recently, it has focused on promoting the development of non-neurotoxic strains of the grass pea to prevent the spastic disease lathyrism and to generate safe, drought-resistant food and animal feed for drought-stricken areas of Africa and Asia.

EDUCATION

Education of Research Scientists

A significant portion of current knowledge about the effects of neurotoxic substances comes from basic research and the application of that research to environmental health problems. Yet many observers believe that there are too few scientists adequately trained in both neuroscience and toxicology. As discussed earlier in this chapter, research training exists in a variety of universities and medical centers, but there are few places in academia where neurotoxicology is a major focus.

The National Institute of Environmental Health Sciences awards grants to educational institutions for the training of environmental toxicologists. These grants support approximately 200 doctoral students in 24 universities. Only about half the schools offer intensive training in any aspect of neurotoxicology. Few institutions have comprehensive academic programs with adequate faculties to undertake a substantial research program. Since it takes about 5 years for a graduate student to earn a doctorate, fewer than 40 students supported by these training grants finish their degrees each year. Only some 10 to 15 students graduate from strong programs in neurotoxicology in the United States each year. While this does not mean that positions demanding an education in neurotoxicology will necessarily go unfilled—there are many other, usually small, programs that award the doctorate but do not have training grants-it does mean that the primary Federal program targeted to the Nation's manpower needs in toxicology can make only a small contribution in the area of neurotoxicology (23).

The NIEHS institutional training grants also support about 80 postdoctoral trainees, and another 5 students receive fellowships directly though individual training grants. Of course, many of these trainees come from predoctoral training programs in toxicology and thus represent no net gain in numbers. Since postdoctoral training takes a minimum of 2 years and only a fraction of the trainees stay in the field of neurotoxicology, this source yields only a small number of fully trained neurotoxicologists per year (23).

The American Board of Toxicology (ABT) certifies professionals in general toxicology. The certification examination includes neurotoxicology and clinical toxicology. More than 90 percent of the ABT-certified toxicologists possess a doctorate and have more than 3 years of professional experience. Questions about neurotoxicology and clinical toxicology are a routine part of the examination, including questions on the neurotoxicity of pesticides, the behavioral effects of metals, and neurotoxic drugs. Certification is for 5 years, and recertification includes continuing education and practice in toxicology (5).

Education of Health-Care Professionals

Much of the illness resulting from exposure to neurotoxic substances occurs among workers. Often, neurotoxic chemicals are first identified because of the occupational illness they have caused. Increased research and testing are needed so that harmful chemicals can be identified and worker exposure limited. Prevention of occupational illness is a challenging undertaking and involves identifying hazards, controlling hazards at the source, monitoring workers, and educating, training, and disseminating information to all persons involved. These topics have been addressed in a previous OTA report (45) and will not be covered in detail in this section. Instead, this discussion will be limited to the potential role that better education of health-care professionals might play.

Physicians, nurses, and industrial hygienists deliver most health care to workers who have been exposed to toxic substances in the workplace. The

number of professionals trained in the area of occupational health is not adequate to meet public health needs in the United States.

Physicians

A large percentage of physicians who provide occupational health services are employed by industry, yet many workers have no source of occupational health services and must rely on their family physicians. Family physicians are rarely trained in occupational medicine and thus are less likely to obtain histories of occupational exposure.

General training in occupational medicine during medical school is not extensive. Two surveys of medical schools, one conducted in 1977-78 (24) and the other in 1982-83 (25), found that the proportion of medical schools offering courses in occupational health in the preclinical years increased from 50 percent at the time of the first survey to 66 percent at the time of the second. The proportion of schools requiring that students take such courses increased from 30 percent to 54 percent. However, in those schools that required coursework in occupational health, there was a median curriculum time of only 4 hours over 4 years. A survey conducted by the Association of American Medical Colleges found that 70 percent of medical schools offer clinical electives in occupational medicine or environmental health. However, of the students responding to the survey (65 percent), only 1 percent actually took the offered elective (42).

Residency programs in primary care specialties—namely, family and general practice, pediatrics, internal medicine, obstetrics and gynecology, and psychiatry-rarely include training in occupational medicine. However, organizations such as the American College of Occupational Medicine, whose members are board-certified in occupational medicine, sponsor conferences and seminars to educate primary care and other physicians about occupational health issues (19).

Occupational medicine is one of the areas in which physicians specializing in preventive medicine can choose to be certified. The Institute of Medicine recently emphasized the need for a greater number of physicians specializing in occupational medicine. In 1987, there were 25 residency programs with 118 residents (0.1 percent of the total number of residents that year) (7). Between 1955 and April 1989, the American Board of Preventive Medicine certified 1,378 physicians in occupational medicine. The number of those physicians no longer practicing is not known (17). The requirements for board certification include 1 year of postgraduate training in preventive medicine; 1 year of residency in occupational health; 1 year of training, research, teaching, or practice of occupational medicine; and the completion of a master's degree in public health. The requirements are somewhat different for physicians who graduated from medical school before January 1984 (40).

Some effort to encourage medical students to enter the field of occupational medicine is being made. The American College of Occupational Medicine has a scholarship fund for medical students and residents interested in occupational medicine (41). Also, there is a mechanism under current law by which Congress could encourage the training of physicians in occupational health. Public Law 100-607 (sec. 613) states that:

> The Secretary [of the Department of Health and Human Services] may make grants to and enter into contracts with schools of medicine, osteopathy, and public health to meet the costs of projects (A) to plan and develop new residency training programs and to maintain or improve existing residency training programs in preventive medicine; and (B) to provide financial assistance to residency trainees enrolled in such programs.

Advocates of expanded training programs in occupational medicine note that the current language in the law says "may" and that changing the wording to "shall" would strengthen the law.

Nurses

Nurses provide a crucial aspect of care for workers exposed to toxic substances in the workplace. Indeed, they constitute the largest group of health professionals in the workplace-approximately 24,000 in 1980 (10). Occupational health nursing synthesizes principles from several disciplines in the health sciences, including, but not limited to, nursing, medicine, safety, industrial hygiene, toxicology, administration, and public health epidemiology. Activities focus on promotion, protection, maintenance, and restoration of health. The occupational health nurse is primarily concerned with the preventive approach to health care, which includes early detection of disease, health teaching, and counseling (2).

The American Board of Occupational Health Nurses is the only board that certifies nurses in occupational health. It has certified over 45,000 nurses since 1973 and estimates that 2,800 of them are still practicing (36). Certification requires a passing score on a national examination. Eligibility for the examination entails 5 years of experience in the specialty and a satisfactory record of formal and continuing education in designated subjects (3).

University-based baccalaureate programs in nursing provide courses and clinical experience in community and public health nursing and adult health that are basic to the practice of occupational health nursing. Specialty education in occupational health at the master's degree level is offered in several schools of nursing and public health. Although programs differ in their course requirements, most include adult health, elements of workplace exposures, epidemiology, toxicology, biostatistics, and opportunities for field work. Some programs provide education in neurotoxicology through courses, clinical experiences, and reviews of research (l). Doctoral-level education for nurses in occupational health has been offered for the past 10 years, and graduates are employed in the private sector as well as by governmental agencies and universities.

Federally supported programs for occupational health nurses have provided significant resources and continue to encourage training in this field. Since 1977, graduate-level academic programs have been funded as one component of the interdisciplinary Educational Resource Centers. These regional centers were developed under the Occupational Safety and Health Act of 1970 in response to the need for an adequate supply of trained professionals in occupational health (l).

The American Association of Occupational Health Nurses is the professional organization that represents registered nurses engaged in that specialty as practitioners, managers, consultants, and educators. The association develops standards of practice, monitors legislation related to occupational and environmental health, sponsors continuing education, and publishes a journal (l).

Industrial Hygienists

The role of the industrial hygienist is to recognize and reduce occupational health hazards in the workplace. Industrial hygienists thus attempt to anticipate, recognize, evaluate, and control those environmental factors or stresses stemming from the workplace that cause sickness, discomfort, or inefficiency among workers or members of the community (31). Industrial hygienists examine the overall safety of the working environment and recommend plant improvements. Part of their duty is to collect samples of dust, gases, liquids, vapors, and raw materials and determine the extent of worker exposure. For example, an industrial hygienist might sample the air inhaled by an employee working with organic solvents throughout an 8-hour shift (many organic solvents have potential or known neurotoxic properties, see ch. 10).

Most industrial hygienists have a bachelor's degree in engineering, physical science, biological science, or natural science, and some also obtain a master's degree in industrial hygiene. There are two levels of industrial hygienists, certified and uncertified. To become certified, one must complete a baccalaureate degree in the sciences or engineering, have 5 years of practical industrial hygiene experience, and pass a 2-day written examination given by the American Board of Industrial Hygiene. Hygienists may seek certification in the general field of industrial hygiene, or they may specialize in a number of areas, one of which is toxicology. Currently, there are approximately 4,000 certified industrial hygienists in the United States (35). Those hygienists who are uncertified rely on their skills, training, and experience but are not required to meet any minimum standards established by a governmental or professional organization (22).

The American Industrial Hygiene Association is a nonprofit professional society for persons practicing industrial hygiene in industry, government, labor, academic institutions, and independent organizations. The association, composed of some 7,400 members, publishes a journal and sponsors continuing education courses in industrial hygiene (15).

NIOSH Educational Resource Centers

Many of the professional organizations for toxicology, occupational medicine, occupational nursing, and occupational hygiene offer conferences and seminars as continuing education. The Federal Government also plays a role, through NIOSH's Educational Resource Centers, mentioned earlier. There are 14 centers located within universities throughout the United States. The centers conduct both ongoing research projects and programs offering academic degrees and continuing education. The

four main areas on which they focus are industrial hygiene, occupational medicine, occupational health nursing, and occupational safety. Courses are offered in toxicology and to a limited extent in neurotoxicology (1,47).

NIOSH also offers some in-house courses. None of these focuses on toxicology or neurotoxicology specifically, but some address the broader issues of occupational health and industrial hygiene.

SUMMARY AND CONCLUSIONS

Federal research related to neurotoxic substances is conducted primarily at the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration; and the Environmental Protection Agency. Limited research programs are under way at the Food and Drug Administration, the Centers for Disease Control, the Department of Defense, the Department of Energy, the Department of Veterans' Affairs, the Department of Agriculture, and the National Aeronautics and Space Administration. Total Federal funding for neurotoxicology -related research (excluding research related to alcoholism and cigarette smoking) is $56.8 million. The bulk of this funding (85.2 percent) is through NIH and ADAMHA and tends to focus on the toxicity of drugs and the biochemical mechanisms underlying neurological and psychiatric disorders. A number of other Federal agencies and organizations provide limited funding for neurotoxicological research.

Research related to environmental neurotoxicology is confined primarily to the intramural program at EPA and the extramural program at the National Institute of Environmental Health Sciences within NIH.

The extent of academic research related to neurotoxicology is strongly dependent on the availability of grant support from the Federal Government. Academic research in neurotoxicology is supported almost exclusively by NIH and ADAMHA. Most extramural research funded by NIH is through the National Institute of Neurological Disorders and Stroke and the National Institute of Environmental Health Sciences, although several other Institutes have substantial programs. ADAMHA funds research through the National Institute on Drug Abuse and the National Institute of Mental Health.

EPA has a relatively large intramural neurotoxicology research program that has been limited in recent years by lack of funding for supplies and equipment. EPA has a small extramural grants program that has rarely funded neurotoxicology-related projects. Traditionally, Federal agencies have supported both intramural and extramural efforts to ensure a balanced, comprehensive, and cost-effective program.

FDA funds several research projects related to neurotoxicology, primarily through its intramural research programs. The National Center for Toxicological Research is conducting a number of intramura1 research projects related primarily to developmental neurotoxicology. The Center for Food Safety and Applied Nutrition has a small in-house program and is supporting three extramural research projects.

Within CDC, the National Institute for Occupational Safety and Health has small intramural and extramural programs devoted to the identification and control of neurotoxic substances in the workplace. CDC's Center for Environmental Health and Injury Control conducts epidemiological investigations of human exposure to environmental hazards.

Industry undertakes neurotoxicology-related research through several mechanisms, including in-house scientists, contract laboratories, consortia, contracts with universities, and grants to universities. Toxicity evaluations conducted as part of internal applied research are necessary to develop safe and effective products, to protect employees, to protect the environment, and to control liability costs. Research programs vary considerably, depending on the types of products manufactured and various economic considerations. Industry and government consortia, such as the Health Effects Institute, which studies the health effects of emissions from motor vehicles, are useful in bringing the regulated and the regulator together to support research projects of mutual interest.

The education of research scientists in neurotoxicology is limited, in part, by inadequate Federal support for training programs. Part of the difficulty in obtaining funding is due to the nature of neurotoxicology—the intersection of neuroscience and toxicology. Few academic departments devote significant resources to neurotoxicology, and few major Federal organizations devote their primary efforts to it. The National Institute of Environmental Health Sciences supports training in the neurotoxicology

field; however, funding limitations allow for support of only a relatively small number of trainees.

Millions of American workers are exposed to neurotoxic substances in the workplace, but illness stemming from these exposures often goes undetected and untreated. The subtlety of neurotoxic responses is one reason for this situation; for example, complaints of headache and nervousness are often ascribed to other causes. Another reason is the lack of adequately trained health-care professionals to diagnose and treat neurotoxic disorders. Medical schools, in general, devote little of their curricula to occupational health issues. After medical school, physicians may undertake residency training in occupational medicine, but in 1987 only about 1 in every 1,000 residents was specializing in occupational medicine. Nurses are also needed in the occupational health field to provide emergency services, monitor employee health, and provide counseling and referral to physicians. Industrial hygienists are needed to evaluate and control health hazards in the workplace.

CHAPTER 4 REFERENCES

1. Agnew, J., Johns Hopkins University, personal communication, June 21, 1989.
2. American Association of Occupational Health Nurses, "Standards of Practice, " *American Association of Occupational Health* Nurses Journal 36:162-165, 1988.
3. American Board of Occupational Health Nurses, *Certification Program* (Santa Monica, CA: 1988).
4. Andrews, J. S., Agency for Toxic Substances and Disease Registry, personal communication, 1989.
5. Bean, J. R., U.S. Department of Energy, personal communication, 1989.
6. Biersner, R., National Institute for Occupational Safety and Health, personal communication, 1989.
7. Crowley, A. E., and Etzel, S.1., "Graduate Medical Education in the United States, " *Journal of the American Medical Association 260: 1093-1101,1988.*
8. de Souza, E.R., Addiction Research Center, National Institute on Drug Abuse, personal communication, 1989.
9. Dyer, R., U.S. Environmental Protection Agency, personal communication, 1988.
10. Ebert, F., "The Occupational Health Nurse," *Occupational Medicine: Principles and Practical Applications,* LaZenz (cd.) (Chicago, IL: Year Book Medical Publishers, 1988).
11. Erinoff, L., National Institute on Drug Abuse, personal communication, June 1989.
12. Evans, H. L., Institute of Environmental Medicine, New York University, personal communication, July 1989.
13. Evans, H. L., "Behaviors in the Home Cage Reveal Toxicity: Recent Findings and Proposals for the Future," *Journal of the American College of Toxicology* 8:35-51, *1989.*
14. Gause, E., Alcohol, Drug Abuse, and Mental Health Administration, personal communication, Apr. 25, 1989.
15. Gerbec, L., Administrative Assistant for Member Services, American Industrial Hygiene Association, personal communication, Apr. 6, 1989.
16. Griesemer, R. A., National Institute of Environmental Health Sciences, personaI communication, June 8, 1989.
17. Griest, J., Administrative Assistant, American Board of Preventive Medicine, personal communication, Apr. 6, 1989.
18. Health Effects Institute, 2987 *Annual Report* (Camridge, MA: 1988).
19. Imbus, H. R., "Is Occupational Medicine a Specialty?" *American Journal of Industrial Medicine* 14:109-1 *16, 1988.*
20. Krasavage, W. J., O'Donoghue, J. L., DiVincenzo, G. D., et al., "The Relative Neurotoxicity of Methyl n-Butyl Ketone and Its Metabolizes, " *Toxicology and Applied Pharmacology* 52:433-441, *1980.*
21. Kunde, M. L., U.S. Department of Agriculture, personal communication, Sept. 14, 1989.
22. Landrigan, P. J., and Markowitz, S. B., *Occupational Disease in New York State: Proposal for a Statewide Network of Occupational Disease Diagnosis and Prevention Centers: Report to the New York State Legislature (New* York, NY: Department of Community Medicine, Mount Sinai School of Medicine of the City University of New York, 1987).
23. Laties, V., University of Rochester, School of Medicine, personal communication, 1989.
24. Levy, B. S., ''The Teaching of Occupational Health in American Medical Schools," *Journal of Medical Education* 55:18-22, *1980.*
25. Levy, B. S., ''The Teaching of Occupational Health in American Medical Schools: Five-Year Follow-Up of an Initial Survey," *American Journal of Public Health* 75:79-80, *1985.*
26. Mirer, F., United Auto Workers, personal communication, Jan. 10, 1990.
27. National Archives and Records Administration, Office of the Federal Register, *U.S. Government Manual 1988/89* (Washington, DC: U.S. Government Printing Office, 1988).
28. National Institute on Aging, Neuroscience and Neuropsychology of Aging Program, Aging and Neurotoxins, correspondence to OTA, June 1989.

29. National Institutes of Health, Associate Director for Science Policy and Legislation, correspondence to OTA, November 1989.
30. Nelson, N., Griesemer, R. A., and McMillan, D., letter to Lee M. Thomas, Adrninistrator, U.S. Environmental Protection Agency, Sept. 9, 1988.
31. Olishifski, J.B. (cd.), *Fundamentals of Industrial Hygiene* (Chicago, IL: National Safety Council, 1983).
32. Paule, M. G., National Center for Toxicological Research, personal communication, July 17, 1989.
33. Ragsdale, N.N., U.S. Department of Agriculture, personal communication, June 15, 1989.
34. Ruckelshaus, W. D., speech before the World Industry Conference on Environmental Management, Nov. 14, 1984.
35. Snow, B., Administrative Assistant, American Board of Industrial Hygiene, personal communication, May 1, 1989.
36. Snyder, M., Executive Director, American Board of Occupational Health Nurses, personal communication, Apr. 7, 1989.
37. Sobotka, T., U.S. Department of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, personal communication, Sept. 15, 1987.
38. Sobotka, T., U.S. Department of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, personal communication, Jan. 27, 1989,
39. Sobotka, T., U.S. Department of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition, personal communication, May 30, 1989.
40. "Special Report: Establishing Eligibility for Examination in the Specialty of Occupational Medicine, ' *Journal of Occupational Medicine* 28:303-305, *1986.*
41. Strasser, A. L., 'Occupational Medicine Matures into Diverse, Specialized Field," *Occupational Health and Safety Special, sec. 52,* April 1988.
42. Swanson, A., Association of American Medical Colleges, personal communication, Feb. 7, 1989.
43. Tilson, H. A., "Animal Neurobehavioral Test Battery Used in NTP Assessments," paper presented at the Third International Symposium on Neurobehavioral Methods in Occupational and Environmental Health, Washington, DC, Dec. 12-13, 1988.
44. U.S. Congress, House of Representatives, Committee on Appropriations, Subcornrnittee on the Departments of Labor, Health and Human Services, Education, and Related Agencies, *Appropriations for 1990,* hearings Mar. 21 through Apr. 3, 1989 (Washington, DC: U.S. Government Printing Office, 1989).
45. U.S. Congress, Office of Technology Assessment, *Preventing Illness and Injury in the Workplace, OTA-H-256* (Washington, DC: U.S. Government Printing Office, April 1985),
46. U.S. Department of Energy, Office of Energy Research, Office of Health and Environmental Research, correspondence to OTA, Nov. 29, 1988.
47. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, *Projects of the National Institute for Occupational Safety and Health* (Cincinnati, OH: 1988).
48. Wood, R., "Neurotoxicity Research-Current Activities and Future Directions, ' paper prepared for the Office of Technology Assessment, November 1988.
49. ''Worker Participation in Health and Safety: Lessons From Joint Programs of the American Automobile Industry," presentation to the American Industrial Hygiene Conference, San Francisco, CA, May 16, 1988.

Chapter 5

Testing and Monitoring

"Over the last 10 to 15 years, cancer had dominated the discussion of occupational standards and it continues to remain terribly important. At the same time, information on neurotoxins has increased. The notion of chronic and subclinical neurotoxicity has developed. Although these things are progressive and don't occur overnight, you'll see more attention paid to neurotoxicity in the years ahead. "

Philip Landrigan
Occupational Hazards 49:36, 1987

"The reasons for inadequate neurobehavioral testing of chemicals. . relate to economic factors and political decisions, not to inadequacies of the test methods. "

Donald McMillan
Occupational Hazards 49:37, 1987

''We need to know a lot more about how toxicity is expressed in behavior. We need to be able to recommend tests for chemicals before they move into the marketplace. This is why we need more of what NIOSH is doing. As it is, we are still using workers as part of an early-warning system. "

Ronald Wood
Psychology Today, July 1982, p. 30

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Chapter 5
Testing and Monitoring

INTRODUCTION

People are exposed to chemicals every day in the course of eating, working, and recreation. Some of these chemicals are synthetic; others, whose properties may be unknown, occur naturally in the environment and in food. Modern society could not exist without them. However, the same chemicals that contribute to our high standard of living may also produce unanticipated and undesired effects. Regulatory officials are concerned with weighing the benefits of use against the risks of adverse health effects.

All substances, even water, can be toxic at a high enough level of ingestion. Determining the risk posed to human health by toxic substances requires information about the potential hazard and about the expected level of exposure, resulting in an estimate of the probability that a substance will produce harm under certain conditions (see ch. 6) (105).

There are many approaches to testing for neurotoxicity, and each has both advantages and limitations. Toxic substances can be evaluated through whole animal (in vivo) tests, tissue and cell culture (in vitro) tests, and tests on human subjects. The latter is the best means of predicting the effects of potentially toxic substances on human health. This approach, however, is generally difficult, expensive, and in some circumstances unethical. Consequently, it is usually necessary to rely on animal or in vitro tests.

Most toxicity testing is performed on animals, usually mice and rats. Animals are used for several reasons, one of which is that, biologically, they resemble humans in many ways and can often serve as adequate models for toxicity studies. On the other hand, it can be difficult to extrapolate the results of animal studies to humans. It is also important to keep in mind that the biochemical and physiological processes underlying human neurological and psychiatric problems are highly complex and often cannot be modeled in any single system.

In vitro tests can be used to complement animal tests and reduce the number of animals used in routine toxicity testing. In vitro testing may also be less expensive and less time-consuming. By understanding the structure or function affected by a toxic substance in vitro, it is sometimes possible to predict adverse effects in the whole animal. Like all testing strategies, in vitro tests have limitations, including the inability to analyze behavioral effects such as loss of memory or irritability.

Some human toxicological data are derived from accidental exposures to industrial chemicals and some from epidemiological studies. Prescription drugs are tested on humans to determine safety and efficacy.

This chapter briefly describes some methods of neurotoxicity testing and the advantages and limitations of each. The first section addresses animal toxicity tests, including the types of neurotoxicity tests currently proposed for regulatory use by the U.S. Environmental Protection Agency (EPA). The second section describes alternatives to animal tests, including in vitro approaches, and the third section describes human testing. Finally, approaches to monitoring of toxic substances are briefly discussed.

ANIMAL TOXICITY TESTS

In designing animal tests and evaluating data, appropriate weight is given to the following factors on a case-by-case basis, taking into account the seriousness of the hazard and the assumptions needed to estimate human health risks (105):

- the relationship between dose and response;
- the effects at the molecular, cellular, organ, organ system, and whole organism levels;
- the reproducibility of the study results and possible explanations for lack of reproducibility;
- the effects of structurally similar substances on humans or animals;
- any known metabolic differences between humans and the test species that could affect response;
- statistical uncertainties and difficulties in extrapolating to a low dose; and
- other factors, such as sex, species differences, and route of administration.

An Office of Technology Assessment (OTA) report, *Alternatives to Animal Use in Research, Testing, and Education*, contains a detailed discussion of the use of animals in research and associated ethical

concerns (105). The issues raised there will not be readdressed in this report.

Toxicity testing should aim to obtain all the data needed for accurate risk assessment at the lowest possible cost. Factors that influence cost include the number of appropriate test species, the nature of the parameters studied, the choice of test subjects, the controls required, and the skilled staff necessary to perform the studies. In addition, toxicity testing requires a substantial investment in labor. Aside from the maintenance needs of the animals used, many observations are necessary. Acute studies often involve observations of behavior and appearance as well as histopathological observations. Subchronic and chronic studies require more detailed pathological studies as well as weekly clinical examinations of all the animals used in the studies (92). Testing costs will be discussed in more detail in chapter 8.

Designing Useful Tests

Animal tests are used to determine the functional, structural, and biochemical effects of toxic substances. Experimental animal models have limitations, however, and the accuracy and reliability of a quantitative prediction of human toxicity depend on a number of conditions, such as choice of species, choice of tests, similarity of human and animal metabolism, design of the experiment, and method of extrapolation of animal data.

When designing animal toxicity tests, therefore, it is essential that the examiners clearly define the objective of their study and understand how the resulting data will be used. Several questions should be answered in advance: Will the data obtained from the animal tests be meaningful? Will the data be useful in the risk assessment process? Can the data be extrapolated from animals to humans?

The World Health Organization (WHO) recently suggested several general objectives of neurotoxicology testing (123):

- identify whether the nervous system is altered by the toxic substance,
- characterize the nervous system alterations associated with exposure,
- ascertain whether the nervous system is the primary target for the chemical, and
- determine dose- and time-effect relationships to establish no observed adverse effect levels (NOAELs).

The initial goal is to determine whether or not the nervous system is affected by a substance for which no toxicological data exist. This often involves screening for neurotoxicity using tests that predict the potential of a substance to produce adverse effects. To be most effective, the tests should be simple, rapid, and economical to administer. Once a chemical is known to produce a neurotoxic effect, further studies can be performed in order to characterize the nature and mechanism of the alterations. Screens are generally designed to explore the consequences of exposure and to indicate whether or not the nervous system is adversely affected.

Chemicals are unlikely to affect all major components of the nervous system at the doses tested; therefore, it is important to use a variety of tests that measure different functional, morphological, or chemical alterations in order to maximize the probability of detecting neurotoxicity. The methods used may differ with the objective of the study, the age of the animal, and the species examined (123).

Potential neurotoxic risks are difficult to assess because of the complexity of the nervous system. Some of the problems in assessment are associated with the wide variations in response that can occur. Other problems are related to the examiner's incomplete understanding of what is being measured by a given test. Therefore, no single test can be used to examine the total functional capacity of the nervous system (123).

Animal Choice

In preliminary screening of known or suspected toxic substances, numerous economic factors influence the design of the evaluation. It is useful if there exist adequate anatomical, physiological, and toxicological databases on the species chosen for study to allow meaningful interpretations of effects and appropriate hypotheses about mechanisms and sites of action (123).

Most routine toxicity testing is carried out with only one or two species. For example, cancer bioassays frequently involve the use of rats and mice, and the monkey may be used for identifying the effects of MPTP, a byproduct in the illicit synthesis of a meperidine analog. Hens have been used to evaluate the neurotoxic potential of organo-

phosphorous pesticides. Most other neurotoxicity screening studies use laboratory rats. Ideally, more than one animal species should be tested—if only a single species is tested, it is possible to conclude that human exposure is acceptable when in fact it is not. However, routine multispecies testing is a costly and demanding enterprise. The facilities and services needed for animal husbandry and the equipment and technical expertise needed to carry out the research make multispecies testing economically impractical in many instances (59).

There are other variables besides species that should be considered. For example, the sex of the test animal may influence results of the study. Some toxic substances may have a greater adverse effect on females than males or vice versa. Consequently, EPA testing guidelines require both male and female rats for neurotoxicity testing.

Another important factor is the age of the animal. The effects of a toxic substance may vary dramatically, depending on the stage of maturation of the animal. For example, cell loss in the nervous system due to natural aging processes may predispose an animal to the adverse effects of toxic substances. Most preliminary assessments are designed to provide information on the population with the greatest potential for exposure, namely, adults. However, aged populations or those undergoing rapid maturation are often especially vulnerable to environmental exposures; thus, tests to assess the neurobehavioral functioning of these populations are necessary for a complete evaluation.

The ideal tests are those that permit longitudinal assessment of animals of both sexes at any stage of development (i.e., at young childhood, prepuberty, and adulthood) (67). Whenever possible, the choice of animal model should take into account such factors as the differences in metabolism of substances between species, genetic composition of the species, and the sensitivity of the test animals to the toxic effects of the substances (50 FR 39458).

Dosing Regimen

Some compounds produce one kind of toxic effect following a single exposure and other effects following prolonged or repeated exposure. In environmental toxicology, a major objective is the detection of cumulative toxicity following continued (or intermittent) exposure. Thus, a multiple-dosing regimen is most commonly used. This is particularly important in neurobehavioral testing, since both quantitative and qualitative changes in the response to environmental factors can occur with repeated exposure, or at some later time following a single exposure (67,123). Normally, assessments are made for a period of time following termination of the dosing regimen, both to determine the reversibility of any observed effects and to see if any new effects appear (123).

Substances are administered in varying doses, the dose being a function of the concentration of the substance and the duration and frequency of exposure. Significant differences in response may occur when the same quantity of toxic material is administered over different exposure periods. Acute exposure to substances may produce both immediate and delayed toxic effects (such is the case for some organophosphorous pesticides). These effects may differ from the effects following long-term exposure. Repeated exposure to certain solvents may produce immediate effects after each dosing as well as delayed adverse effects from long-term exposure (47).

Acute toxic responses result when an animal is subjected to high concentrations of a substance over a short period of time. The acute response may be sudden and severe, and usually lasts for a brief period of time; in some cases, however, it is permanent. If the dose is sufficiently high, death may result. Lower doses (lower concentrations over longer periods of time) may not immediately cause death. As the dose decreases, the response is generally less severe and may take longer to develop. In chronic exposures, clinically adverse effects may take years to develop (47).

Route of Exposure

The most common routes by which toxic substances enter the body are, in descending order, inhalation (through the lungs), **oral** (through ingestion), and dermal (through the skin). Although substances generally produce the greatest effect and most rapid response when given intravenously, this is an unlikely route of entry except in the case of drug therapies or drug abuse. The manner in which a potentially toxic agent enters the body can influence the time of onset, intensity, and duration of the toxic effects. The route of exposure may also influence the degree of toxicity and the organs most severely affected.

Exposure to toxic chemicals in the atmosphere is unavoidable unless devices are used to remove the contaminants from the air before they enter the respiratory tract. In order for any contaminant to reach the alveoli of the lungs (where gas exchange takes place), it must be either a gas or of a certain particulate size (less than 10 microns in diameter) so that it is not removed in the airway to the lungs. The actual and potential' hazards associated with exposure to toxic agents via inhalation are evident in industrial workplaces and in urban areas with polluted atmospheres (55,1 17).

Most episodes of acute toxicity result from intentional or accidental ingestion of a chemical. For instance, a person may deliberately take an overdose of a psychoactive drug. Poisonous mushrooms may be accidentally ingested. Sufficiently large particles of inhaled toxic matter may collect in the throat and be swallowed.

The simplest route of exposure for humans and animals is accidental or intentional contact of the chemical with the skin. The skin is the most readily accessible organ to all forms of foreign chemicals, yet it is also an efficient barrier to many toxic substances. Many substances can be absorbed through the skin, including substances in fragrances (AETT), antidandruff shampoos (zinc pyridinethionine), and solvents (methyl n-butyl ketone) that have proven to be neurotoxic in humans or animals, or both (3,44,47). The degree of absorption is influenced by the type of compound(s) involved and the condition of the skin. For example, cuts or abrasions on the skin's surface will allow the agent to bypass the epidermis, the outer, protective layer of the skin. Once through the epidermis, the substance can easily pass into the circulatory system. Depending on the concentration and duration of the exposure, some substances, solvents, for example, can easily pass through the epidermis.

Extent and Duration of Exposure

The exposure of animals to chemicals is often divided into four categories: acute, subacute, subchronic, and chronic. **Acute is** defined as exposure to a chemical for less than 24 hours. The purpose of an acute test is to observe the evidence of toxicity after administration of the compound and the degree of lethality (55). While acute exposure usually refers to a single administration, repeated or continuous doses may be given within a 24-hour period for some substances with limited acute toxicity. An example is acute exposure by inhalation, which refers to continuous exposure for less than 24 hours. Repeated exposures are divided into subacute, subchronic, and chronic categories. Subacute exposure refers to repeated exposure to a chemical for 1 month or less, subchronic exposure occurs typically from 1 to 3 months, and chronic exposures occur for more than 3 months (47).

As mentioned earlier, the toxic effects following a single exposure to a substance may be quite different from those produced by repeated exposure. This may occur because of compensatory changes elicited by repeated administration or because of cumulative effects of mechanisms different from those causing acute toxicity. For example, the primary acute toxic effect of carbon disulfide is depression of central nervous system activity; however, repeated exposures can result in peripheral neuropathy or parkinsonism. Acute exposure to rapidly absorbed substances is likely to produce immediate toxic effects, but acute exposure can also produce prolonged toxicity that may or may not be similar to the toxic effects of chronic exposure. Likewise, chronic exposures may produce some immediate effects after each administration in addition to the chronic effects (47).

The extent of exposure is another important factor in the characterization of exposure parameters. Generally, but not always, fractionation of the dose reduces the effect. A single dose of a compound that produces an immediate, severe effect might produce less than half the effect when given in two equal doses and no effect when given in 10 doses over a period of several hours or days. Chronic toxic effects occur if the compound accumulates in the organism's system, if it produces irreversible toxic effects, or if there is insufficient time for the system to recover from the toxic damage (47).

Other Considerations

Several additional factors are considered in designing neurotoxicological tests. One condition that may affect toxicity is the nutritional state of the animal. Changes attributed to exposure to toxicants might be due to relatively nonspecific effects related to inhibition of growth or decreases in food or water consumption.

Another factor is the housing conditions of the experimental animals. Sometimes animals are housed individually in cages during toxicological

studies, an arrangement that may alter their responsiveness to the test compounds. For example, a chemical that causes depletion of the neurotransmitters norepinephrine and dopamine produces less depression of motor activity in isolated rats than in grouped rats (125).

Temperature of the environment is another important factor. Normally, the response of an animal to a toxic compound decreases as the environmental temperature is lowered, but the duration of the overall response may be delayed. Also, some drugs are more toxic in certain environmental temperatures than in others. For example, compounds affecting the neurotransmitter acetylcholine may produce significantly greater toxicity in a warm environment than in a colder one. Some substances inhibit sweating. Eventually, the body temperature becomes elevated because the absence of perspiration prevents cooling (38). In such a case, toxic effects may result from hyperthermia, not directly from the effect of the substance on the nervous system.

Validation

Validation is a critical component of the test development process because it ensures that data generated as a result of testing will be useful in evaluating the health risk posed by a particular substance. The value of any toxicity test lies in its ability to measure the endpoint it is designed to detect. For neurotoxicity, the endpoints are adverse changes in the structure or function of the nervous system. General acceptance of a new toxicity test usually requires demonstration that the test is reliable, sensitive, and specific. For validation studies, chemicals with known neurotoxic potential and those known not to be neurotoxic are studied to determine the ability of the test to distinguish between them. Because toxic substances can have many different effects on the nervous system, known neurotoxic substances with different effects on the nervous system are chosen for validation studies. Before test guidelines are proposed for national or international use, validation studies commonly include a multilaboratory phase to test the reproducibility of the testing paradigm in different laboratories (58,81).

Evaluating Chemicals for Neurotoxicity

It is impossible to thoroughly examine the neurotoxicity of each of the chemicals in commerce.

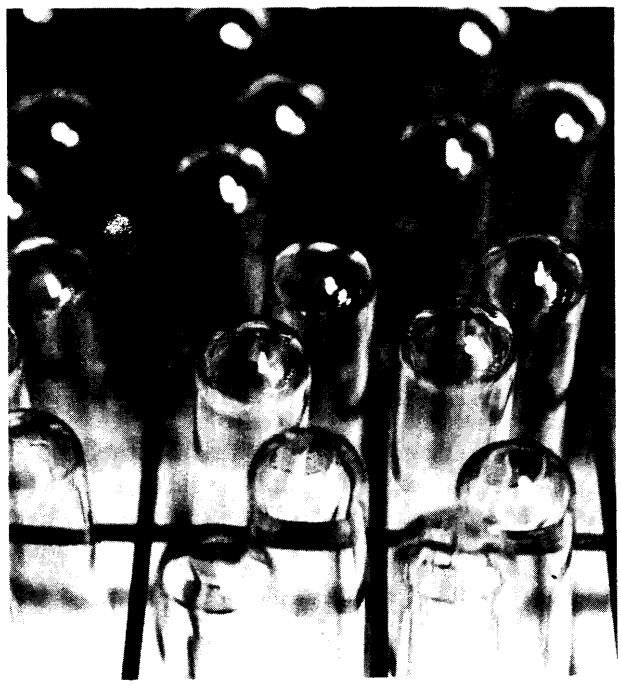


Photo credit: U.S. Environmental Protection Agency

However, it may be possible through a well-developed screening program to flag the substances either currently in use or recently introduced that have neurotoxic potential. Screening is conducted to provide an initial evaluation of the effects of various substances on the nervous system. The results of screening may be used to reduce the number or quantity of hazardous substances in commerce or to aid in determining which additional studies should be undertaken to further characterize their toxicological properties (67). An efficient screen should evaluate a variety of neurological effects rather than just one. Screens should also be sensitive, reproducible, and capable of being administered rapidly (32,33),

Testing strategies often involve a tiered approach. Tiered testing involves a stepwise progression of more specific and sophisticated tests, beginning with a general screen to determine if further testing is necessary. In the initial screen of the tiered testing approach, the outcomes of acute studies are interpreted. If acute effects are identified, then experiments involving repeated exposures are performed in the second tier. The third tier is composed of detailed studies of subtle effects or mechanisms of toxicity. At each stage the examiner builds on the data collected from the previous tier.

Typically, 5 to 10 animals of the same species and strain are used in the tests. It is important to select the proper animal model initially because it is desirable to use the same model in subsequent tiers. Using the same animal is more efficient, costs less, and allows consistent analysis of data. Some toxicity tests only require the acute dosing regimen, and it is not necessary to conduct repeated dosages. Box 5-A illustrates one example of a tiered testing approach. Other investigators have proposed slightly different schemes (32-34,62).

As in vitro tests become available, tiered testing schemes may be modified to take advantage of both whole animal and tissue and cell culture testing approaches. For example, a future scheme might call for in vitro tests as a screen, followed by in vivo tests (32,37). In vitro tests will be described later in this chapter.

Types of Animal Tests

The EPA has taken the lead in devising neurotoxicity tests for use in regulatory programs. In 1985, the Agency devised a final rule on general toxicity testing guidelines under the Toxic Substances Control Act (50 FR 39398-39418). The guidelines are categorized into three subparts: subpart B describes the procedures for general toxicity testing (i.e., acute dermal, inhalation, and oral exposure); subpart C includes testing procedures for subchronic dermal, inhalation, and oral exposure; and subpart D describes testing procedures for chronic exposure.

General toxicological tests evaluate a broad spectrum of potential toxicological effects, including some effects on the nervous system; however, these tests are not designed to examine comprehensively the possible neurotoxic properties of chemicals. In 1985, EPA proposed specific guidelines for neurotoxicity testing (50 FR 39458-39470). EPA has proposed guidelines for the functional observational battery (FOB) and specific tests to analyze motor activity, schedule-controlled operant behavior (SCOB), developmental neurotoxicity, neuropathology, and the effects of organophosphorous pesticides (1 12). When specific neurotoxicity testing is necessary, EPA currently plans to require the FOB, together with motor activity and neuropathology tests. At the present time, these three tests are referred to by EPA as the core test battery. EPA's Office of Toxic Substances and Office of Pesticides Programs are currently considering a requirement to use the core tests routinely in evaluating new and old chemicals and pesticide products. When appropriate, other tests may also be required.

Box 5-A—Tiered Animal Testing To Identify Adverse Neurobehavioral Effects of Substances

Tiered testing is an efficient and cost-effective approach to evaluate the toxicity of chemicals. In the first tier of an experiment, the recommended strategy is to identify acute hazards of substances. The second tier is designed to characterize the toxicity in repeated exposure, and the third is used to undertake detailed studies of special impairments or of mechanisms of chemical injury. Each tier provides useful information for subsequent tiers.

First tier—Animals are exposed to the substance being evaluated. The exposure period is short and covers a wide range of concentrations. The investigator seeks to identify any evidence of mortality, morbidity, or morphological changes. The experimenter also observes behavior. The first tier helps establish the parameters of exposure that are appropriate for the second tier. It may also suggest mechanisms by which the effect is produced, which may assist in the design of more sensitive experiments in the third tier.

Second tier—Animals are repeatedly or continuously exposed to substances being evaluated. This tier provides an opportunity to characterize delayed toxicity, to observe the development of tolerance, and to characterize the reversibility of adverse effects.

Third tier—At this stage, highly focused studies are performed to fully characterize toxicity, using methods dictated by the nature of the system. This tier can identify subtle sensory or perceptual impairments, affective disorders, or cognitive and intellectual dysfunction. A detailed hazard characterization not only can facilitate the identification of the most sensitive situation, but also may clarify the mechanism of action of the substance.

The above schemes may be modified in the future as in vitro tests become available.

SOURCES: A.M. Goldberg and J.M. Frazier, "Alternatives to Animals in Toxicity Testing," Scientific *American* 261(2):24-30, *1989;* R.W. Wood, American Psychological Association, testimony before the Neurotoxicity Subpanel of the FIFRA Science Advisory Panel, U.S. Environmental Protection Agency, Washington, DC, Oct. 15, 1987.

In August 1989, EPA sponsored a meeting of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel to examine various issues related to proposed guidelines for neurotoxicity and mutagenicity testing under the Act and to review the classification of several selected compounds (54 FR 35387).

Unless otherwise specified, it is assumed that both acute and subchronic testing will be conducted for both FOB and motor activity. Although some experts have recommended that neuropathological examinations be conducted following acute exposures, at the present time EPA anticipates requiring such analysis only after repeated exposures. These neurotoxicity tests represent an initial approach to identifying hazardous chemicals and are not specifically designed to develop the data necessary for full-scale risk assessments (101). (See ch. 6.)

The EPA core battery does not represent a complete screening assessment of the nervous system. For example, it does not adequately assess cognitive function, neurophysiology, or neurochemistry. Some neurotoxicologists have challenged the usefulness of the core battery, saying that it does not go far enough. Nevertheless, EPA plans to require just the core battery, with the option of using more comprehensive tests for selected compounds. Additional tests that EPA might require in conjunction with or in place of the core battery include SCOB, developmental neurotoxicity, and neurotoxic esterase assay (101).

Which tests are most appropriate for routine use in screening for neurotoxicity is the subject of disagreement in the scientific community. Some scientists believe that developmental and SCOB should be part of the EPA core test battery because they measure different aspects of neurotoxicity than do the FOB, motor activity, and neuropathology tests. Others believe that the motor activity and SCOB tests should not be used as part of an initial screen, because they may not be direct measures of neurotoxicity. EPA believes that the initial screen should include FOB, motor activity, and neuropathology assessments because these tests provide adequate initial measures of neurotoxicity and enable investigators to judge whether or not additional (second tier) testing is necessary. Descriptions of various neurotoxicity tests follow.

Functional Observational Battery

An FOB is a collection of noninvasive tests to evaluate sensory, motor, and autonomic dysfunction in either animals exposed to substances or animals having endured direct damage to the nervous system (57). FOBS are generally used as screens to determine which substances require additional testing.

EPA published a test guideline for an FOB in 1985. The EPA guideline incorporates aspects of tests developed and used in industry and academia (32-34,42,79,80). The battery is designed to be used in conjunction with general toxicity tests or neuropathological examinations, or both (50 FR 39458-39460). It serves as a screening tool (thus, it is considered a first tier test), indicating which substances should be further characterized using second tier methods. It is not intended to provide an overall evaluation of neurotoxicity. EPA is currently refining and validating its FOB.

The EPA test battery is administered to female and male rats, usually 10 per dose group per sex. Three doses of the test substances are used, with doses chosen so that the highest dose produces obvious signs of toxicity. The doses are selected on the basis of values from previous literature and experiments in order to ensure the detection of neurobehavioral effects (69,70). The observer is not aware of the dose identification. The observer records each response subjectively, using established rating scores. After all data are collected, they are entered into a computer, summarized, and analyzed using statistical methods (17,68-70). Box 5-B summarizes the procedures for conducting the EPA FOB.

The FOB is advantageous because it can be easily administered and can provide some notion of the possible functional changes produced by exposure to neurotoxic substances. It also allows evaluation of the dose-response and time course characteristics of the neurological and behavioral changes produced by exposure to a substance. Furthermore, the equipment used is relatively inexpensive, and the total time to complete an entire evaluation is short (68,69). Potential problems include difficulty in defining certain measures, a tendency toward subjective biases in assessing behavior (123), and the need for trained observers.

Box 5-B-Conducting the EPA Functional Observational Battery

In conducting the EPA functional observational battery (FOB), the technician first observes and describes the rat's posture in the home cage, then closure of the rat's eyelid and any convulsions or tremors that may be present. Next, the animal is picked up and rated for ease of handling and removal from the cage. The rat is observed and rated for signs, such as lacrimation and salivation, that the autonomic nervous system has been adversely affected. The rat is then placed on a cart top for 3 minutes, during which time the number of rears are counted and the gait, mobility, and level of arousal are rated. At the end of the 3 minutes, fecal and urine output are recorded.

Next, the technician rates the rat's responses to several stimuli, such as the approach of a pencil, snap of a metal clicker, touch of the pencil on the rat's rump, and pinch of the tail with forceps. Using a pen flashlight, the observer tests the rat for pupil constriction in response to light. The righting reflex is then measured by the ability of the rat to flip over in midair and land on its feet. Using strain gauges, the rat's forelimb and hindlimb grip strength are measured. The rat's hind feet are painted, and the technician then holds the rat a few inches above the cart top and drops it in order to measure landing foot splay. Finally, the rat's weight and rectal temperature are recorded. The entire procedure takes approximately 6 to 8 minutes per animal.

SOURCES: V. Moser, Director, NSJ Technology Services Corp., Research Triangle Park, NC, personal communication, Nov. 16, 1988; V. Moser, J. McCormick, J.P. Creason, et al., "Comparison of Chlordimeform and Carbaryl Using a Functional Observational Battery," ***Fundamental and Applied Toxicology*** 11:189-206, 1988.



Photo credit: John O'Donoghue

One component of the functional observational battery (FOB) evaluates a rat's response to an auditory stimulus.

Motor Activity

Motor activity is generally defined as any movement of the experimental animal, and it is most often evaluated after acute and subchronic exposures. The acute motor activity test is used to examine changes in animal movement following the administration of a range of acute doses. This test can also be used to determine the potential of a substance for producing acute neurotoxicity, and it may be used as a screen to evaluate certain classes of substances for neurotoxicity. The subchronic motor activity test is used to determine whether repeated dosing with suspected chemicals results in changes in activity, This test may be used to determine a substance's potential for producing subchronic neurotoxicity (50 FR 39460) (60). There is disagreement as to whether motor activity is a primary indicator of neurotoxicity. For example, the primary action of a toxicant may be at some site other than the nervous system; the changes in motor activity maybe secondary, that is, a result of the primary effect.

Proposed EPA guidelines require that the test substance be administered in different amounts to groups of animals. Levels of exposure that result in significant changes in motor activity are compared to levels that produce toxic effects not originating in the central nervous system (50 FR 39460). Observation measurements may be either quantitative or qualitative. The quantitative approach measures the frequency, duration, and sequencing of various motor components of behavior. The qualitative approach is used to gather data on the presence or absence of certain components of activity (90).

The use of observational methods to detect subtle changes in behavior has limitations. Many man-hours are required to obtain and evaluate the data. Some studies also require more than one observer. Because of possible subjective influences on data collection, a great deal of technical knowledge is required to ensure reliability. Finally, subject-observer interaction is an important consideration.

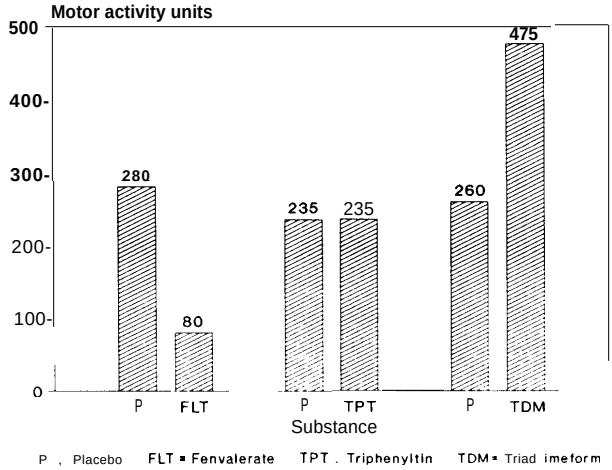
For example, the presence of the observer may modify the animal's behavior (90).

The techniques of observational analysis have included videotape recordings and computerized pattern recognition. In most cases, videotaping has minimized the problem of subject-observer interaction and has provided a permanent record of behavior which can be used for standardizing observations. The computer techniques have alleviated the problems of subjectivity (subject-observer interaction and subjective bias) and laborious data-collection procedures (90).

Some of the automated techniques that have been developed for motor activity testing include photocell devices, mechanical devices, field detectors, and touch plates. Photocell devices provide direct measures of motor activity in which beams of light traverse a cage and collide with photoreceptors. This technique involves placing the rat in a figure-8 maze and recording any movement of the experimental animal that interrupts the beam of light. The number of beam interruptions is counted and recorded by a computer for a l-hour time period (60,68). The figure-8 maze is only one of a variety of chambers used for motor activity examinations. For example, another device commonly employed for assessing motor activity is the Motron Electronic Mobility Meter, which differs from the figure-8 maze because of its rectangular shape and the density and arrangements of the photodetectors that are used to record motor activity (60). Automated motor activity measures may be used to generate dose-response data. This is typically done by placing rats in a plexiglass box, Two video cameras monitor the animal's behavior, and the video signals are transferred to computers in order to identify common patterns in movement and behavioral classification of the data (71).

Toxic substances may have a variety of effects on motor activity. To generate the data illustrated in figure 5-1, motor activity was measured for 1 hour in a group of rats in a figure-8 maze after administration of a toxic substance or placebo (P). The numbers represent motor activity units for the entire hour. Group FLT received the pesticide fenvalerate, which depressed activity. Group TPT received the pesticide triphenyltin, which had no effect on activity. Group TDM received the pesticide triadimeform, which stimulated activity, Experiments are ordinarily conducted with many doses of a toxic substance to determine how motor activity changes with level of exposure (59).

Figure 5-l—The Effects of Toxic Substances on Motor Activity



SOURCES: K.M. Crofton and L.W. Reiter, "The Effects of Type I and II Pyrethroids on Motor Activity and the Acoustic Startle Response in the Rat," *Fundamental and Applied Toxicology* 10:624-634, *1988;* K.M. Crofton, V.M. Boncek, and R.C. MacPhail, "Evidence for Monoaminergic Involvement in Triadimefon-induced Hyperactivity ," *Psychopharmacology* 97:326-*330, 1989;* S. Padilla, R.C. MacPhail, and L.W. Reiter, "Neurotoxic Potential of Pesticides: Age-related Effects of Pesticides to Youth in Agriculture," U.S. Environmental Protection Agency report, Health Effects Research Laboratory, 1985.

Motor activities recorded with mechanical devices involve a vertical or horizontal displacement of the chamber in response to the animal's motions. Some of the mechanical devices used include stabilimeters and running wheels. Stabilimeters record the movement of the animal when it causes the chamber floor to be displaced from its resting position. Running wheels are designed so that the wheel is positioned on a horizontal axle and the animal's running causes the device to rotate. Running wheels have been used in behavioral toxicology for over three-quarters of a century to study the effects of food deprivation, water deprivation, estrus, lesions of the central nervous system, and locomotor activity (90).

Field detectors are used to record the disturbances that an animal creates in moving within a test cage. Touch plates measure motor activity by recording contacts of the animal with sections of the chamber floor (90).

There are many advantages of motor activity tests. These include the availability of automated test equipment, ease of testing, and objectivity of data (60). Additional factors include obtaining reproducible data that are sensitive to the effects of acute exposure to various toxic substances. These methods do not require any special training or surgical preparations prior to testing.

Several organizations, including the National Academy of Sciences, the World Health Organization, and the Federation of American Societies for Experimental Biology, have recommended that motor activity testing be included in evaluating the toxicity of potential and known neurotoxic substances (30,64,74,123). However, further testing is usually needed to provide more specific information on the adverse health effects of the test substance. Furthermore, the data collected may not provide information on the origin of the problem or indicate what subsequent tests should be administered (64). There is general agreement within the scientific community that questions remain concerning the specificity of motor activity measures. For example, sickness resulting from chemical exposure is not always associated with changes in motor activity (60).

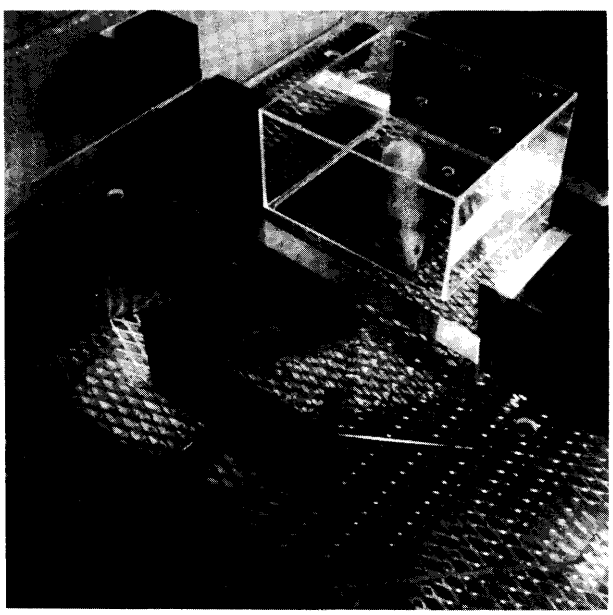


Photo credit: V Moser and R.C. MacPhail

The figure-8 maze is used to evaluate changes in motor activity after exposure to neurotoxic substances.

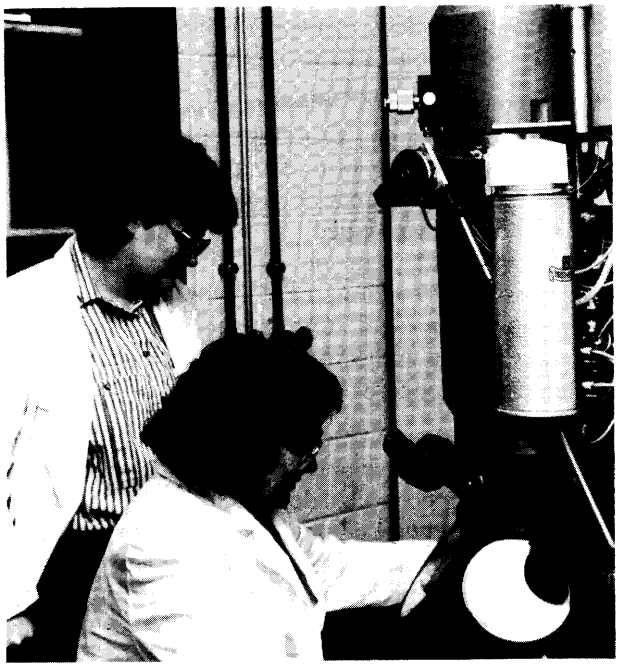


Photo credit: Julia Davis, NSI Technology Services Corp., Research Triangle Park, NC

The electron microscope is a useful tool in examining nerve tissue damaged by toxic substances.

Neuropathology

Neuropathology is the third component of the EPA core test battery (50 FR 39461). The neuropathological examination is designed to develop data on structural and functional changes in the nervous system as a result of exposure to toxic substances. EPA's guidelines recommend procedures to detect pathological alterations produced by neurotoxic substances. Morphological examination of animals exposed to neurotoxic substances helps to distinguish between pharmacological and structural types of adverse effects, describes the relative frequency and severity of the lesions, establishes the location of structural changes in the central nervous system, serves as a basis for relating particular classes of compounds to particular kinds of damage, and reveals the cellular components that have been damaged. Additional neuropathological techniques are currently in use to determine NOAELs and to examine the effects of toxic substances on the nervous system (48,100).

There is general agreement that neuropathological studies should be conducted in parallel with other neurotoxicity tests. Neuropathological evaluations may be performed following acute, subchronic, and

chronic exposures to toxic substances (50 FR 39461).

Developmental Neurotoxicology

Developmental neurotoxicology (behavioral teratology), an emerging discipline within the toxicological sciences, is concerned with behavioral and related effects in the offspring of parents exposed to neurotoxic substances prior to conception, during gestation, during lactation, or any combination of these times (45). Research efforts are under way to understand the basic principles of behavioral neurotoxicity, the biological mechanisms involved, and the appropriate methods for testing and obtaining data to be used by regulatory agencies in setting standards (45). In recent years, major advances have been made in methods for detecting the adverse behavioral effects of toxic substances on the developing organism. In 1979, the National Center for Toxicological Research (NCTR) developed a battery of tests to be used for the Collaborative Behavioral Teratology Study. NCTR served as the pilot test facility for conducting the study, and five other laboratories were involved in evaluating a standard protocol. The study was designed to assess the reliability of the test methods used and to detect the sensitivity of each (1,14,45,114,115).

Regulatory efforts in behavioral teratology began in 1975, when Great Britain and Japan produced guidelines for testing pharmaceutical substances. In 1983, the European Economic Community developed similar guidelines. WHO proposed draft testing guidelines for drugs and other substances in 1986 (45). That same year, EPA proposed testing guidelines for several glycol ethers (51 FR 17883; 51 FR 27880). A final test rule for diethylene glycol butyl ethers (53 FR 5932) was set in 1988 and for triethylene glycol monomethyl ethers (54 FR 13472) in 1989. These were the first testing guidelines directly related to developmental neurotoxicity to be promulgated by a U.S. regulatory agency.

Developmental neurotoxicity tests are used to characterize various aspects of damage to the developing nervous system, including adverse structural and functional changes. This information serves as a basis for relating particular classes of compounds to particular kinds of damage; it can then be used to predict what classes of compounds may be neurotoxic. Developmental neurotoxicity tests are also used in determining the magnitude of damage resulting from particular exposure levels, and they aid in establishing NOAELs (51 FR 17890). The guidelines for glycol ethers consist of evaluations of morbidity and mortality, growth and physical development, neurological and physical abnormalities, auditory startle habituation, learning and memory, developmental locomotor activity, and neuropathology. Recently, a consent order for the testing of 1,1,1 -trichloroethane was published (54 FR 34991); it includes developmental neurotoxicity testing.

In 1987, FIFRA's Science Advisory Panel approved the development of a generic testing guideline for developmental neurotoxicity testing (along with a guideline for adult neurotoxicity testing). Generic guidelines have also recently been proposed for developmental and adult neurotoxicity testing of pesticides. These tests are designed to determine the effects of maternal exposure to pesticides on the nervous systems of offspring. The proposed generic test guidelines require administration of the test substance to several groups of pregnant animals during gestation and lactation. Selected offspring are then tested for neurotoxicity. This evaluation is designed to detect any effects on growth and development, gross neurological effects, or behavioral abnormalities. These guidelines will be required for the testing of pesticides on a case-by-case basis. Testing may be required for substances that cause central nervous system malformations, substances already known to be neurotoxic in adults, hormonally active substances, and substances that are structurally related to known neurotoxicants (46).

In April 1989, a workshop on the comparability of human and animal developmental neurotoxicity was sponsored by EPA and the National Institute on Drug Abuse to evaluate and compare the effects of known neurotoxic substances on the developing nervous system. The workshop focused initially on several agents known to adversely effect humans, including selected abused substances (primarily methadone and cocaine), alcohol, lead, polychlorinated biphenyls, diphenylhydantoin, methyl mercury, and X-irradiation. It is possible to make qualitative comparisons of effects across species, especially when major categories of function are compared. Making quantitative comparisons in data is more difficult (46).

Based on this information, work groups then focused on the underlying basis for comparability of

effects across species, the appropriateness of current testing approaches, alternative approaches to risk assessment, and the considerations (triggers) that should be used in determining when to require testing. Participants agreed that the support for cross-species comparability was great enough that a reliable effect (including permanent and transient effects) should be considered a potentially adverse effect in humans. Also, developmental effects, in the presence or absence of maternal toxicity, should be considered adverse. Since no single category of function was found to be routinely the most sensitive, it was agreed that a battery of functions should be included in any developmental neurotoxicity testing screen. Although limitations were identified, workshop participants felt that a reference dose should be established to identify a level below which no increase in developmental neurotoxicity is expected, An abbreviated test battery was proposed for screening purposes. Whether to use this abbreviated battery or a full-scale testing protocol may depend on the type of information already available. For example, a substance that causes central nervous system malformations should be thoroughly evaluated for developmental neurotoxicity, whereas a substance that is structurally related to known neurotoxic substances might be tested first using the abbreviated battery (46).

EPA has published risk assessment guidelines for developmental toxicity (51 FR 34028) and has recently proposed amendments to these guidelines (54 FR 9386). Developmental neurotoxicity data may aid in evaluating the long-term consequences of adverse effects discovered at the time of birth and the relationship of the behaviorally effective dose to the toxic dose. These data may also aid in identifying effects that should be monitored in exposed populations (45). EPA is currently developing guidelines for the use of data on adult and developmental neurotoxicity in risk assessments.

Schedule-Controlled Operant Behavior

Changes in behavior are a useful indicator of exposure to neurotoxic substances because behavior involves the integration of motor, sensory, and higher order nervous system activities (102). Regulatory officials increasingly recognize behavioral change as an important endpoint of neurotoxicity. Several organizations, including the National Academy of Sciences and WHO, have recommended that operant behavior testing be included in evaluations



Photo credit: D. Cory-Slechta

Schedule-controlled operant behavior (SCOB) tests are used to evaluate a rat's learned behavior in scheduled intervals.

of potential and known neurotoxic substances (74,75, 123). Operant behavior refers to "behavior that is maintained by its own consequences' (50). Schedule-controlled operant behavior refers to reinforcing an animal's response to stimuli according to an explicit schedule, thereby producing orderly patterns of behavior (50).

There are several reasons why operant behavior tests may be useful. Operant behavior is critical for adaptation and long-term survival of animals. Tests of this kind allow reliable and quantitative examination of the effects of substances on behavior, and the extensive literature on operant behavior provides a conceptual framework for analysis of effects. Finally, operant conditioning allows the researcher to tailor the behavior to the needs of the experiment (98). Disadvantages of using this type of test include the cost of equipment and of data acquisition and analysis systems, the time involved in training animals to certain schedules, and the difficulties in interpreting the toxicological significance of some of the subtle endpoints used as indices of operant performance.

In 1985, EPA established guidelines for evaluating the effects of toxic substances on simple learning processes using SCOB tests. SCOB evaluates the effects of acute and chronic exposures on the rate

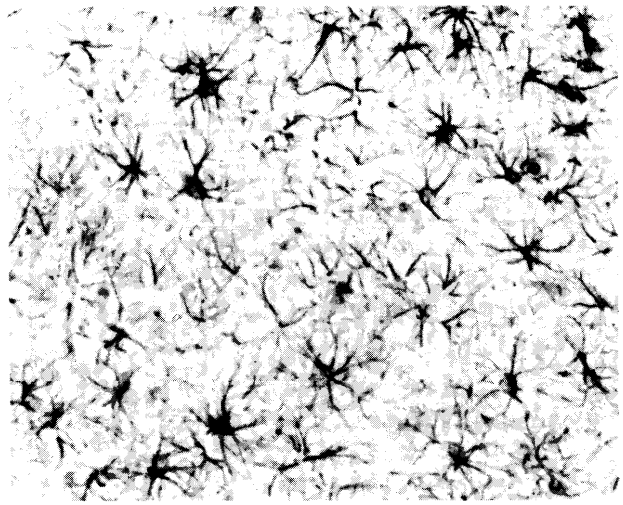
and pattern of responses under schedules of reinforcement (50 FR 39465). Following testing for behavioral effects, additional tests may be necessary. Operant behavior studies may be used in conjunction with neuropathological examinations.

EPA's approach to operant behavior testing involves placing the animal in an apparatus containing a lever and a device to deliver a reinforcer, such as milk. One method is to train the animal under a fixed-ratio reinforcement schedule, in which a fixed number of presses on the lever is followed by a reward of milk. For example, if one rewards an animal for exactly each third lever press that it makes, the ratio between responses (lever presses) and reward is fixed (50,68). Animals may also be trained under variable-ratio reinforcement schedules. In other words, the technician varies the schedules so that sometimes the third response yields milk, sometimes the seventh, and sometimes the hundredth. The animal never knows when the next reward is coming (50). These schedules of reinforcement may be used to generate moderate response rates that may increase or decrease as a function of exposure to toxic substances (50 FR 39466). Several kinds of SCOB tests are currently used in industry (49,50,89,102).

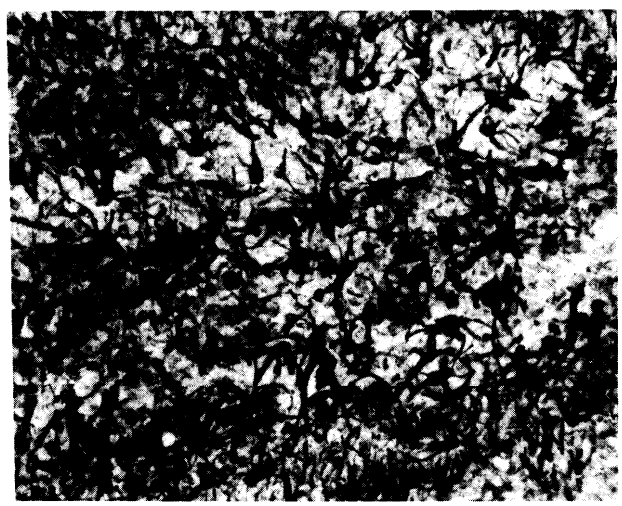
A variety of other testing schemes are commonly used to examine behavior. These include tests to determine the effects of neurotoxic substances on motor coordination, tremor, sensory processes, reflexes, and learning and memory (23,27,29,49,66,102). There is some disagreement in the scientific community as to the optimal approach for evaluating operant behavior.

Biochemical Markers

Various biochemical markers have been used to assess the effects of toxic substances on adult and developing nervous systems. EPA recently developed a proposed guideline for the assessment of developmental neurotoxicity using a glial fibrillary acidic protein (GFAP) radioimmunoassay (77). GFAPs are proteins located in the glia, the non-neuron satellite cells of the central nervous system. When glial cells are damaged by toxic substances, they substantially increase production of GFAP. The proposed test is designed to develop data on changes in the amount of GFAP in the developing nervous system after postnatal exposure to a toxic substance. Such an assay is a useful adjunct to developmental neuropathological examinations (76,77), Assays of proteins in neurons and glia can be used to detect and characterize specific responses and alterations in brain development due to toxic substances. While not designed to uncover basic mechanisms underlying specific neurotoxic effects, this approach can aid in defining neurochemical mechanisms underlying altered brain development (78).



A. Control



B. Rat exposed to trimethyltin.

Photo credit: J.P. O'Callaghan, U.S. Environmental Protection Agency

Trimethyltin increases levels of glial fibrillary acidic protein (GFAP) in astrocytes of the rat brain, a sign of nervous system damage.

Specialized Tests for Organophosphorous Pesticides

Exposure to some organophosphorous pesticides produces delayed effects, including weakness of limbs and improper function of certain motor

neurons. Evidence of toxicity first appears approximately 2 to 3 weeks after initial exposure. In 1985, EPA established guidelines for neurotoxic esterase assay for organophosphates (50 FR 39463). These guidelines describe the procedure for measuring the inhibition of an enzyme known as neurotoxic esterase (NTE) in the brain or spinal cord of hens exposed to organophosphorous substances (50 FR 39463). This assay is intended to serve as an adjunct to behavioral and pathological examinations of hens and is not intended to replace in vivo tests.

EPA also established guidelines in 1985 for a test of acute delayed neurotoxicity of organophosphorous substances (50 FR 39466-39467). This test involves administering a single dose of these substances orally to adult hens and observing them for symptoms such as gait changes, lack of coordination, and paralysis. The animals are observed daily for approximately 3 weeks until effects are determined. All signs of toxicity are recorded, as well as the duration and extent of exposure. In addition, the hens are evaluated for motor ability at least twice a week, with various tests. If neurotoxic effects are not seen immediately, the dosage may be repeated and the observation period extended (50 FR 39466-39467). Later, pathological examinations are also conducted on the animals.

Subchronic delayed neurotoxicity refers to a prolonged lack of coordination resulting from repeated exposure to a toxic substance over a limited period of time. In 1985, EPA established guidelines for a test of subchronic delayed neurotoxicity of organophosphorous substances (50 FR 39467). This test involves administering these substances orally to hens for approximately 3 months. It is usually conducted after obtaining information from acute tests. Evaluators observe the hens daily for such indicators as gait changes, lack of coordination, and paralysis. Following the observation period, pathological tests of selected neural tissues are conducted using perfusion techniques and microscopic evaluations. In addition to providing information on the possible health effects of repeated exposures to organophosphorous substances, this test may provide information on dose-response, thus aiding in determining an estimate of a no-effect level.

Neurophysiology Techniques

Neurophysiological tests for assessing the health effects of potential and known neurotoxic substances are usually adopted by neurotoxicologists from testing techniques used in the basic neurosciences. These tests are designed to provide specific types of information, and the technique or set of techniques chosen for a given application will depend on the nature of the scientific issues under investigation (9).

In general, neurophysiological testing techniques depend on the electrical properties of nerve cell membranes. The firing of a single neuron involves the movement of electrically charged ions across the membrane. This movement of charged particles creates electrical potentials which can be measured. The measured potentials, in turn, reflect the functioning of the neuron or neurons that generated them. Neuronal potentials are usually measured by placing electrodes on or near the neural tissue of interest. In many cases where the neural tissue is not directly available, such as the human brain, the electrodes can be placed at remote sites for detection of electrical activity which is conducted through the cranial tissues. The electrical signals recorded from the electrodes are typically amplified, filtered, and passed on to a data acquisition device such as a computer (9).

It is convenient to categorize electrophysiological testing techniques by the size of the recording electrodes used. These range from a few microns to several millimeters. The former, termed "microelec - trodes," can be used to penetrate cell membranes and measure the function of single neural cells or parts of cells, such as membrane ion channels or synaptic endings. Moving up in size, “multiunit electrodes” can be placed in the vicinity of several cells and can measure the activity of each neuron in a cluster of neurons simultaneously. Still larger ‘‘macroelectrodes’ can measure the summed activity of many neurons, possibly thousands of cells. With macroelectrodes, the activity of individual cells is no longer detectable; instead, the activity of neural systems can be monitored (9). Neurophysiological tests may be used to study neural function either in vitro or in vivo, and they can measure spontaneously emitted neural responses or those evoked in response to some type of stimulation (9).

For neurotoxicological applications, microelectrode techniques and in vitro procedures are useful for investigating mechanisms of action of known neurotoxic substances because of the specificity of the techniques. For investigating the potential neurotoxicity of compounds with unknown properties,

in vivo macroelectrode procedures are more useful because of their generality. One set of macroelectrode techniques, sensory evoked potentials (EPs), is being developed by EPA for potential use in neurotoxicology testing paradigms. This approach has been endorsed by several industrial organizations (9).

Sensory evoked potentials can be used to identify which of the sensory systems in the nervous system are affected by neurotoxic substances and to provide information about the nature of these changes. In addition, sensory systems are model systems for studying 'generic' dysfunctions, since they include all the components of other systems but can be studied relatively noninvasively. Evoked potentials are essentially electrical signals that are generated by the nervous system in response to a stimulus. Using neurophysiological techniques, these signals can be measured and recorded. Various types of evoked potential techniques are currently in use, including brainstem auditory evoked responses, flash evoked potentials, pattern reversal evoked potentials, and somatosensory evoked potentials (25,56,61).

The electroencephalograph (EEG) records spontaneous, ongoing electrical activity in the brain (activity that, unlike EPs, is not associated with presentation of a stimulus). Electrodes are surgically implanted in a rat's skull or pasted onto a human's scalp. The electric potential differences between the electrodes are measured and the changes in the potential difference are recorded. EEGs can provide a detailed record of electrical activity at several brain sites, allowing investigators to identify general regions of the brain that may be adversely affected by acute or long-term exposure to known or potential neurotoxic substances. However, EEG data can be difficult to interpret, and the technique provides limited information on the mechanisms of action of toxic substances (4,43,97). The limitations of EEGs spurred the innovation of methods for measuring evoked potentials.

Brainstem auditory evoked responses (BAERs) can be used to detect specific losses in the auditory system and thus to determine specific regions of the rat's nervous system that have been damaged (25). This approach has been used to assess the effects on hearing of various solvents, such as toluene (56,61, 82,83,88).

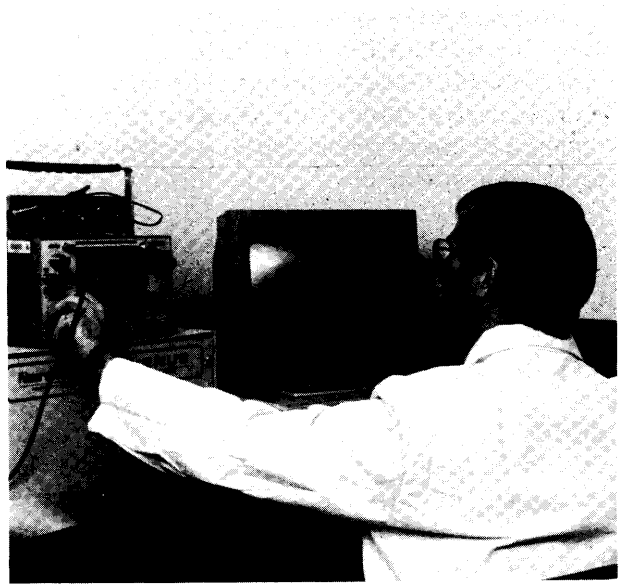


Photo credit: Julia Davis, NSI Technology Services Corp., Research Triangle Park, NC

Experimental neurophysiologist examines a visual evoked potential recorded from a subject watching the checkerboard stimulus seen at right.

Visual evoked potentials, which include flash evoked potentials (FEPs) and pattern reversal evoked potentials (PREPs), are used to evaluate the effects of toxic substances on those components of the nervous system responsible for vision (25,61). The visual system is vulnerable to neurotoxic substances, and acute and chronic exposure to such substances can lead to damage of the retina and the nerve cells in various areas of the brain that process the information received from the retina. Visual evoked potentials have been used to assess the effects of various heavy metals, pesticides, and solvents on visual function in rats. Potentials can be generated using stimuli ranging from diffuse light flashes to complex patterns of shapes and colors (25,61,83).

FEPs in rats are altered by exposure to many heavy metals, pesticides, and solvents. One technique for using FEPs in neurotoxicological studies involves flashing a strobe light of high intensity (turning on and off an intense stimulus) at the test species followed by observing and analyzing the effects on the visual system. One common technique involves placing the rat in a chamber surrounded with mirrors on three walls and on the fourth wall a strobe light which flashes at various intensity levels. Stimulus intensity, pupil diameter, and level of light

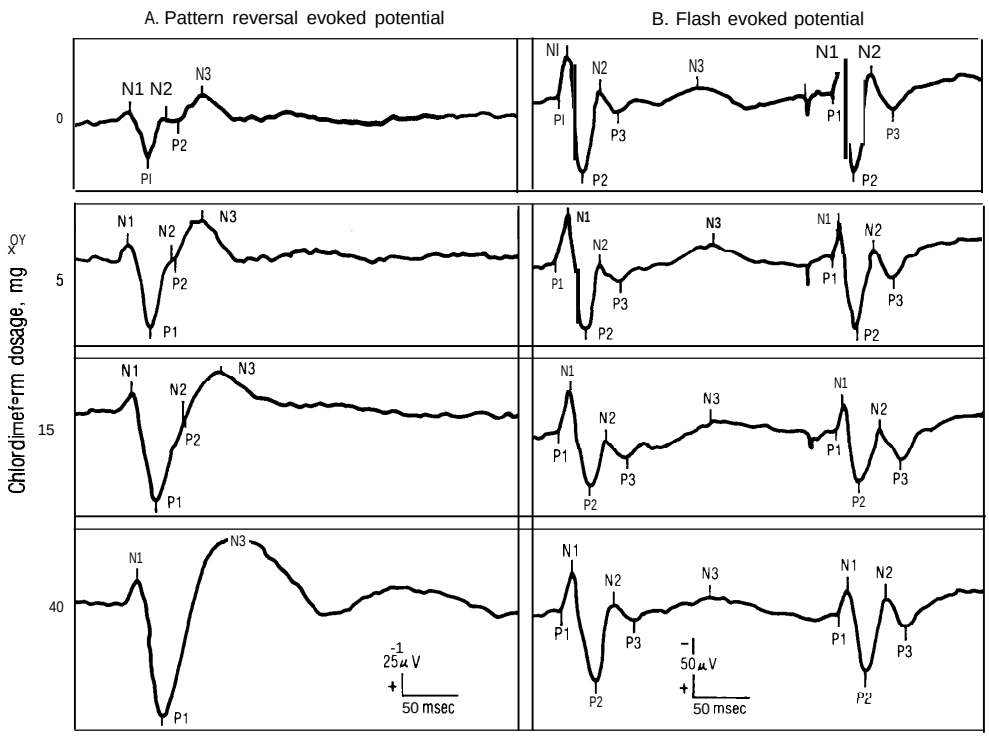
adaptation are the major parameters of concern in recording FEPs (4,25,56,61,82,97). Following FEP examinations, a neuropathological examination may be conducted to identify any retinal or brain lesions (damage or loss of retinal cells) caused by exposure to the toxic substance.

PREPs are used in the diagnosis of optic neuritis, multiple sclerosis, and other illnesses that affect the visual system in humans. Visual evoked potentials can be created by changing a pattern of bright and dark areas on a screen in front of an animal without altering the overall level of illumination. Patterns for PREP testing are generated by reversing the checks on a checkerboard display (black for white and vice versa) or the bars in a horizontal or vertical arrangement. One drawback of this technique is that it is difficult to ensure that animals focus on the patterns, especially without training (4,25,56,61 ,82, 83,97). On the other hand, PREPs can be recorded in awake rats without concern for the focal point. When the stimulus is in the rat's visual field, the eyes will be in focus (10).

Figure 5-2 indicates the results of testing the chemical chlordimeform on the rat visual system. As the dosage of the toxic substance is increased (from O to 40 micrograms per kilogram), the amplitude (size) of the PREPs increases (note, e.g., the distance from points N1 to Pi), but the amplitude of the FEPs is unchanged. The chlordimeform enhances the response to high-contrast, but not to low-contrast, stimuli (12).

Somatosensory evoked potentials (SEPs) are commonly used to determine the effects of both potential and known toxic substances on the nervous system. The somatosensory nerves are the longest cells in the body, extending from the limbs to the head. In testing, an electric current is applied to the sensory nerve of particular interest and the SEPs are measured. Responses can be examined at many points along the nerve. This approach has been used to study the effects of acrylamide (4,25,26,56,61 ,82) and sulfuryl fluoride on the rat's somatosensory system (63).

Figure 5-2-Pattern Reversal Evoked Potential (PREP) and Flash Evoked Potential (FEP) After Treatment With Chlordimeform



SOURCE W Boyes and R S Dyer, "Chlordimeform Produces Profound, Selective, and Transient Changes in Visual Evoked Potentials of Hooded Rats," *Experimenta/ Neurology 86434-447,* 1984

SEPs have been used extensively in neurotoxicological studies because they provide rapid, effective, and quantifiable methods for testing sensory functions (including the visual, auditory, and somatosensory systems). Another advantage is ease in surveying the entire sensory pathway to the brain. However, the equipment associated with this technique is expensive, and special training is often required to operate it. Another limitation is that, due to the large variability among rats, many must be tested to obtain statistically reliable results.

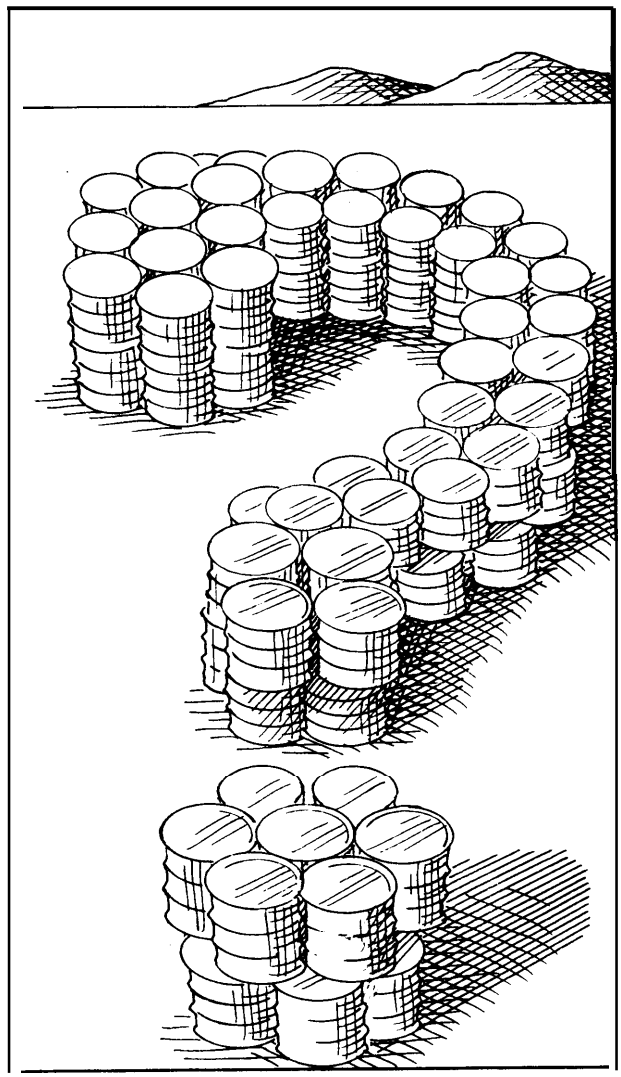
Animal Testing Issues

How Well Are Animal Test Results Extrapolated to Humans?

An important goal of toxicology is to increase the capability of predicting human responses from animal toxicity tests and to understand the causes of interspecies differences in susceptibility to toxic substances. The greatest difficulty in extrapolating animal data to humans is the difference in responses between humans and animals to toxic substances. Humans may be more sensitive to certain substances than animals and vice versa. In addition, since the human population is more heterogeneous than any animal species, the range of doses producing an effect on humans maybe larger than that for animals (122).

Sex, age, health, nutritional state, and genetic makeup may affect an animal's response to toxic substances and must be considered when selecting an animal model. Also, similarity between animal and human metabolism is an important consideration because it may influence the final determination of whether a chemical will be therapeutic or toxic, will be stored or excreted, or will cause acute or chronic effects in humans (65).

When the risks of toxic substances are being assessed, the potential exposure of humans is a critical consideration. Toxicological data on experimental animals should be applied to the situations and routes of exposure that are likely to occur for humans. For example, data collected from the oral administration of a substance to animals have less relevance to a situation in which humans are exposed by inhalation. In addition, an evaluator should be cautious when applying data obtained on young, healthy animals to a human population that is diseased, malnourished, or diverse in its genetic makeup. The data that are to be evaluated to determine a potential risk should be obtained from animal models that are as similar to humans as possible (65). When assessing functional effects, the measures taken in animals should relate to the functions that are at risk in humans. Thus, if human complaints are confusion, memory loss, or irritability, the animal data should be addressed, to the extent possible, to changes in these functions.



Illustrated by: Ray Driver

ALTERNATIVES TO ANIMAL TESTS

Some individuals argue that more animals are used for testing than are needed and that changes in experimental design or improved methods of data analysis could reduce the number of animals used. Alternatives to animal tests, such as in vitro tests,

serve the same fundamental purpose as whole animal tests: to establish the toxicological properties of a chemical in order to protect and improve human health and the environment. In vitro approaches use animal, human, or plant cells, tissues, or explants maintained in a nutritive medium for use as a model system in toxicity testing.

Concern about the use of animals in testing seems to be accelerating at the same time as concern about product and drug safety. However, the need for more experimental animals is an incentive for the development of new techniques, especially faster and less expensive ones (105). While Federal regulatory agencies currently rely on animal tests to predict human toxicity, in vitro alternatives are likely to play an increasingly important role in future toxicological evaluations.

In vitro tests are often used to complement animal tests and reduce the number of animals being used for routine toxicity testing. Methods for integrating in vitro tests into routine toxicity testing are necessary to enhance understanding of the neurotoxic potential of toxic substances (37).

Toxicologists have identified three major reasons for developing in vitro techniques: scientific-**academic, economic,** and humane. There are many scientific-academic reasons for developing in vitro methods. There are more than 60,000 chemicals in EPA's inventory of toxic substances and thousands more chemical formulations, many of which have not been tested for toxicity. Current testing methods are time-consuming; for example, it might take from 3 months to 2 years to complete a battery of chronic studies. With the enormous number of substances that have not been tested and with new substances continually entering commerce, rapid, inexpensive methods are needed for screening.

In vitro testing is already of critical importance in academic scientific research. This approach is often employed to determine the mechanism of action of toxic agents because in vitro systems are less complicated and can be manipulated easily. Tissue culture methodologies have advanced rapidly, and new equipment and facilities will ensure continued progress (36). It has been estimated that more than $70 million has been spent in the United States over the past decade to develop in vitro testing (37). There are numerous opportunities to apply the knowledge that has been gained in basic research to the development of methods of toxicity testing.

The cost of in vivo research and testing is increasing. In vitro approaches are generally more economical, being both less expensive and less time-consuming. In addition, they are also more humane because they reduce animal use and minimize animal suffering (36).

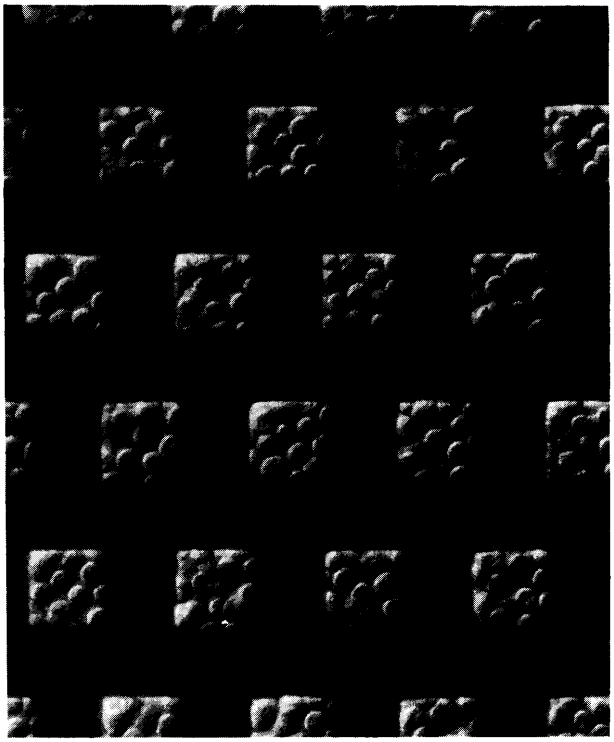
In Vitro Neurotoxicity Test Development

Interest in using in vitro testing approaches to assess neurotoxicity has increased considerably in recent years. In 1980, a symposium on the use of tissue culture in toxicology, held in Sosterberg, Holland, focused on the potential application of in vitro approaches to the study of neurotoxic substances. Participants emphasized the need for improved methodologies and increased awareness in the regulatory community of the utility of in vitro techniques. Since that time, efforts to develop in vitro tests have advanced rapidly (36,37,103).

In vitro tests do have some limitations. They cannot mimic the complex biochemical and physiological interactions that take place in vivo. Also, the supply of normal human cells available for toxicological testing is currently limited. In order for human cells to be used routinely for toxicity testing, some method of making them more readily available must be devised. In addition, not all human cell types can be cultured (103).

A number of companies in the United States are currently developing in vitro toxicological tests. For competitive reasons, industry initiatives are generally not made public. Consequently, they will not be addressed in this report.

The Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Consumer Product Safety Commission (CPSC), and EPA are examining potential in vitro testing approaches (116). In particular, the National Toxicology Program of the Department of Health and Human Services is evaluating in vitro systems and has asked for proposals on alternative test development (1 16). The CPSC is attempting to make greater use of existing chemical, biological, and human data in order to avoid animal tests, to reduce the number of animals used in tests, and to modify existing methods so as to reduce pain and suffering (95). EPA has also taken action to reduce the use of animals in toxicity research and testing.



Photograph by J.C. Owicki and K.M. Kereso

Photomicrograph of living cells in the wells of chambers that allow monitoring of changes in cellular metabolism following exposure to toxic substances.

Numerous in vitro techniques are currently in use. Tissue culture involves maintaining or growing organs, tissues, or cells in vitro for more than 24 hours. Tissue culture can be further subdivided into cell culture and organ culture (22,105).

Tissue Culture

Many tissues from humans and animals can be successfully maintained and studied in culture. Roux originally used tissue culture in 1885 to maintain chick embryos outside the egg (99). Nervous tissue was among the first tissues to be cultured. In 1907, R.G. Harrison developed a method for maintaining frog neural tissues in vitro for weeks (40). In the 1930s, advances were made in defining the media required for maintaining cells and tissues in culture, and by the 1950s, tissues could be cultured in entirely synthetic media. At the same time, scientists became aware of the importance of adding antibiotics to culture systems. Before antibiotics, bacterial growth interfered with the developing cells, and all work had to be done in aseptic conditions. It is now standard procedure to inhibit bacterial growth with antibiotics (99,105).

Pure cultures of cells and mixtures of cells have different properties. These differences may be used to study various aspects of cell activity, such as differentiation. In this process, one can distinguish between cells that have a capacity to form other cells (undifferentiated cells), and cells that have reached their final stage of development and will not undergo any further change (differentiated cells) (21,99).

In cell cultures, the colony consists of a mass of differentiated or undifferentiated cells, and individual cell types are not easily identified. However, where a number of different kinds of cells are growing together, such as in organ cultures, the cells retain their normal function and differentiated form; thus, the different types of cells are easy to identify (99). Tissues can be kept alive outside the living animal for months or years in cell cultures; however, whole organs can be sustained in cultures for only a few days to a few weeks.

Assessing toxicity using tissue culture approaches generally involves adding a test substance to the culture, observing the viability of the cells, and identifying any structural or functional changes.

Applications of In Vitro Techniques to Neurotoxicity Testing

Various types of in vitro techniques are being developed to evaluate the effects of potential and known neurotoxic substances. These approaches can be grouped into three general categories: primary cultures, cell lines, and cloned cells.

Primary Cultures

Primary culture refers to the removal and maintenance of cells, tissues, and organs in vitro. Embryo culture, for example, has proven to be very useful in neurotoxicological studies. Recently, the Chemical Industry Institute of Toxicology (CIIT) in Research Triangle Park, North Carolina, developed a rodent fetal cell culture system for in vitro testing. This approach involves removing certain regions of the brain from mouse embryos and culturing them in a chemically defined environment. After the culture is exposed to various known and potential neurotoxic substances, the tissues and cells can be examined for morphological and biochemical changes (20). This technique is useful because neuronal tissues undergo normal or near-normal development, and cellular and tissue interactions can be analyzed.

CIIT scientists are using a class of substances known as monohalomethanes to validate this test system. Animal and human exposure to monohalomethanes may result in a variety of neurological symptoms, such as tremors, lack of coordination, epileptic seizures, and coma. The results from in vitro studies using monohalomethanes are compared with documented animal studies to determine correlations between in vitro and in vivo methods. Development of a database to compare results from in vitro and whole animal studies, human studies, and epidemiological studies may aid in validating this system (20). A similar embryo culture approach was used successfully by others to demonstrate that ethyl alcohol can retard the growth and differentiation of fetal tissues (13).

Retinal neurons may also be employed to evaluate the effects of toxic substances on the nervous system. This approach involves dispersion and culture of retinal cells removed from chick embryos. Culture methods have recently been improved, allowing growth of low-density, clump, and flat cell-free cultures of chick embryo neurons. These cultures can be used to analyze the effects of toxic substances on cell differentiation using time-lapse video recordings. In addition, various biological techniques may be used to define and characterize observed effects (2).

Techniques for culturing neonatal mouse retinal neurons and photoreceptors have also been developed recently. Cells from the retinas of 2-day-old mice can be cultured in serum-free, completely chemically defined environments. They serve as useful models for evaluating the survival and differentiation of photoreceptor cells, which are critical to visual processes (87).

A "monolayer" culture system has been developed to allow the survival and differentiation of chick embryo retinal neurons and photoreceptors without contamination. Photoreceptor cells can be purified with kainic acid and B-bungarotoxin, which, when added to the culture medium, destroy many retinal neurons without affecting the photoreceptors (86). The technique of selectively destroying cells is a recognized means of cell separation in tissue culture. Once purified photoreceptors are available, the effects of various toxic substances can be determined without the complicating factors introduced by multiple cell types.

Muscle cells can also be cultured, allowing investigators to analyze the effects of toxic substances on the neuromuscular system. Cultured muscle cells from rats and chicks have been used in electrophysiological studies to examine the sensitivity of acetylcholine receptors. Toxic substances have also been used to aid in characterizing the structure and function of acetylcholine receptors (91). This type of system could be adapted to assess the effects of toxic substances on the neuromuscular junction.

Another useful testing method involves organotypic cultures, cultures that preserve the connections and spatial relationships between neurons and glia (126). One such culture used in neurotoxicity studies is of the ganglion (a collection of nerve cells external to the brain or spinal cord) (96). In addition, the mouse embryo spinal cord has been used to study the effects of various neurotoxic substances, including organophosphorous pesticides **(35).** Organotypic cultures have also been used to examine the mechanisms of action of a wide range of neurotoxic substances, including such metals as mercury and thallium and such organic compounds as chloroquine (a drug used to treat rheumatic fever) and 2,5-hexanediol, a metabolize of n-hexane (126).

Explant cultures are also useful in evaluating neurotoxicity. They involve placing a small piece of nerve tissue in a culture medium and maintaining it for several weeks or months at a time. Explants have been used to evaluate the effects of chemicals on the myelin sheath surrounding nerve cells and on the synaptic connections between these cells (96).

Cell Lines

Cell lines take advantage of the immortal properties of certain types of malignant nervous system cells. For example, the neuroblastoma C-1300 and the rat glioma C-6 cell lines have been used in neurochemical and morphological studies for evaluating the effects of a variety of neurotoxic substances (22,35). One group of investigators recently fused rat retinal cells with mouse neuroblastoma cells to create a hybrid cell line that proved to be very useful in evaluating the neurotoxic effects of the amino acid glutamate and related compounds (73). Cell lines are especially useful because a large quantity of single cell types are available for biochemical analysis, the cells can be easily examined microscopically, and electrophysiological evaluations may be undertaken (96).

Advantages and Limitations of In Vitro Testing

In vitro tests are advantageous for several reasons. They involve simpler procedures and consequently take less time to complete than animal tests. For example, technicians can conduct morphological, biochemical, and physiological studies on the same preparation (93). Furthermore, cultures can be transferred from one region of the country to another, allowing evaluation of the same culture in various laboratories specializing in particular tests. Cultures can be made of human cells, hence the difficulty of species variation and of extrapolation of data is minimized. Substances may be studied in isolation, and responses by selected cell populations can be examined. Also, the cellular environment can be controlled through modification of the concentration and nature of specific nutrients, which is difficult using animals (21,99,20).

On the other hand, in vitro tests normally do not account for the route of exposure to a substance, its distribution throughout the body, or its complete metabolism. Also, because in vitro systems generally do not duplicate the neural circuitry of the entire animal, toxic endpoints (e.g., behavioral changes, motor disorders, sensory and perceptual disorders, and lack of coordination) may be difficult to define (93). Other concerns are that substances added to the culture to keep it viable (e.g., antibiotics) might interact with the tested substance, that cell lines of cancerous cells may respond to toxic substances differently than normal cells, and that it may not be possible to perform chronic toxicity studies due to the relatively short lifespan of many cultures (cell lines using immortal cells are a possible exception). Nevertheless, all test systems have limitations, and there is general agreement that the many advantages of in vitro testing present a strong incentive for continued development and increased utilization (21,99,20).

HUMAN TESTING

Millions of U.S. workers are exposed full- or part-time to general toxic or neurotoxic substances (3). Nearly 400,000 cases of occupational diseases are recognized annually (111). Preventing the adverse health effects of chemicals is largely dependent on understanding the toxicological properties of new and existing chemicals. Various standardized human tests are available to assess the adverse effects of toxic substances on the nervous system; however, because of the ethical issues inherent in performing some human tests and the difficulty of obtaining trained staff and expensive equipment, there have been relatively few human studies conducted (24).

Overview of Human Tests

Human testing may occur in response to occupational, environmental, or laboratory exposures. The methods used to assess the toxicity of substances vary from one setting to another, since some approaches are appropriate in one situation but not in others. For example, when determining early symptoms of chronic exposure, subjects exposed occupationally are better test groups than groups exposed environmentally. On the other hand, in certain epidemiological studies, subjects exposed environmentally may be helpful because of the large diversity of individuals and wide range of ages (74).

In the occupational setting, workers are often exposed unintentionally to toxic substances. In the general environment, exposure groups may include individuals and families living near sources of industrial pollution, people living in large industrial cities where they are exposed to vehicle exhaust and fuel additives, and farmers and agricultural workers exposed to pesticides in the field (74). Epidemiological studies of these individuals are required to determine the extent to which neurotoxic substances are affecting human health.

Neurobehavioral Tests

Neurobehavioral tests can provide objective evaluations of nervous system and neurobehavioral functions. Test methods have been utilized both in evaluation of groups of workers exposed to substances and in laboratory examinations of individuals suspected of having occupational illnesses. In the evaluation of a group of workers, neurobehavioral tests are used to assess exposure-effect relationships and, in some cases, to serve as guides for establishing standards for workplace exposures. In the laboratory setting, neurobehavioral methods are useful in quantifying the degree of functional disability and in making a diagnosis (44).

Several considerations are involved in the selection of testing techniques to determine the effects of neurotoxic substances on workers' health. It is very important to consider the purpose of the examina-

tion. For example, the study may be designed to identify effects on individual workers who are exposed or on a population of workers exposed as a group. Furthermore, the frequency and duration of exposure must be determined: a study of acute effects may require tests measuring different functions and properties than a study of chronic effects. Finally, in some tests a certain time period must elapse before effects become apparent (44,67). Researched most commonly select tests that are known to measure functions affected by several neurotoxic substances; provide a complete analysis of nervous system effects, ranging from reflexes to complex behaviors; are known to measure one or more well-defined functions, whether psychological or neurophysiological; and are cost-effective in terms of the information they provide (44,67).

Neurobehavioral test results are influenced by many factors. These can be divided into three general classes: subject, examiner, and environmental. Subject factors include the individual's age, sex, education, socioeconomic status, health and drug history, and motivation. Table 5-1 summarizes the subject factors influencing neurobehavioral test results. Examiner factors are another important consideration. In order to ensure the cooperation of subjects and to maximize the reliability of the data, it is important to establish a good working relationship between examiner and participants. It is also important that a well-trained examiner speak and interact with all subjects in a consistent and standardized manner (44). Environmental factors that influence neurobehavioral studies include the test surroundings, subject-experimenter interaction, and season of the year.

Table S-l-Subject Factors Influencing Neurobehavioral Test Results

Age: The performance on neurobehavioral tests varies with age. When comparing exposed groups, subjects should be matched by age as closely as possible.
Sex: There are biological and social differences that must be considered when designing tests that include male and female workers.
Years of school **education:** Amount of education also influences the performance on neurobehavioral tests.
Socioeconomic status: Socioeconomic status includes a combination of educational, cultural, and occupational factors that may affect test results. This factor takes into account the years of school education, regular income, and special occupational training.
Health and drug history: Any disease that affects neurological functions will affect neurobehavioral studies. Some of these diseases include epilepsy, diabetes, and arthritis. If an individual has any of these health problems, the evaluator may want to exclude the individual from the study. Drugs must also be considered. Psychoactive drugs, in particular, can alter performance on the study. In addition, certain consumed foods and beverages may alter the individual's alertness and performance. These include coffee, colas, and chocolate, all of which contain caffeine.
Motivation: The attitude of the participants must also be taken into account.

SOURCE: B.L. Johnson (cd.), *Prevention of Neurotoxic Illness in Working Populations (New York, NY:* John Wiley& Sons, 1987).

Finland's Institute of Occupational Health Approach

During the 1950s, the first neurotoxicity test battery for occupational exposure was developed at Finland's Institute of Occupational Health (FIOH). The battery was designed to study the effects of various substances, especially solvents, on workers. The 14 neurobehavioral tests listed in table 5-2 are typical methods used at FIOH to evaluate effects on intelligence, short- and long-term memory, learning ability, perception, motor performance, and personality. The battery is now used routinely in Finland (39).

Psychological testing is usually conducted at the Institute, although sometimes it is conducted at an industrial facility. The tests are usually performed on an individual basis. Before the tests are administered, the patient is interviewed. The tests are presented in a fixed order, as indicated in table 5-2. The examination takes 1 to 3 hours, depending on the tests used and the time available for interviews (39).

World Health Organization's Recommended Approach

During a meeting cosponsored by WHO and the National Institute for Occupational Safety and Health in 1983, neurotoxicologists recommended a core set of tests, known as the Neurobehavioral Core Test Battery, that could be used in screening for neurotoxic effects. This test battery is particularly useful in developing countries or in places where there are limitations in the setting or the literacy of the test population (3).

Table 5-3 lists the tests used in this battery. They were chosen to allow development of uniform, consistent data from a variety of occupations and neurotoxic exposure situations (3). Most of the core tests require the use of paper and pencil in order to minimize the need for mechanical instruments (a concern for developing countries). These tests generally require minimal training to administer; how-

Table 5-2-Behavioral Test Battery for Toxicopsychological Studies Used at the Institute of Occupational Health in Helsinki

Test method+Test description
Wechsler Adult Intelligence: -determining similarities between items; measures verbal ability -determining synonyms of words; measures general intelligence and verbal ability —reproducing patterns of design using blocks; measures visual ability -determining the missing parts of pictures; measures perception —associating symbols and digits; measures memory and speed —recalling digits in series; measures verbal memory
Wechsler Memory Scale: –logical memory, visual reproduction, and associative learning
Benton Visual Retention Test: —recalling and reproducing figures; tests memory and visual retention ability
Kuhnburg Figure Matching Test: —recalling various figures on cards; measures speed and memory
Bourdon *Wiersma Vigilance Test:* —strike over all groups of 4 dots as printed on the test sheet (50 rows); each row contains 25 groups of 3,4, or 5 dots; performed as accurately and quickly as possible; measures speed and perception
Figure Identification: —identifying figures; measures speed and perception
Symmetry ***Drawing Test:*** -drawing the other symmetric half of figures; measures perception and motor speed
Santa Ana Dexterity Test: —test for manual dexterity; hand-eye coordination; measures the ability to perform skillful movements with hands and arms
Flnger Tapping Test: —taps a counter with thumb rapidly; measures motor speed
Reaction Time: —reactions of hands or feet from visual and auditory signals; measures simple reaction time to respond to stimulus
MIra Test: -draw simple, straight, and broken lines without seeing the paper and pencil; measures psychomotor behavior and psychomotor ability
Rorschach Inkblot Test: —variables: adaptability, emotionality, spontaneity v. inhibition, rational self-control, originality of the perception; measures personality, nonintellectual personality disturbances, changes in mood, readiness for affective reactions
Eysenck Personality Inventory: —measures two dimensions of personality: neuroticism and extroversion-introversion
Questionnaire: —measures changes in mood, emotionality, and subjective well-being; two forms used: 1) measures sleep disturbances, fatigue, neurotoxic behavior; and 2) measures disturbances in control of mood, emotions, attention, fatigue

SOURCE: H. Hanninen and K. Lindstrom, ***Behavioral Test Battery for Toxicopsychological Studies Used*** at ***the Institute of Occupational Health in Helsinki*** **(Helsinki: Institute of Occupational Health, 1979), pp. 1-58.**

Table 5-3—WHO Neurobehavioral Core Test Battery

Functional domain	Core test
Motor speed, motor steadiness	**Aiming (Pursuit Aiming ii): assess** the control and precision of hand movements; individual is required to follow a pattern of small circles, placing a dot in each circle around the pattern; subject's score is the number of taps in the circle within 1 minute
Attention, response speed	Simple reaction time; see table 5-2 for description
Perceptual-motor speed	**Wechsler Adult Inteiiigence** Scale: a sheet contains a list of numbers that are associated with certain simple symbols and a list of random digits with blank spaces below them; subject asked to write correct symbols in blank spaces as fast as possible
Manual dexterity	**Santa Aria: see** table 5-2 for description
Visual perception, memory	**Benton Visual Retention:** see table 5-2 for description
Auditory memory	**Wechsler Adult intelligence Scale:** recall digits in series forwards and backwards immediately after hearing them

SOURCE: B.L. **Johnson, (cd.),** ***Prevention of Neurotoxic Illness in Working Populations (New York, NY:*** John Wiley & -Sons, 1987).

ever, the reaction time test requires the use of an electrical instrument that necessitates some training. The total amount of time necessary to complete the core test battery is approximately 45 minutes (44).

Computer-Based Testing

Computer-based neurobehavioral tests have recently been developed in response to the need for standardized testing methods that objectively and efficiently collect data on various neurotoxic effects seen in exposed workers. Computer testing has been used to study acute exposures of workers in laboratory (experimental) studies and to study chronic effects on workers in epidemiological studies. Some computer-based tests are reliable for conducting comparative studies of workers, but methods appropriate for clinical studies have not been developed (52).

The most extensively used computer-based test battery is the Neurobehavioral Evaluation System. The tests selected analyze a broad range of central nervous system functions, including psychomotor performance, memory, perceptual ability, vocabulary ability, and mood (53,7).

Various computer-based tests have been developed for epidemiological applications, including the

MicroTox System (27); Swedish Performance Evaluation System (41); Milan Automated Neurobehavioral System, a computer implementation of many of the tests in the WHO Neurobehavioral Core Test Battery (15); and the Cognitive Scanner, developed in Denmark (51).

Computerized techniques have several advantages and limitations. Some of the primary advantages are reproducibility of testing conditions, ease of scoring, immediate reporting of results to the subjects, and storage of data in the computer's memory for future use. In addition, highly trained staff are not required (52,7). The limitations of these techniques center on the cost and availability of equipment. In addition, computer techniques usually emphasize speed of response; thus, other behavioral responses may not be adequately measured.

Neurophysiological Techniques

As is the case for animal testing, a variety of neurophysiological techniques can be used to assess the health effects of potential and known neurotoxic substances on humans. Many of the same techniques used in animal studies can be employed for evaluating worker exposure to various neurotoxic substances. These include the sensory evoked potentials, electromyograph, and electroneurograph. Sensory evoked potentials include brainstem auditory evoked responses, flash evoked potentials, pattern reversal evoked potentials, and somatosensory evoked potentials. Most of these techniques have been summarized earlier in this chapter; they will not be readdressed here. (See the section on neurophysiological techniques of animal testing.) EPA summarized several situations in which analysis of sensory evoked potentials would be useful (82), including determining the sensory effects of injured workers who are unconscious, immobile, or unable to respond verbally; sensory testing of workers claiming compensation when malingering is suspected; sensory testing of workers whose complaints do not correspond to clinically significant deficits in routine clinical examination; distinguishing peripheral from central nervous system damage in sensory pathways; and monitoring of workers chronically exposed to chemicals known to be neurotoxic.

Electromyography (EMG) and electroneurography (ENG) are established testing techniques well-suited to studies of various neuromuscular disorders. They are also often used in clinical examinations in neurology, orthopedics, and neurosurgery. EMG records electrical activities using a needle electrode inserted into the muscle. Researchers note several characteristics, including electrical activity in the muscle when the needle is inserted, electrical activity of the resting muscle, and electrical activity of motor conduction velocity during voluntary muscle contraction (43). ENG measures the electrical signals generated by the nerves. The electromyograph has not been used extensively for evaluating the health effects of neurotoxic substances on test animals, because few toxicologists are trained in EMG procedures. Interpretation of the results requires special training, and it can be difficult to control the degree of muscle contraction in test animals (97,43).

Human Exposure Studies

Information collected in human neurotoxicity studies may have several important uses, including:

- providing indications of toxic effects that can serve as early warnings of chronic disease processes;
- testing the adequacy of existing or proposed exposure limits;
- identifying human performance capacities that may be impaired by short-term exposure to toxic chemicals; and
- providing data on the neurotoxic effects of exposure to more than one chemical or other workplace conditions (e.g., physical agents, work level, drugs) that may interact to modify the neurotoxicity of single substances (44).

Fundamental components of this type of study are controlled exposure to the substances being studied, methods for estimating the body burden of the substances, appropriate tests and experimental design to reflect the neurobehavioral response of the subjects to the substance, and control groups or control conditions. However, human exposure studies are among the most difficult and expensive controlled laboratory experiments to conduct. Because humans have complex personalities, each individual brings to the experiment several attributes that may be difficult for an investigator to control. Such variables include age, sex, education, motivation, and work history (24).

Human studies typically require more examiner-subject interaction than other types of tests. A certain amount of controlled and consistent interaction is necessary to reduce the anxiety caused by the test

situation. Several factors may affect the interaction, including the presence of more than one examiner, and the personality, experience, and sex of the examiner. Interaction effects occur when subjects are tested in groups in large exposure chambers. The results of a study may change if the subjects are tested in groups of two or more rather than singly, in groups of both sexes rather than one sex, or in groups in which the subjects are friends rather than strangers (24).

Selection of Study Populations

The success of any human toxicity test depends on a well-designed study that has a clearly defined purpose. Two major reasons for conducting a study in the industrial setting are: 1) an awareness that a group of people collectively has similar health complaints and that a potential occupational health problem exists, or 2) a potential hazard has been identified and more information is needed to define the extent of the hazard. When undertaking human studies, it is important to select a well-defined group. If the purpose of the study is a potential health problem, the study population may have been identified by a formal complaint from an individual or company to a Federal agency. Usually, the source of the complaint appears to be limited to a work site or a plant. In this circumstance, a preliminary screening questionnaire may be conducted to determine the study group (125).

Steps in Conducting Workplace Research

There are several fundamental steps in conducting a workplace research study, and there are several significant dangers to be avoided. The identification of a suitable work group is the first, difficult step. The evaluator should consider the willingness of a company to allow worker participation. Prior to beginning the test, the evaluator must seek out the companies involved and convince them of the value of the test in order to ensure participation. Most employees will cooperate as long as they are convinced that data on them will be kept confidential (3).

Testing conditions are determined by the industry involved and past experience with the test selection. Testing sites are usually clinics, hospitals, laboratories, and conference centers. It is standard practice to describe the purpose and the benefit of the study to test subjects, what unpleasant tests they will encounter, who is responsible for the study, and whom to contact if they have questions or experience difficulties. They should also be informed that they may withdraw from the study at any time if they feel that it is unsatisfactory in any way (3).

Records should be kept on file for each research project. They should contain information on the day-to-day decisions regarding the study and any unusual events that take place. In addition, there should be a comprehensive report containing information on worker characteristics such as age, sex, race, and education; the number of years that the worker has been at his or her profession; the measurements or pattern of exposure over the years; the methods used to obtain the measurements; complete descriptions of all tests; descriptions of statistical tests used; and any adverse effects and diseases that were determined (3).

Epidemiological Studies

Epidemiological studies play a very important role in evaluating the effects of neurotoxic substances on workers and in developing strategies for the prevention of occupational diseases affecting the nervous system (44). The advantage of such studies over animal testing is that they provide direct evidence of effects on human health. However, human studies are difficult to conduct and evaluate. One limitation is that if the exposure results only in acute effects, epidemiological studies must be performed shortly after exposure occurred.

Another limitation is the complex relationship that exists between toxic exposures and human disease. Humans vary greatly not only in their exposure to substances, but also in their physiological response to exposure. Despite these difficulties, extensive techniques for evaluating data from human studies have been developed. Epidemiology has proved to be a reliable means of evaluating qualitative and quantitative relationships between exposure to toxic substances and human disease (16). Because epidemiological studies generally identify correlations between exposures and effects, it is often necessary to undertake animal studies to identify cause and effect relationships.

Occupational epidemiology is the study of the distribution of a disease among a working population and the factors that influence this distribution. This field attempts to identify relationships between diseases and occupational exposures to chemicals. The value of such epidemiological studies is in-

creased when they are used with toxicological studies on humans or animals. They are important in identifying possible associations that can be tested in laboratory environments. Furthermore, they can be used to evaluate human health risks suggested by laboratory exposures (16).

Legal and Ethical Considerations in Neurotoxicity Testing and Monitoring

Deliberate exposure of humans to neurotoxic substances in the course of research calls for all of the basic protections afforded research subjects under existing Federal law. Department of Health and Human Services regulations require institutions performing research on human subjects to create and use Institutional Review Boards to check proposed projects for compliance with regulations if those projects are funded by the Department or its constituent agencies (45 CFR 46.103(b)). Although these regulations are legally binding only on institutions receiving Federal funds, they are usually considered minimum standards for other institutions and research situations as well.

After there has been an appropriate evaluation of the value, scientific merit, probability of generating knowledge, and risk-benefit ratio of a proposed study, subjects can be selected and their consent solicited. Federal law requires that specific information be disclosed before valid consent can be obtained. Under Federal regulations (45 CFR 46.116) and some State statutes, all reasonably foreseeable risks and discomforts that subjects might experience must be disclosed.

Risk information is not the only type of information that requires greater elaboration in the research setting. Federal law also mandates disclosure regarding the nature and purpose of the research; anticipated length of the subject's participation in the study; procedures to be followed; identification of experimental procedures; benefits that may reasonably be expected to accrue to the subject or others from the study; steps to be taken, if any, to maintain confidentiality of records identifying participants; whether compensation and treatment are available for injury arising from a study where more than minimal risk is involved; and who should be contacted if subjects have questions regarding the research or their rights, as well as the contact person in the event of research-related injury (45 CFR 46.1 16(a)).

Workplace exposures to neurotoxic substances may be accidental or nonaccidental. The primary ethical obligation in the case of an accidental exposure to a neurotoxic substance is prevention. Box 5-C illustrates the important ethical issues that arise from chronic workplace exposure to neurotoxic substances such as mercury, A continuing issue in both types of workplace exposure is whether it is appropriate to notify workers about past exposures to hazardous substances, including neurotoxic substances. Many persons believe that groups of workers who have been exposed to hazardous substances in the past should be informed of this whenever possible. However, the possibility that some workers will be mistakenly identified and informed has to be weighed against the value of a retrospective notice procedure.

Prevention of Human Exposure to Neurotoxic Substances

Some of the disorders caused by neurotoxic substances can require extensive therapy and medical care. In addition, a significant number of these may be irreversible if exposure levels are high. The severity of these effects is an excellent reason for implementing methods of preventing exposure to neurotoxic substances.

Several approaches are used. One method is to increase awareness of the effects of neurotoxic substances through educational programs (6). These programs are designed to educate supervisors and workers about the signs and symptoms associated with exposure to certain toxic substances in the workplace. Managers may reduce risk of exposure to substances by substituting a less hazardous substance for the substance of concern, using adequate engineering controls, developing improved working conditions, and providing proper protective equipment, such as respirators, gloves, eye shields, and boots (6,125).

All occupational safety and health programs should be directed toward recognizing and preventing problems early. This includes communication among Federal agencies, manufacturers, and users of potentially neurotoxic substances.

Medical controls are another important aspect of an exposure prevention program. The extent of the controls will depend on the hazards and seriousness of the risks involved. Preemployment physical examinations, including detailed histories of previ-

Box 5-C—Ethical Issues Associated With Chronic Exposure to a Neurotoxic Agent

One example of an occupational exposure to a neurotoxic agent is the case of workers assigned the task of recovering mercury from old or broken thermometers.

On October 16, 1986, two executives and a supervisor of the Pymm Thermometer Company were indicted on charges of assault for allegedly endangering the lives of workers by knowingly and continually exposing them to mercury, conspiracy for hiding the existence of a cellar workshop from the Occupational Safety and Health Administration (OSHA) inspectors, and falsifying records in an attempt to conceal the cellar operation. According to the brief filed on behalf of the workers:

> Already aware of the dangerous conditions on their main manufacturing floor, defendants created and maintained even worse conditions in a cellar mercury-reclamation operation. In order to salvage some of the valuable mercury that was being wasted in its main manufacturing process, Pymm constructed a crushing machine that ground up broken and defective thermometers, spewing mercury-laden dust into the face of the machine operator. The machine was housed in a windowless, underventilated cellar, where defendants stored boxes leaking mercury from the broken and faulty thermometers to be processed (85).

One worker who was employed in this area for approximately 11 months suffered permanent brain damage from mercury poisoning (85). Exposure to mercury can cause tremors, headaches, and nausea, and more severe cases of mercury poisoning have been linked to brain damage, kidney disease, loss of vision and hearing, and motor impairment. Humans can absorb mercury by inhaling the vapors in the air. Mercury passes from the lungs into the bloodstream, which transports and deposits it first in the brain and then in other parts of the body, including the spinal cord and peripheral nervous system. Once in the body, mercury binds to proteins in the central nervous system. As long as mercury circulates and remains in the body's soft tissue, some of it can be returned to blood and plasma, to be extracted and excreted through the kidneys and intestines. In this way, the body rids itself of about half of one day's intake over a period of 40 to 70 days. When, however, a person takes in mercury faster than it be can excreted, the body begins to store mercury in bones and teeth (47). OSHA's limit for exposure during an 8-hour day is 0.1 milligram per cubic meter of air.

Chronic exposure of workers to a known neurotoxic agent like mercury raises ethical arguments about the duties of employers not to knowingly inflict harm on workers, the use of coercion in exposure to neurotoxic agents, the right of an employee to know that he or she is working in a harmful area, and the right of the employee to experience the full benefit of Federal efforts to ensure a safe workplace through OSHA inspectors and accurate record keeping. The employers in a case such as this could make an ethical argument that the greatest good for the greatest number entails recovery of mercury, but they are not ethically or legally free to pursue this objective when it clearly inflicts a known hazard on workers. The ethical dilemma in a case such as this would be an arguable ethical right of the worker to assume the risks of exposure to a known neurotoxic agent, such as mercury, in order to pursue some other value, such as increased pay. In order to explore whether the worker would have such a right it would be necessary to ensure that the worker was freely and knowingly opting to take such a risk. In addition, it would be important that the individual not impose unnecessary risk on others, for example, by exposing family members to mercury by bringing it home on work clothes. In the Pymm case, it is alleged that when the workers asked about any possible dangers of working with mercury, the employer lied and provided no training, protective clothing, or other safety equipment (85). Although the company officers were convicted by the jury on the assault charges, the trial court judge overturned the verdict. The State appealed to the appellate division of the Supreme Court of the State of New York. The case is continuing.

SOURCES: C.D. Klaassen, M.O. Amdur, and J. Doull (eds.), ***Casarett and Doull's Toxicology (New*** York, NY: Macmillan, 1986); ***People of the State of New York v. William Pymm, Edward A. Pymm, Pym Thermometer, Inc., and Pak Glass Machinery Corp.,*** Brief for the Appellant, Mar. 21, 1988.

ous exposures to substances and relevant preexisting conditions, are often very useful. Such examinations can identify persons who are likely to be susceptible to specific toxic substances. In addition, they allow the occupational physician to take necessary steps to limit employee exposure to certain hazards. Routine medical examinations also aid in monitoring the effectiveness of worker safety programs and verify the effectiveness of engineering controls. Symptoms of a high level of exposure to a substance in a-group of workers may indicate a failure that must be corrected. Consequently, more stringent engineering controls may be implemented to improve the working environment. A variety of engineering controls may be used to minimize exposure to neurotoxic substances. Because OTA described these in detail

in a previous report (104), they will not be addressed here.

MONITORING OF TOXIC SUBSTANCES

Numerous methods are currently being used to monitor exposure to and adverse health effects of toxic substances, including substances that may affect the nervous system. These methods include specimen banking (long-term storage of biological specimens for toxicological analysis), monitoring of animal tissues (e.g., marine mammal tissues and mussel tissues), and biological monitoring. Monitoring studies are used to develop baseline data, to determine whether and to what extent humans and other organisms are exposed, and to assess exposure trends. The following discussion summarizes some of the current domestic and international monitoring programs.

Specimen Banking

Domestic and International Programs To Monitor Toxic Substances

The purpose of specimen banking programs is to track the concentrations of contaminants in tissues over time. Data from programs of this kind are very useful to public health and regulatory officials, who must ensure that human exposure to toxic substances is limited. These data are also critical to epidemiological and other scientific investigations designed to link adverse health effects with particular toxic substances. Human tissue monitoring was first undertaken in the Federal Republic of Germany and the United States. Other countries now have plans to collect and store human tissues, including Canada, Japan, and Sweden. In 1980 and 1981, the West German Specimen Banking Program began collecting and storing human specimens at the University of Munster and at the central bank at the Atomic Research Center in Julich (54). Three types of human material were collected: whole blood, adipose tissue (fat tissue), and liver tissue. Biological specimens from terrestrial, freshwater, and marine environments were also collected (54).

In 1973, EPA, in collaboration with the National Bureau of Standards (NBS),[1] proposed the establishment of a National Environmental Specimen Bank, a systematic approach to specimen banking and monitoring for effects of toxic substances. Since 1975, EPA and NBS have been involved in research-related programs for specimen sampling, analysis, and storage (118,120,1 19). Furthermore, in 1975, the Federal Republic of Germany and EPA agreed to cooperate in general activities of specimen banking (120). A workshop was sponsored by EPA and NBS in 1976 to design a pilot National Environmental Specimen Bank program and to evaluate the long-term storage of samples. The primary goals of this program are the collection, processing, storage, and analysis of specimens (120).

In addition, EPA has established two monitoring programs to assess exposure to pesticides and to identify changes in exposure levels. The first program analyzes pesticides in urine and blood serum; the second monitors and stores adipose tissue (54).

From 1976 to 1980, the National Center for Health Statistics (NCHS) sponsored the National Health and Nutritional Examination Survey II (NHANES II) to establish base-line data on public exposure to various classes of pesticides, including the organophosphate, carbamate, chlorophenoxy, and organochlorine classes (54,72). Researchers set out to obtain health and nutritional information by conducting direct physical examinations and tests (including blood, serum, and urine specimens) for pesticide exposure in the general population in various regions of the United States. The program has provided estimates of the total prevalence of selected illnesses, impairments of health and nutritional status, and the distribution of many conditions in the population by sex, age, income levels, race, and region (72). Technicians have developed systematic methods of collecting, analyzing, and interpreting the data for the studies in order to detect potentially toxic substances. In addition, from 1982 to 1984, the Hispanic Health and Nutrition Examination Survey (HHANES) was conducted by NCHS to provide data on the health and nutritional status of the Hispanic population of the United States (31).

In 1985, NCHS began planning NHANES III (a survey to be conducted between 1988 to 1994) to assess nutrition status, osteoporosis (abnormal decrease in density and loss of calcium in the bone), arthritis, lung disease, heart disease, diabetes, AIDS, kidney disease, growth and development of children, and health and disability of older citizens (54,109).

[1] In 1988, the National Bureau of Standards became a component of the National Institute of Standards and Technology.

Currently, all data are collected by computerized methods in mobile examination centers, which increases the quality and availability of the data for analysis.

The current goals of NHANES III include examining the national prevalence of various diseases and risk factors, documenting and investigating reasons for trends, understanding disease etiology, and investigating the natural history of selected diseases (109),

Another type of program was established by EPA some years ago to monitor toxic substances in human adipose tissue. In 1970, the Agency initiated and sponsored a National Human Adipose Tissue Survey to determine incidence, levels, and other indicators of exposure to pesticides in the general population of the United States (54). This program monitors the levels of various pesticides in adipose tissue collected from cadavers during autopsies (54).

WHO is conducting a multinational specimen banking program for human tissues. Specimens from the heart, brachial artery, aorta, and diaphragm of cadavers are being evaluated. This program is designed to compare exposure to trace metals with the development of cardiovascular diseases (54). Additional human monitoring programs include a serum program conducted by the Centers for Disease Control and collection of preserved human tissues in formaldehyde at the EPA Pesticide Research Laboratory (54)$_0$

Monitoring of Nonhuman Tissues

In 1987, the Alaskan Marine Mammal Tissue Archival Project was established by the Minerals Management Service to collect and store Alaskan marine mammal tissues in order to monitor toxic substances. To reach this goal, three objectives were set: to collect marine mammal tissues that are suitable for determining levels of organic and inorganic substances; to transport and archive tissues in a condition that is ideal for long-term storage and analysis; and to determine the most appropriate collection protocols for long-term storage of marine mammal tissues (8,1 11).

In 1984, the National Oceanic and Atmospheric Administration within the U.S. Department of Commerce conducted studies through its National Status and Trends Program for Marine Environment Quality to determine the environmental quality of the coastal and estuarine regions of the United States. The objectives of this program are to determine concentrations of substances in biological tissues and sediments and to examine and record changes in these concentrations. Since 1984 and 1986, respectively, samples have been collected at approximately 50 benthic surveillance sites and 150 Mussel Watch sites. Benthic (bottom-dwelling) fishes are collected at the Benthic Surveillance sites and their livers are removed and stored for further chemical evaluation. At the Mussel Watch sites, molluscs are collected for chemical analysis. Commonly assayed substances include polyaromatic hydrocarbons, polychlorinated biphenyls, pesticides, and the elements arsenic, cadmium, chromium, lead, mercury, silver, and tin (106,107,108).

Biological Monitoring

Monitoring programs are designed to observe, measure, and judge on a continuous basis the potential health effects of substances and make proper decisions on the adequacy of control measures. Monitoring is more than just sampling the air where workers are being exposed or conducting medical examinations of workers. It is an entire series of activities that are undertaken to make proper judgments on the protective controls needed or the adequacy of the control measures in place, or both. One approach commonly used in occupational health is biological monitoring. This makes it possible to determine both the occurrence of exposure and the presence of particular substance(s) in body fluids (i.e., blood or urine) or organs in order to evaluate health risk (5).

Biological monitoring programs are designed to detect the presence in the body of substances from all routes of exposure. The appropriate frequency of monitoring may be influenced by several factors, including intensity and duration of exposure and toxicity of the substances. Monitoring is generally done more often when the toxic substances being evaluated are expected to produce irreversible changes.

One limitation of biological monitoring is that it is sometimes difficult to establish whether exposure to toxic substances is responsible for observed changes in the biological parameters. Individuals are often exposed to several substances simultaneously, and one must consider whether a different substance or a combination of substances caused the observed toxic effects. Variability in individual responses may be another limitation to monitoring. Multiple



Photo credit: U.S. Environmental Protection Agency

factors may cause variability in response among workers exposed to the same substance. Thus, it may be difficult to determine the normal response for a given individual (5).

Internationally, the Global Environment Monitoring System created a biological monitoring system to evaluate the health risks from exposure to lead, cadmium, and pesticides. The study of lead exposures was conducted between 1979 and 1981 and involved 10 countries. In 1984, a follow-up study was conducted in four countries. Blood samples from volunteers were taken and analyzed for lead and cadmium content. In 1981, a study of selected organochlorine pesticides, including DDT and PCBs in human milk, was conducted in 10 countries to assess the population's exposure to these substances (124).

Other Monitoring Programs

As part of the Federal Emergency Planning and Community Right-to-Know Act of 1986, EPA was required to generate a database on toxic substances released into the environment from industrial sites throughout the country. Commonly known as the Toxics Release Inventory (TRI), the database contains information on approximately 328 toxic substances (see box 5-D). Results of the inventory indicate that in 1987, approximately 18 billion pounds of toxic substances were released directly into the air, surface waters, land, or underground injection wells in the United States. In addition, 4.6 billion pounds were transported offsite for disposal or treatment. TRI will enable regulatory and public health officials, researchers, and the public to monitor what quantities of particular chemicals are being released from sites around the country. The first data were published in 1989, and the inventory will be updated annually. The database pertains only to manufacturing industries; Federal facilities are not accounted for (94,1 13). Figure 5-3 illustrates the neurotoxic substances among the TRI's top 25 chemicals emitted into the air.

Box 5-D-Neurotoxicants Released Into the Environment by Industry: The Toxics Release Inventory Supplies New Evidence

Until recently, regulators had no comprehensive answer to a basic question underlying toxic substances regulation: What amounts of toxic substances are we actually dealing within the United States? Despite dozens of databases devoted to toxic chemical regulation, such as data on air pollution permits, surface water discharges controlled under Federal water pollution control regulations, and hazardous wastes regulated under the Resource Conservation and Recovery Act, no single compendium contained estimates of the overall amounts of chemicals released into the environment. The Toxics Release Inventory, which grew out of reporting requirements mandated in the 1986 Superfund amendments (Superfund Amendments and Reauthorization Act sec. 313), provides a preliminary answer—at least for the 327 chemicals covered by the statute that are discharged into air or water or dumped on land by manufacturers in 20 specified industries.

Inventory data show, for example, that manufacturing facilities emitted significant amounts of neurotoxicants to the air in 1987. Overall, facilities released 2.6 billion pounds of the 327 toxic chemicals on the Inventory list. A brief review of the scientific literature reveals that 17 of **the top 25 chemicals, accounting** for 1.8 **billion pounds (77 percent) of the total for the top 25, have documented neurotoxic effects ranging from narcotic effects (drowsiness or fatigue) to more permanent and debilitating effects, such as hearing impairment and blindness. Of these 17 neurotoxicants, only benzene, which is a known human carcinogen, has been regulated as a hazardous pollutant under the Clean Air Act.** The neurotoxic effects of two additional chemicals-l,l,l - trichloroethane and glycol ethers, which account for another 189 million pounds (8 percent) of the top 25-are being investigated under the Toxic Substances Control Act section 4 test rules. In sum, manufacturers released a total of nearly 2 billion pounds of potential or known neurotoxicants (85 percent of the top 25) in 1987. Figures on 1988 releases, which will become available in 1990, should give some indication as to whether emissions of these neurotoxicants are increasing or decreasing.

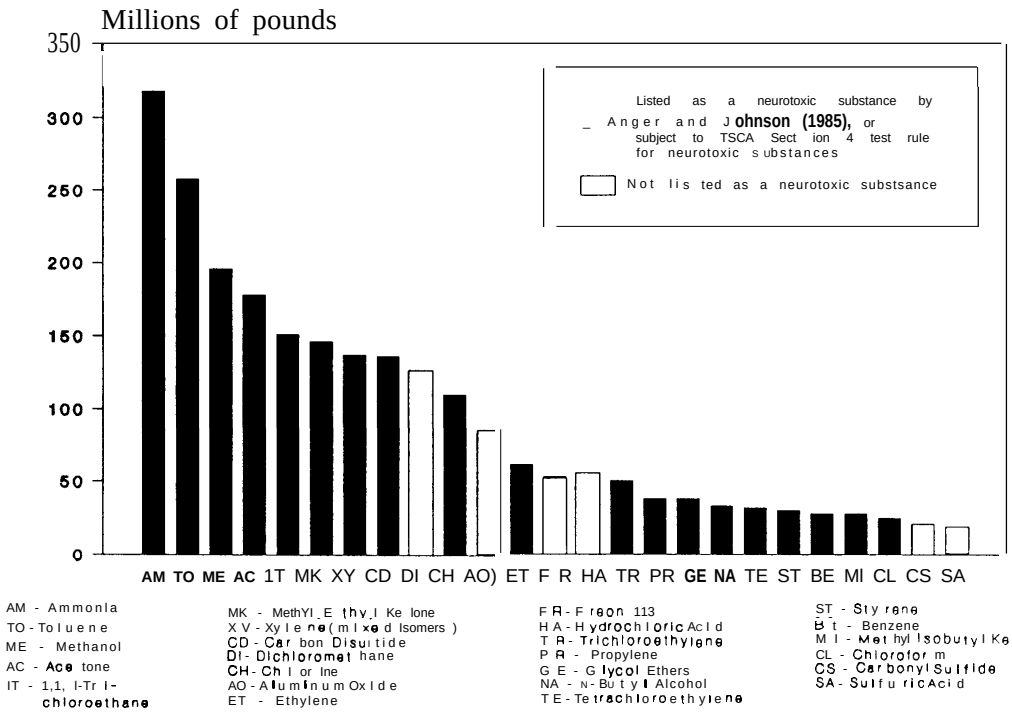
The Inventory data do not cover many sources of toxic chemicals in the environment, notably consumer products and agricultural chemicals, nor do they address the chemical releases and exposures in the occupational setting. Furthermore, the data do not reveal the amounts to which people are actually exposed (chemicals may break down or be transported rapidly through the environment after being released, or they may accumulate in the environment) or the probable risks from exposure. The Inventory data do, however, suggest that significant amounts of identified neurotoxicants are finding their way out of factories and into the environment; these releases are plausible candidates for further study or control.

SOURCES: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances, ***The Toxics Release Inventory: A National Perspective, 1987,*** EPA 560/4-89-006 (Washington, DC: 1989); W.K. Anger and B.L. Johnson, "Chemicals Affecting Behavior," ***Neurotoxicity of Industrial and Commercial Chemicals,*** vol. 1, J.L. O'Donoghue (cd.) (Boca Raton, FL: CRC Press, 1985), pp. 51-148.

A wide variety of additional monitoring programs has been undertaken by several Federal agencies. For example, in 1978, the U.S. Department of Agriculture (USDA) and the Human Nutrition Information Service devised a survey called the Nationwide Food Consumption Survey to measure the food and nutrient content of the U.S. diet, the dollar value of food used in the average U.S. household, and food and nutrient intakes of individuals at home and away from home. In addition, since 1965, FDA has conducted a survey known as the Total Diet Study to collect and analyze diet samples from retail markets to assess concentrations of metals, pesticide residues, and other substances commonly found in the diet. In 1987, FDA analyzed 936 food samples in the diets of U.S. consumers and found that the levels of intake of the pesticides assayed for were less than 1 percent of acceptable levels set by WHO and the United Nation's Food and Agriculture Organization (110). Also, the National Residue Program is conducted by USDA to evaluate pesticide residue levels and other potentially hazardous substances present in meat and poultry. In 1984, EPA's Office of Pesticide Programs developed a Tolerance Assessment System in order to estimate potential human exposure to pesticides in the diet and analyze the risks that could result from exposure (31).

The Agency for Toxic Substances and Disease Registry of the Department of Health and Human Services recently set up a registry of persons exposed to toxic substances at hazardous waste sites and at emergency chemical spills. The registry will

Figure 5-3-Neurotoxic Substances Are Prominent Among the Toxics Release Inventory's Top 25 Chemicals Emitted Into the Air in 1987



SOURCES: Data obtained from W.K. Anger and B.L, Johnson, "Chemicals Affecting Behavior," ***Neurotoxicity of industrial and*** Commercial ***Chemicals,*** vol. 1, **J.L. O'Donoghue (ad.) (Boca Raton, FL: CRC Press, 1985), tables 1 and 2, pp. 70-141; TSCA sec.4,52FR31445; TSCA sec. 4,53 FR 5932; 54 FR 13470; 54 FR 13473; U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances,** ***The*** Toxics ***Release Inventory: A National Perspective, 1987,*** **EPA** ***560/4-89-006*** (Washington, DC: 1989).

provide information needed by researchers to assess the long-term health effects of both low-level chronic exposures and high-level acute exposures (108).

SUMMARY AND CONCLUSIONS

The adverse effects of toxic substances on the nervous system may be evaluated through three categories of toxicological tests: whole animal, tissue and cell culture, and human subjects. Each approach has both advantages and limitations, and in practice combinations of these tests may be used in a complete toxicological evaluation. The best means of predicting human health effects is to evaluate the effects of potentially toxic substances directly on human subjects. However, this approach is difficult and frequently presents ethical dilemmas. Consequently, it is often necessary to rely on animal tests in making predictions of human health effects. In some cases, in vitro tests can be used to detect the neurotoxic potential of toxic substances. As more in vitro testing techniques become available and are validated, they will be useful in initial screening, as complements to various animal tests, or both.

Several industrial and Federal organizations have developed animal tests to evaluate the effects of known and potential neurotoxic substances. In industry, various testing approaches are currently in use and protocols are continually being revised and improved. In the Federal arena, EPA has developed guidelines under the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act specifically for determining neurotoxic properties of toxic substances. The guidelines are composed of a core set of tests consisting of the functional observational battery (a series of tests designed to screen rapidly for neurotoxic potential), tests of motor activity, and neuropathological examinations. For regulatory purposes, EPA plans to utilize the core tests and supplement them with additional neurotoxicity tests when appropriate. These may include schedule-controlled operant

behavior, neurotoxic esterase assay for organophosphorous substances, acute and subchronic delayed neurotoxicity of organophosphorous substances, and developmental examinations. Neurophysiological evaluations are also used in identifying neurotoxic substances and in evaluating their adverse effects; however, EPA currently has not developed guidelines for using these tests in regulatory activities.

Several human tests are in use to determine the neurotoxic potential of suspected and known toxic substances. These include neurobehavioral evaluations and various neurophysiological tests. In addition, computerized techniques are rapidly advancing to aid in studies of neurotoxicity.

Monitoring of toxic substances is critical because it enables investigators to systematically trace toxic pollutants and their sources that are contaminating the air, land, and water. Monitoring programs include human and animal specimen banking, biological monitoring, and related efforts. Toxicity monitoring programs now under way in Federal agencies address neurotoxicological concerns in varying degrees. However, much more could be done in this area.

Until recently, Federal agencies have devoted little attention to neurotoxicity testing. EPA is the leader in developing test guidelines to evaluate neurotoxicity. The regulatory programs of other agencies would benefit from joint test development, and more active involvement of industry and academia in test development and validation programs would help ensure the optimal design of neurotoxicity tests for general use in regulatory programs,

EPA is continuing to examine the testing guidelines already produced to determine whether a wider range of tests is needed to evaluate the neurotoxic properties of toxic substances, For example, the schedule-controlled operant behavior and developmental tests provide additional information about certain effects that cannot be determined by the FOB, motor activity, and neuropathology examinations.

The Federal Government is encouraging the development of in vitro neurotoxicological tests. As these tests become available, testing schemes may be modified to take advantage of both in vivo and in vitro approaches. Finally, monitoring programs under way at various organizations and Federal agencies would benefit by giving greater attention to substances with neurotoxic potential and by incorporating a wider range of neurological and behavioral effects into monitoring schemes.

CHAPTER 5 REFERENCES

1. Adams, J., "Methods of Behavioral Teratology," *Handbook of Behavioral Teratology, E.P. Riley* and C.V. Voorhees (eds.) (New York, NY: Plenum Press, 1986), pp. 23-48.
2. Adler, R., "Cell Culture Systems for Purified Retinal Neurons and Photoreceptors," *Model Systems of Development and Aging of the Nervous System,* A. Vernadakis (cd.) (Martinus Nijihoff Publishing, 1987), pp. 3-16.
3. Anger, W, K., "Workplace Exposures," *Neurobehavioral Toxicology, Z.* Annau (cd.) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 331-347.
4. Arezzo, J. C., Simson, R., and Brennan, N. E., ''Evoked Potentials in the Assessment of Neurotoxicity in Humans, ' *Neurobehavioral Toxicology and Teratology 7:299-304, 1985.*
5. Ashford, N. A., Spadafor, C.J., and Caldart C. C., "Human Monitoring: Scientific, Legal and Ethical Considerations, " *Harvard Environmental Law Review 8(2):292-304, 1984.*
6. Association of Schools of Public Health under cooperative agreement with the National Institute for Occupational Safety and Health, "A Proposed National Strategy for the Prevention of Neurotoxic Disorders," *Proposed National Strategies for the Prevention of Leading Work-Related Diseases and Injuries,* part 2, 1988, pp. 31-50.
7. Baker, E., Letz, R., Fidler, A., et al., "A Computer-Based Neurobehavioral Evaluation System for Occupational and Environmental Epidemiology: Methodology and Validation Studies, ' *Neurobehavioral Toxicology and Teratology 7:369-377, 1985.*
8. Becker, P. R., Wise, S. A., Koster, B. J., et al., *Alaskan Marine Mammal Tissue Archival Project: A Project Description Including Collection Protocols* (Gaithersburg, MD: National Bureau of Standards, March 1988).
9. Boyes, W., U.S. Environmental Protection Agency, Research Triangle Park, NC, personal communication, July 11, 1989.
10. Boyes, W., and Dyer, R. S., "Pattern Reversal Visual Evoked Potentials in Awake Rats," *Brain Research Bulletin 10:817-823, 1983.*
11. Boyes, W., and Dyer, R. S., "Chlordimeforrn Produces Profound, Selective and Transient Changes in Visual Evoked Potentials of Hooded Rats, ' *Experimental Neurology 86:434-447, 1984.*

12. Boyes, W. K., Jenkins, D.E., and Dyer, R. S., "Chlordimeform Produces Contrast-dependent Changes in Visual Evoked Potentials of Hooded Rats,' *Experimental Neurology 89:391, 1985.*
13. Brown, N. A., Goulding, E. H., and Fabro, S., "Ethanol Embryotoxicity: Direct Effects on Mammalian Embryos in Vitro, ' *Science 206:573-575, 1979.*
14. Buelke-Sam, J., Kimmel, C. A., and Adams, J. (eds.), "Design Considerations in Screening for Behavioral Teratogens: Results of the Collaborative Behavioral Teratology Study," *Neurobehavioral Toxicology and Teratology 7:537-789, 1985.*
15. Camerino, D., "Presentation, Description and Preliminary Evaluation of M.A.N.S. Institute of Occupational Health," University of Milan, 1987.
16. Cone, J.E, Reeve, G.R., and Landrigan, P. J., "Clinical and Epidemiological Studies," *Toxic Substances and Human Risk-Principles of Data Interpretation (New* York, NY: Plenum Press, 1987), pp. 95-120.
17. Creason, J.P., "Data Evaluation and Statistical Analysis of Functional Observational Battery Data Using a Linear Models Approach," *Journal of the American College of Toxicology 8(1):157-169, 1989.*
18. Crofton, K. M., Boncek, V. M., and MacPhail, R. C., "Evidence for Monoaminergic Involvement in Triadimefon-induced Hyperactivity,' *Psychopharmacology 97:326-330, 1989.*
19. Crofton, K. M., and Reiter, L. W., "The Effects of Type I and II Pyrethroids on Motor Activity and the Acoustic Startle Response in the Rat,' *Fundamental and Applied Toxicology 10:624-634, 1988.*
20. Davenport, C.J., Williams, D. A., and Morgan, K.T., "Neurotoxicology Using Cell Culture, " *Chemical Industry Institute of Toxicology 9(1):1-8, 1989.*
21. Dawson, M., *The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing* (Washington, DC: National Academy of Sciences, 1977), pp. 185-206.
22. Dewar, A.J., '' Neurotoxicity,' *Animals and Alternatives in Toxicity Testing,* M. Balls, R. Riddell, and A. Worden (eds.) (London: Academic Press, 1983), pp. 230-284.
23. Dews, P. B., "Epistemology of Screening for Behavioral Toxicity," ***Nervous*** *System Toxicology,* C.L. Mitchell (cd,) (New York, NY: Raven Press, 1982), pp. 229-236.
24. Dick, R. B., and Johnson, B. L., "Human Experimental Studies, " *Neurobehavioral Toxicology, Z.* Annau (cd.) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 348-387.
25. Dyer, R. S., "The Use of Sensory Evoked Potentials in Toxicology, '' *Fundamental and Applied Toxicology 5:24-40, 1985.*
26. Dyer, R. S., "Somatosensory Evoked Potentials," *Electrophysiology in Neurotoxicology; vol. II,* H.E. Lowndes (cd.) (Boca Raton, FL: CRC Press, 1987), pp. 1-33.
27. Eckerman, D. A., Carrel, J. B., Force, D., et al., "An Approach to Brief Field Testing for Neurotoxicity," *Neurobehavioral Toxicology and Teratology 7:387-393, 1985.*
28. Evans, H. L., ''Behaviors in the Home Cage Reveal Toxicity: Recent Findings and Proposals for the Future,' *Journal of the American College of Toxicology 8(1):35-52, 1989.*
29. Evans, H. L., Bushnell, P. J., Taylor, J. D., et al., "A System for Assessing Toxicity of Chemicals by Continuous Monitoring of Homecage Behaviors," *Fundamental and Applied Toxicology 6:721-732, 1986.*
30. Federation of American Societies for Experimental Biology, *Predicting Neurotoxicity and Behavioral Dysfunction from Preclinical Toxicological Data* (Washington, DC: 1986), pp. 35-37.
31. Federation of American Societies for Experimental Biology, "Estimation of Exposure to Substances in the Food Supply,' prepared for the Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, S.A. Anderson (cd.) (Bethesda, MD: 1988).
32. Gad, S. C., "A Neuromuscular Screen for Use in Industrial Toxicology," *Journal of Toxicology and Environmental Health 9;691-704, 1982.*
33. Gad, S. C., "Principles of Screening in Toxicology with Special Emphasis on Applications to Neurotoxicology," *Journal of the American College of Toxicology* 8(1):21 -27b, 1989.
34. Gad, S. C., "Statistical Analysis of Screening Studies in Toxicology with Special Emphasis on Neurotoxicology," *Journal of the American College of Toxicology* 8(1):171-183a, 1989.
35. Goldberg, A. M., ''Mechanisms of Neurotoxicity as Studied in Tissue Culture Systems," *Toxicology 17:201-208, 1980.*
36. Goldberg, A. M., "Approaches to the Development of In Vitro Neurotoxicological Methods, " *Model Systems in Neurotoxicology: Alternative Approaches to Animal Testing (New* York, NY: Alan R. Liss, 1987), pp. 1-11.
37. Goldberg, A. M., and Frazier, J. M., "Alternatives to Animals in Toxicity Testing," *Scientific American 261(2):24-30, 1989.*
38. Gossel, T. A., and Bricker, D.J., "Factors That Influence Toxicity," *Principles of Clinical Toxicology (New* York, NY: Raven Press, 1984), pp. 17-27.
39. Hanninen, H., and Lindstrom, K., *Behavioral Test Battery for Toxicopsychological Studies Used at the Institute of Occupational Health in Helsinki*

(Helsinki: Institute of Occupational Health, 1979), pp. 1-58.
40. Harrison, R.G., ''Observation on the Living Developing Nerve Fiber,'' *Anatomical Record 1:1* 16,1907.
41. Iregren, A., Gamberale, F., and Kjellberg, A., "A Microcomputer-based Behavioral Testing System,' *Neurobehavioral Methods in Occupational and Environmental Health* (Copenhagen: World Health Organization, 1985).
42. Irwin, S., "Comprehensive Observational Assessment: Ia. A Systematic Quantitative Procedure for Assessing the Behavioral and Physiologic State of a Mouse," *Psychopharmacologia 13:222-257, 1968.*
43. Johnson, B. L,, "Electrophysiological Methods in Neurotoxicity Testing,'' *Experimental and Clinical Neurotoxicology,* P.S. Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980), pp. 726-742.
44. Johnson, B.L.(ed.), *Prevention of Neurotoxic Illness in Working Population (New* York, NY: John Wiley & Sons, 1987).
45. Kimmel, C.A., "Current Status of Behavioral Teratology: Science and Regulation," *CRC Critical Reviews in Toxicology 19(1):1-10, 1988.*
46. Kimmel, C.A., U. S. Environmental Protection Agency, Washington, DC, personal communication, Aug. 29, 1989.
47. Klaassen, C. D., Amdur, M. O., and Doull, J. (eds), *Casarett and Doull's Toxicology (New* York, NY: Macmillan, 1986).
48. Krinke, G.J., "Neuropathologic Screening in Rodent and Other Species," *Journal of the American College of Toxicology 8(1):141-145, 1989.*
49. Laties, V., Dews, P., McMillan, D., et al., "Behavioral Toxicity Tests, ' *Principles and Procedures for Evaluating the Toxicity of Household Substances* (Washington, DC: National Academy of Sciences, 1977), pp. 111-118.
50. Laties, V., and Wood, R., "Schedule-Controlled Behavior in Behavioral Toxicology,' *Neurobehavioral Toxicology,* Z. Annau (cd.) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 69-93.
51. Laursen, P., and Jorensen, T., "Computerized Neuropsychological Test System," *Neurobehavioral Methods in Occupational and Environmental Health* (Copenhagen: World Health Organization, 1985).
52. Letz, R., ''Occupational Screening for Neurotoxicity: Computerized Techniques, *Toxicology 49:417-424, 1988,*
53. Letz, R., and Baker, E., "Computer-Administered Neurobehavioral Testing in Occupational Health," *Seminars in Occupational Medicine 1(3):197-203,* September 1986.
54. Lewis, R.A. (cd.), *Guidelines for Environmental Specimen Banking With Special Reference to the Federal Republic of Germany* (Washington, DC: U.S. Department of the Interior, National Park Service, 1987).
55. Loomis, T. A., "Influence of Route of Administration on Toxicity," *Essentials of Toxicology* (Philadelphia, PA: Lea and Febiger, 1978).
56. Lowndes, H.E. (cd.), *Electrophysiology in Neurotoxicology,* vol. II (Boca Raton, FL: CRC Press, 1987), pp. 34-52.
57. MacPhail, R. C., "Observational Batteries and Motor Activity, " *International Journal of Microbiology and Hygiene 185:21-27, 1987.*
58. MacPhail, R. C., U.S. Environmental Protection Agency, Research Triangle Park, NC, personal communication, July 26, 1989.
59. MacPhail, R. C., U.S. Environmental Protection Agency, Research Triangle Park, NC, personal communication, Aug. 30, 1989.
60. MacPhail, R.C., et al., ''Motor Activity and Screening for Neurotoxicity, ' *Journal of the American College of Toxicology 8(1):117-125, 1989.*
61. Mattsson, J. L., and Albee, R.R., "Sensory Evoked Potentials in Neurotoxicology," *Neurotoxicology and Teratology 10:435-443, 1988.*
62. Mattsson, J. L., Albee, R.R., and Eisenbrandt, D.L., "Neurological Approach to Neurotoxicological Evaluation in Laboratory Animals," *Journal of the American College of Toxicology 8(2):271-286, 1989.*
63. Mattsson, J. L., Albee, R,R., Eisenbrandt D. L., et al., "Subchronic Neurotoxicity in Rats of the Structural Fumigant, Sulfuryl Fluoride," *Neurotoxicology and Teratology 10:127-133, 1988.*
64. Maurissen, J. P. J., and Mattsson, J. L., "Critical Assessment of Motor Activity as a Screen for Neurotoxicity,' *Toxicology and Industrial Health 5(2):195-202, 1989.*
65. Menzer, R. E., "Selection of Animal Models for Data Interpretation,' *Toxic Substances and Human Risk,* R. Tardiff and J. Rodricks (eds.) (New York, NY: Plenum Press, 1987), pp. 133-152.
66. Mitchell, C. L., and Tilson, H. A., "Behavioral Toxicology in Risk Assessment: Problems and Research Needs," *Critical Reviews in Toxicology 9(1):265-274, 1982.*
67. Mitchell, C. L., Tilson, H., and Cabe, P. A., "Screening for Neurobehavioral Toxicity: Factors to Consider, " Nervous *System Toxicology (New* York, NY: Raven Press, 1982), pp. 239-245.
68. Moser, V., Director, NSI Technology Services Corp., Research Triangle Park, NC, personal communication, Nov. 16, 1988.
69. Moser, V., "Screening Approaches to Neurotoxicity: A Functional Observational Battery, " *Journal of the American College of Toxicology 8(1):85-93, 1989.*

70. Moser, V., McCormick, J., Creason, J.P., et al., ''Comparison of Chlordimeform and Carbaryl Using a Functional Observational Battery," *Fundamental and Applied Toxicology 11:189-206, 1988.*
71. Mullenix, P.J., Kernan, W.J., Tassinari, M. S., et al., "Generation of Dose-Response Data Using Activity Measures, " *Journal of the American College of Toxicology 8(1):185-197, 1989.*
72. Murphy, R., and Harvey, C., "Residues and Metabolites of Selected Persistent Halogenated Hydrocarbons in Blood Specimens from a General Population Survey," *Environmental Health Perspectives 60:115-120, 1985.*
73. Murphy, T. H., Malouf, A.T, Sastre, A., et al,, "Calcium-dependent Glutamate Cytotoxicity in a Neuronal Cell Line,' *Brain Research 444:325-332, 1988.*
74. National Academy of Sciences, *Principles for* Evaluating *Chemicals in the Environment* (Washington, DC: 1975).
75. National Academy of Sciences, "Reference Protocol Guidelines for Neurobehavioral-Toxicity Tests' *Toxicity Testing-Strategies To Determine Needs and Priorities* (Washington, DC: National Academy Press, 1984), pp. 169-174.
76. O'Callaghan, J.P., "Neurotypic and Gliotypic Proteins as Biochemical Markers of Neurotoxicity, " *Neurotoxicology and Teratology, vol.* 10 (New York, NY: Pergamon Press, 1988), pp. 445-452.
77. O'Callaghan, J.P., and Jensen, K., "Proposed Guidelines for Assessment of Developmental Neurotoxicity by GFAP Radioimmunoassay " (Washington, DC: U.S. Environmental Protection Agency, June 1988).
78. O'Callaghan, J.P., and Miller, D., "Assessment of Chemically Induced Alterations in Brain Development Using Assays of Neuron and Glia Localized Proteins," *Neurotoxicology 10:1-28, 1989.*
79. O'Donoghue, J. L., "Screening for Neurotoxicity Using a Neurologically Based Examination and Neuropathology," *Journal of the American College of Toxicology, in* press.
80. O'Donoghue, J.L., "Screening for Neurotoxicity Using a Neurologically Based Examination and Neuropathology," *Journal of the American College of Toxicology 8(1):97-115, 1989.*
81. O'Donoghue, J. L., Eastman Kodak Co., Rochester, NY, personal communication, July 18, 1989.
82. Otto, D., "The Use of Sensory Evoked Potentials in Neurotoxicity Testing of Workers, " *Seminars in Occupational Medicine 1(3):175-183, 1986.*
83. Otto, D., Hudnell, K., Boyes, W., et al., "Electrophysiological Measures of Visual and Auditory Function as Indices of Neurotoxicity," *Toxicology 49:205-218, 1988.*
84. Padilla, S., MacPhail, R.C., and Reiter, L.W., "Neurotoxic Potential of Pesticides: Age-related Effects of Pesticides Relevant to Youth in Agriculture," U.S. Environmental Protection Agency report, Health Effects Research Laboratory, 1985.
85. *People of the State of New York v. William Pymm, Edward A. Pymm, Pymm Thermometer, Inc., and Pak Glass Machinery Corp.,* Brief for the Appellant, Mar. 21, 1988.
86. Politi, L. E., and Adler, R., 'Generation of Enriched Populations of Cultured Photoreceptor Cells," *Investigative Ophthalmology and Visual Science 27(5): 656-665, 1986.*
87. Politi, L.E., Lehar, M., and Adler, R., "Development of Neonatal Mouse Retinal Neurons and Photoreceptors in Low Density Cell Culture," *Investigative Ophthalmology and Visual Science 29(4):534-543, 1988.*
88. Rebert C. S., Sorenson, S.S., Howd, R.A., et al., ''Toluene-induced Hearing Loss in Rats Evidenced by the Brainstem Auditory-evoked Response," *Neurobehavioral Toxicology and Teratology 5:59-62, 1983.*
89. Rieter, L. W., "Use of Activity Measures in Behavioral Toxicology, ' *Environmental Health Perspectives* 26:9-20, 1978.
90. Reiter, L. W., and MacPhail, R. C., "Motor Activity: A Survey of Methods with Potential Use in Toxicity Testing," *Test Methods for Definition of Effects of Toxic Substances on Behavior and Neuromotor Function Neurobehavioral Toxicology 1(1):53-66, 1979.*
91. Richelson, E., "Use of Tissue culture To Study Cholinergic Function," *Biology of Cholinergic Function,'* A.M. Goldberg and I. Hanin (eds.) (New York, NY: Raven Press, 1976), pp. 452-484.
92. Rowan, A.N,, "Of Mice, Models, and Men," *A Critical Evaluation of Animal Research* (Albany, NY: State University of New York Press, 1984).
93. Rowan, M,J., "Central Nervous System Toxicity Evaluation in Vitro: Neurophysiological Approach," *Neurotoxicology,* K. Blum and L. Manzo (eds.) (New York, NY: Marcel Dekker, 1985), pp. 585-588.
94. Russell, C., "How EPA's New Toxics List Can Help Trace Nearby Hazards," *Washington Post,* June 19, 1989.
95. Scanlon, T., U.S. Consumer Product Safety Commission, letter to Henry Spira of Animal Rights International, Washington, DC, Dec. 4, 1987.
96. Schrier, B. K., "Nervous System Cultures as Toxicologic Test Systems, " Nervous *System Toxicology,* C.L. Mitchell (cd.) (New York, NY: Raven Press, 1982), pp. 337-346.
97. Seppalainen, A.M. H., "Neurophysiological Approaches to the Detection of Early Neurotoxicity in

Humans,' *CRC Critical Reviews in Toxicology 18(4):245-298, 1988.*

98. Sette, W.F., and Levine, T.E., "Behavior as a Regulatory Endpoint," *Neurobehavioral Toxicology,* Z. Annau (cd.) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 391-403.
99. Smyth, D. H., *Alternatives to Animal Experiments* (London: Scolar Press, 1978).
100. Spencer, P. S., Bischoff, M. C., and Schaumberg? H. H., "Neuropathological Methods for the Detection of Neurotoxic Disease, " *Experimental and Clinical Neurotoxicology, P.S.* Spencer and H.H. Schaumberg (eds.) (Baltimore, MD: Williams & Wilkins, 1980), pp. 743-757.
101. Tahan, L., U.S. Environmental Protection Agency, Washington, DC, personal communication, June 30, 1989.
102. Tilson, H. A., ''Behavioral Indices of Neurotoxicity: What Can be Measured?" *Neurotoxicology and Teratology 9:427-443, 1987.*
103. Tyson, C. A., and Stacey, N. H., "In Vitro Screens from CNS, Liver, and Kidney for Systemic Toxicity," *Toxicology and Industrial Health 5(1):107-132, 1989.*
104. *U.S.* Congress, Office of Technology Assessment, *Preventing Illness and Injury in the Workplace, OTA-H-256* (Washington, DC: U.S. Government Printing Office, April 1985).
105. U.S. Congress, Office of Technology Assessment, *Alternatives to Animal Use in Research, Testing, and Education, OTA-BA-273* (Washington, DC: U.S. Government Printing Office, February 1986).
106. U.S. Department of Commerce, National Oceanic and Atmospheric Administration, "National Status and Trends Program for Marine Environmental Quality, Progress Report-A Summary of Selected Data on Chemical Contaminants in Tissues Collected During 1984, 1985, and 1986" (Rockville, MD: 1987).
107. U.S. Department of Commerce, National Oceanic and Atmospheric Administration, "National Status and Trends Program for Marine Environmental Quality, Progress Report-A Summary of Selected Data on Chemical Contaminants in Sediments Collected During 1984, 1985, 1986, and 1987," NOAA Technical Memorandum NOS OMA 44 (Rockville, MD: 1988).
108. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, "National Exposure Registry: Policies and Procedures for Establishing a National Registry of Persons Exposed to Hazardous Substances, ' Atlanta, GA, 1988, pp. 3-33.
109. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, ''Third National Health and Nutrition Examination Survey (NHANES III)," 1988.
110. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, "Food and Drug Administration Pesticides program Residues in Foods-1987,' *Journal of the Association of Official Analytical Chemists 71,* November/December 1988.
111. U.S. Department of Health and Human Services, Public Health Service, "Occupational Safety and Health," *Promoting Health/Preventing Disease-Objectives for the Nation* (Washington, DC: U.S. Government Printing Office, 1980), pp. 39-43.
112. U.S. Environmental Protection Agency, Neurotoxicology Division, *Advances in Neurotoxicity Methods,* vol. 1 (Research Triangle Park, NC: February 1988).
113. U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances, *The Toxics Release Inventory: A National Perspective, 1987,* EPA 560/4-89-006 (Washington, DC: 1989), pp. 1-24.
114. Vorhees, C., "Origins of Behavioral Teratology," *Handbook of Behavioral Teratology,* E.P. Riley and C. Voorhees (eds.) (New York, NY: Plenum Press, 1986), pp. 3-22.
115. Vorhees, C., "Principles of Behavioral Teratology, " *Handbook of Behavioral Teratology,* E.P. Riley and C. Voorhees (eds.) (New York, NY: Plenum Press, 1986), pp. 23-48.
116. Weiss, R., "Test Tube Toxicology—New Tests May Reduce the Need for Animals in Product Safety Testing," *Science News 133:42-45, 1988.*
117. Williams, P. L., and Burson, J. L., *Industrial Toxicology: Safety and Health Applications in the Workplace (New* York, NY: Van Nostrand Reinhold, 1985), pp. 17-39,
118. Wise, S. A., Koster, B.J., Parris, R.M., et al., "Experiences in Environmental Specimen Banking,' *International Journal of Environmental Analytical Chemistry, 1988.*
119. Wise, S. A., and Zeisler, R., "The Pilot Environmental Specimen Bank Program, *Environmental Science and Technology 18(10) :302A-3O7A, 1984.*
120. Wise, S. A., and Zeisler, R. (eds.), *International Review of Environmental Specimen Banking,* National Bureau of Standards (Washington, DC: U.S. Government Printing Office, 1985).
121. Wood, R. W., American Psychological Association, testimony before the Neurotoxicity Subpanel of the FIFRA Science Advisory Panel, U.S. Environmental Protection Agency, Washington, DC, Oct. 15, 1987.
122. World Health Organization, *Principles and Methods for Evaluating the Toxicity of Chemicals,* part 1, Environmental Health Criteria 60 (Geneva: 1978).

123. World Health Organization, *Principles and Methods for the Assessment of Neurotoxicity Associated with Exposure to Chemicals,* Environmental Health Criteria 60 (Geneva: 1986),
124. World Health Organization and United Nations Environment Programme, *Global Pollution and Health, Results of Health-related Environmental Monitoring* (Geneva: 1987).
125. Xintaras, C., and Burg, J. A. R., "Screening and Prevention of Human Neurotoxic Outbreaks: Issues and problems," *Experimental and Clinical Neurotoxicology,* P.S. Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams& Wilkins, 1980), pp. 663-673.
126. Yonezawa, T., Bornstein, M. B., and Peterson, E. R., ''Organotypic Cultures of Nerve Tissue as a Model System for Neurotoxicity Investigation and Screening," *Experimental and Clinical Neurotoxicology,* P.S. Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980), pp. 788-802.

Chapter 6

Assessing and Managing Risk

'The alternative to not performing risk assessment is to adopt a policy of either reducing all *potentially toxic* emissions to the greatest degree technology allows or banning all substances for which there is any evidence of harmful effect, a policy that no technological society could long survive. "

William D. Ruckelshaus
Issues in Science and Technology
Spring 1985

"Risk assessment has become a central focus of environmental policy in the past couple years. In part, this is a matter of fashion. But it also arises from the real need to compare the relative importance of the vast number of environmental threats, because it has become obvious that not all threats can receive maximum attention.'

William K. Reilly
The Conservation Foundation
1985

"Over the past decade increasingly sophisticated methods have been developed to identify health hazards and assess risks quantitatively. But society has yet to agree on the most critical step in risk management: identifying risk goals and translating them into practical regulations. Does society seek to eliminate all risks, eliminate all nontrivial risks, all significant risks, or only those risks that are not outweighed by benefits?"

Daniel Byrd and Lester B. Lave
Issues *in Science and Technology*
Summer 1987

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Risk assessment is the analytical process by which the nature and magnitude of risks are identified. Risk, as it pertains to the health effects of toxic substances, is the probability of injury, disease, or death for individuals or populations undertaking certain activities or exposed to hazardous substances. It is sometimes expressed numerically (e.g., 1 in 1 million); however, quantification is not always possible, and risk may sometimes be expressed in qualitative terms such as high, medium, or low risk.

Risk management, a process guided by risk assessment, and by political, social, ethical, economic, and technological factors as well, involves developing and evaluating possible regulatory actions and choosing among them (15). The four components of risk assessment and the process of risk management are summarized in figure 6-1 and are discussed in more detail below. In practice, risk assessment and risk management frequently overlap and become difficult to distinguish (27). This is partly because definitions such as "adverse,' "harmful," and "toxic" involve both scientific and social judgments.

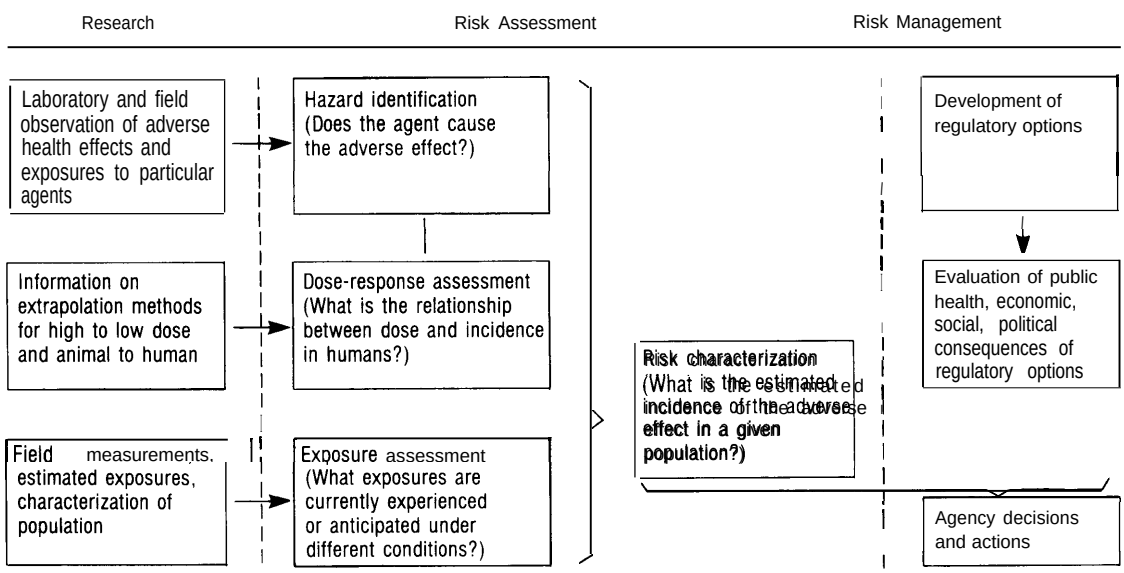
Some degree of risk is associated with almost every aspect of modern living. For example, traveling in an automobile involves a risk of accidental death of 1 in 4,000, a relatively high risk. In contrast, the risk of being killed by lightning is 1 in 2 million. Whether a risk is acceptable or not depends on many factors, including benefits. Defining acceptable risk is the task not only of scientists and regulatory officials, but of society in general. Everyone evaluates risks on a daily basis and makes individual choices depending on experience and numerous other factors. At times, one's perception of risk may not be entirely logical. For example, some people are reluctant to travel by air, even though the risk of death associated with automobile travel is 25 times greater (table 6-1) (13). People tend to overestimate the number of deaths from rare, dramatic risks and

Table 6-l-Estimated Risk of Death to an individual From Various Human-Caused and Natural Accidents

Accident	Risk
Automobile	1 in 4,000
Drowning	1 in 30,000
Air travel	1 in 100,000
Lightning	1 in 2.000.000

SOURCE: C.D. Klaassen, "Principles of Toxicology," *Casarett and Doull's Toxicology,* C.D. Klaassen, M.O. Amdur, and J. Doull (ads.) (New York, NY: Macmillan, 1986).

Figure 6-l-The Relationship Between Risk Assessment and Risk Management

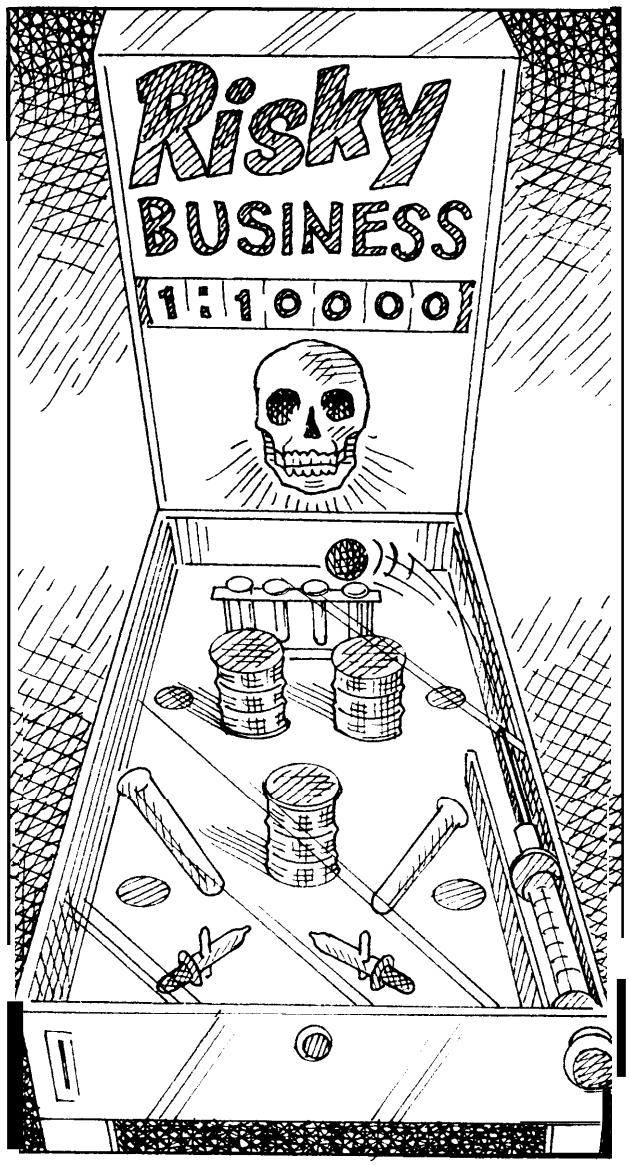


SOURCE: National Research Council, *Risk Assessment in the Federal Government: Managing the Process* (Washington, DC: National Academy Press, 1983).

underestimate the number from common, undramatic causes (6). For example, public perception of the annual death rates from floods or tornadoes are typically overestimated, while the risk from smoking or drinking alcoholic beverages is typically underestimated (6).

Risk assessment practices are the subject of ongoing debate within the regulatory and scientific communities, and in the last two decades strategies for regulating toxic substances have changed considerably. In the early 1970s, environmental legislation focused on regulating a relatively small number of pollutants of known toxicity. Today, concern is focused on thousands of toxic substances, for many of which little information is available. Consequently, regulatory strategies have changed. This change has been forced in part by improved methods of detecting toxic substances in the environment, improved capability of identifying the adverse effects of those substances, and difficulty in determining threshold levels below which no adverse effects occur. A major question facing both regulators and the public is how much risk is acceptable. A wide variety of views has been expressed on the topic of acceptable risk (4,6). A risk of death of less than 1 in 100,000 (10^{-5}) to 1 in 1 million (10^{-6}) is sometimes considered an acceptable risk for exposure to a chemical (13).

Policies regarding risk assessment have been controversial. Some people believe that Federal agencies overestimate risk by making overly conservative assumptions in developing risk assessments. Others feel that risk assessment practices do not take into account the complex interactions of multiple pollutants that often occur in the environment. Still others point out that risk assessments focus primarily on adverse effects on human health and devote little attention to other organisms and the environment in general. Critics of established risk assessment procedures believe that too little attention is being paid to the potential effects of toxic substances on children, infants, and the unborn, and efforts to address these concerns are under way at regulatory agencies. Regardless of the various viewpoints, risk assessment has become an integral component of regulatory strategies, and it is important to appreciate the scientific issues underlying this process in order to understand how toxic substances are controlled (6).



illustrated by: Ray Driver

In this chapter, the basic principles of risk assessment as they relate to the neurotoxicity of industrial chemicals are described. The risks posed by pharmaceuticals, for example, are typically evaluated through other approaches. The Environmental Protection Agency (EPA) has actively pursued regulatory strategies based on risk assessment (17), and the National Research Council (NRC) of the National Academy of Sciences has examined the issue of evaluating the risk posed by neurotoxic

substances. The reader may wish to refer to the NRC report for further information on this subject (16).

RISK ASSESSMENT

A complete risk assessment comprises four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization (15). Each of these is discussed in the sections that follow.

Hazard Identification

Hazard identification involves gathering and evaluating toxicity data on the types of injury or disease that may be produced by a substance and on the conditions of exposure under which the injury or disease may be produced. Toxicity data typically derive from epidemiological and experimental animal studies. Hazard identification involves judgments about the quality and relevance of these data. Of special importance is the question of whether specific toxic effects observed in one human population or in a particular experimental setting are likely to be produced in populations for which such data have not been or cannot be collected.

The most relevant toxicity data for identifying human hazards are usually derived from studies in humans. However, such information is often unavailable or limited and can be obtained only *after* human exposure has occurred. Consequently, it has become common practice to rely on data from animal studies to assess the toxic properties of chemicals. As discussed in chapter 5, a substantial body of evidence indicates that results from animal studies, with appropriate adjustments and qualifications, can be used to infer human hazard (1 3). There are important exceptions to this generalization, but unless existing data on human toxicity convincingly contradict a specific finding in animals, or there are other physiological reasons to consider certain types of animal data irrelevant to humans, the assumption is generally made that animal toxicity data can be used to identify potential human hazards (8).

The hazard identification section of a risk assessment report typically includes an evaluation of all available toxicity data to identify those adverse effects that are best documented and those that are most relevant to human health. In most cases, the toxic effects **causing greatest concern are those that** are most severe, occur at lowest exposures, and persist after exposure ceases.

A complete hazard identification also includes a discussion of the limitations of the available data. The absence of relevant data cannot, of course, be taken as evidence that a particular substance does not pose a hazard.

Dose-Response Assessment

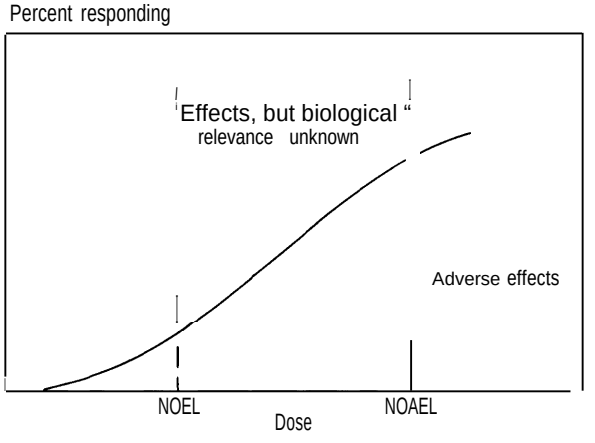
In the second step of risk assessment, assessors derive the quantitative relationship between exposure to a substance, usually expressed as a dose, and the extent of toxic injury or disease. There may be more than one relationship per substance, because several different kinds of responses may be elicited.

For any given chemical and exposure route, the severity and frequency of an effect generally increase with dose. Because humans are typically exposed at lower doses than those used in toxicity studies, it is necessary to *extrapolate* dose-response relations. At present, there are differences between dose-response extrapolations for noncarcinogenic types of toxicity, such as neurotoxicity, and for carcinogenicity. Noncarcinogenic effects are generally assumed to occur only when a certain level of exposure has been exceeded. This level is referred to as the threshold. It is frequently assumed that most carcinogens pose some risk at any level of exposure. However, the assumption that there is a threshold for all neurotoxic substances is questioned by some scientists (21).

The dose-response evaluation for noncarcinogens is derived from observations of a no observed effect level (NOEL) or no observed adverse effect level (NOAEL) in exposed people or experimental animals (figure 6-2). The NOAEL or NOEL represents an approximate threshold for the group that has been studied. The NOEL is that dose at or below which *no* biological effects of any type are noted (a determination that is influenced by the sensitivity of analytical techniques), and the NOAEL is that dose at or below which no *harmful* effects are seen. As noted earlier, definitions of "harmful" effects are influenced by social norms and values. If more than one effect is seen in animal tests, the effect occurring at the lowest dose in the most sensitive animal species and sex is generally used as the basis for estimating a NOEL or NOAEL. The NOAEL is most commonly used in current neurotoxicological evaluations.

Experimental studies are often conducted using relatively high doses of a chemical to increase the probability of observing effects in small groups of

Figure &2—Hypothetical Placement of a No Observed Effect Level (NOEL) and No Observed Adverse Effect Level (NOAEL) for a Single Chemical on a Dose-Response Curve



SOURCE: Office of Technology Assessment, 1990.

animals. Human exposures tend to be in low doses, where responses are not generally directly observable. Therefore, in moving from laboratory exposures to human exposures, it is usually necessary to extrapolate from high dose-responses to low dose-responses. Extrapolations are also necessary to adjust for differences between animals and humans with regard to conditions of exposure and certain physiological factors, such as size, lifespan, metabolism, brain maturation rate, and absorption. Adjustments are also made for variations in sensitivity among individuals in a population (intraspecies differences) (15). Some of these extrapolations and adjustments take the form of safety factors; these are discussed in more detail in the risk characterization section of this chapter.

Exposure Assessment

The next step in risk assessment is determination of the extent and nature of human exposure (including source, route, dose, and duration). An assessment of subgroups in the population expected to experience unusual exposures is also appropriate (15).

Exposure can occur from many sources (e.g., soil, food, air, or water) and may enter the body by several routes, including ingestion, inhalation, or contact with skin. It is important to note that an individual may incur exposures from more than one source or route. Determination of environmental concentrations and means of human exposure, route of entry, site of the exposed population, and uncertainties in exposure estimates are important factors in exposure assessment. The degree of exposure to some toxic substances is strongly influenced by occupation. For example, industrial workers may be exposed to high concentrations of some chemicals that the public may encounter at much lower levels.

Duration refers to the period of time over which individuals are exposed. An acute exposure is generally a single exposure that occurs over a short period of time. An exposure is considered chronic when it occurs over extended periods of time or a substantial portion of a person's lifetime (see ch. 5). Exposures of intermediate duration are called subchronic. Chronic and subchronic exposures may be episodic (occurring at various intervals) or continuous (occurring over extended periods).

The pattern of exposure-the dose, duration, frequency, and route—is an important determinant of risk. Other concerns include knowledge of the age, sex, health status, and presence or absence of other environmental exposures for a given population. Obtaining such information requires a comprehensive monitoring program; however, data of this kind for a given toxic substance are often not available.

Risk Characterization

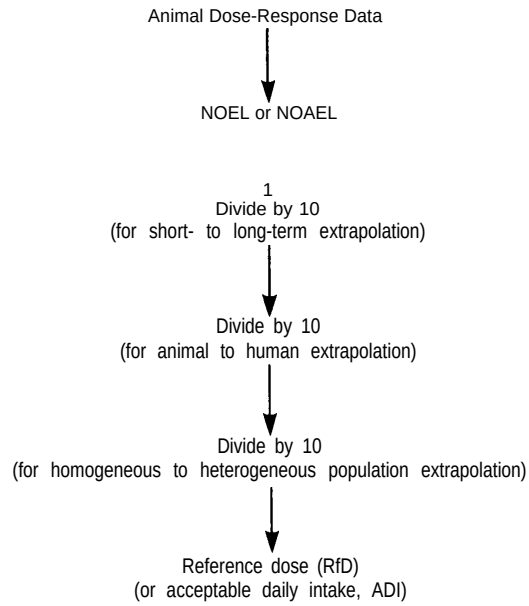
The final step of risk assessment combines the results of hazard identification, dose-response assessment, and exposure assessment to produce a characterization of risk. The NOAEL (or, less frequently, the NOEL) derived in the assessment of dose-response is divided by a safety factor, or uncertainty factor, yielding what is called the reference dose (RfD) (2). At **the present time,** risk characterization for noncarcinogenic forms of toxicity, including neurotoxicity, is based on the NOAEL (or NOEL) safety factor approach. The RfD (also called the acceptable daily intake)[1] is used to characterize risk. If human exposure is consistently below the RfD, risk assessors assume there is little health risk. If exposures exceed the RfD, it is assumed a significant risk exists. Generally, no

[1]Reference dose is considered by EPA to be a more appropriate term than acceptable daily intake, in part because of the difficulty of defining "acceptable."

attempt is made to describe the magnitude of the risk.

Three safety factors are commonly used to develop an RfD. The NOAEL or NOEL is divided by 10 when epidemiological or human experimental data are used to predict human risk. This safety factor is applied in order to protect sensitive members of the population when data have been obtained from average, healthy persons. Another factor of 10 is applied to the NOAEL or NOEL when extrapolating from animals to humans. To develop a chronic RfD when only subchronic animal studies are available, another factor of 10 is added, for a total safety factor of 1,000. Sometimes a factor is added for an incomplete database. The magnitude of the safety factor employed can vary from chemical to chemical. Scientific judgment may be exercised in evaluating species differences, the nature and extent of human exposure, the types of toxic effects, and the relative doses at which toxicity occurs in test species (see, e.g., 51 FR 34040). The application of safety factors is diagramed in figure 6-3.

Figure 6-3-Use of Safety Factors in Deriving a Reference Dose



SOURCE: Office of Technology Assessment, 1990.

A variation on the safety factor approach is the margin of safety (MOS), or margin of exposure (MOE). This involves dividing the NOAEL (or NOEL) by the current, desired, or most feasible human exposure level. This margin is sometimes compared with the safety factors mentioned above in order to judge its adequacy. Risk assessors generally employ the MOS approach to make judgments about the safety of existing or proposed exposure levels. They use the safety factor approach in circumstances where guidelines or regulations specify maximum allowable or safe exposure limits (3).

For substances that produce carcinogenic effects, the NOAEL (or NOEL) safety factor approach is not used. Instead, various extrapolation models are applied to develop estimates of risk (typically, the probability of developing cancer over a lifetime) associated with various levels of exposure. There is little scientific literature on the application of this type of extrapolation to noncarcinogenic effects.

Currently, cancer risks and RfDs are expressed numerically, but these quantitative figures may be qualified with factors such as the strength of the evidence of toxicity on which the risk or RfD is based. The uncertainties and assumptions inherent in any risk assessment should also be stated. This information is as essential as the quantitative description of risk associated with exposure to a toxic substance.

RISK MANAGEMENT

The purpose of risk management is to determine whether an assessed risk should be reduced and to identify the degree of risk reduction that is appropriate to a given situation. Risk management depends on information derived from the risk assessment, but it may also depend on political, social, ethical, economic, and technological factors. NRC has recommended that regulatory agencies take steps to establish and maintain a clear conceptual distinction between risk assessment and risk management (15). Different risk management approaches are taken by different regulatory agencies, depending largely on the kind of exposure being evaluated and the agency's statutory authority. The three most common risk management approaches mandated by the various environmental and public health laws are risk only, risk balancing (risk-benefit), and technological control (25), Public perceptions may also influence risk management decisions.

A regulatory decision using the *risk only* approach takes into account only the level of risk that is considered necessary to protect public health. However, the *risk balancing* approach may consider

social, economic, and technological factors as well. This approach involves developing a consensus among interest groups and making trade-offs for the public well-being. The third risk management approach, *technological control,* involves reducing risk by applying the best available, most feasible technologies.

RISK ASSESSMENT AND NEUROTOXIC SUBSTANCES

The risk assessment approaches outlined above have been discussed extensively in various Federal and State regulations and guidance documents (see, e.g., 51 FR 33992-34003; 50 FR 10372-10442) (5), as well as in the scientific literature (50 FR 10372-10442) (15). Practical applications of these methods of risk assessment can be found in hundreds of regulations promulgated by EPA, the Food and Drug Administration, the Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission, as well as in the scientific literature. A representative sampling of the latter, and references to many more assessments, can be found in the National Academy of Sciences' series *Drinking Water and Health (8* volumes through 1988). While legitimate scientific differences exist regarding many issues in risk assessment, particularly those concerning extrapolation, consensus exists regarding the need for some type of analysis of the risk posed by toxic substances. Differences in approaches to risk assessment can result in different conclusions with respect to the degree of risk posed by a toxic substance and how much of society's resources should be used to address toxicological concerns.

To date, most risk assessments have been devoted to carcinogenic substances. As mentioned above, some basis has been found for development of explicit descriptions of noncarcinogenic risk, and most of the guidance documents mentioned above deal with this issue. There is some discussion of noncarcinogenic effects in the *Drinking Water and Health series* cited above, in EPA's Toxic Substances Control Act Test Guidelines (50 FR 39398-39418; 50 FR 39458-39470), and in various documents issued by the World Health Organization (28). EPA's "Guidelines for the Health Assessment of Suspected Developmental Toxicants," issued in 1986 (51 FR 34040), were the first noncancer risk assessment guidelines produced.

Risk assessment strategies were originally developed for evaluating carcinogens, which have often been viewed as exerting "all-or-none" effects (although this view is changing for some carcinogens). Neurotoxic substances differ from carcinogens in that adverse effects are strongly dependent on dose—severe effects may result from exposure to large concentrations of a substance, but little effect may result from exposure to low concentrations. Also, cancer is a relatively well-defined, discrete endpoint. Neurotoxicity may result in multiple endpoints (e.g., seizures, memory loss, hearing loss), thus complicating risk assessment strategies. In most of these cases, and in many specific regulatory applications, the RfD approach to risk characterization (or its equivalent in occupational settings) is accepted.

Examples of Regulatory Approaches

Federal regulatory agencies have not developed uniform risk assessment approaches to neurotoxic substances, although EPA has been particularly active in developing risk assessment guidelines (1 2). To illustrate how various agencies have used risk assessment, one may focus on four widely recognized neurotoxic substances: lead, ethyl-p-nitrophenyl phosphonothionate (EPN, an organophosphorous pesticide), acrylamide (a chemical often used because of its ability to polymerize), and n-hexane (a commonly used industrial solvent) (9). Each of these substances is representative of a major category of environmental exposure: lead (general exposure), EPN (pesticide), and acrylamide and n-hexane (occupational exposures).

Two of the four chemicals examined, EPN and n-hexane, are regulated primarily on the basis of neurotoxic concerns. Risk assessments for the two focus on histopathologica1 analyses, as opposed to examinations of functional effects. Lead is regulated because of its neurotoxic properties, especially prenatally and in early life, and its effects on the blood-forming system. Acrylamide is regulated because of both its carcinogenic and its neurotoxic potentials (box 7-E).

The methodological approaches used by EPA (for lead and EPN) and OSHA (for acrylamide and n-hexane) were generally the same. In identifying hazards, the agencies placed greatest reliance on human data, when they were available, but also relied on animal data. Principal emphasis was placed



Photo credit: National Arhives, EPA Documerica Collection

on identifying NOAELs and determining the appropriate margin of exposure for humans.

In determining the bases for the occupational standards, OSHA adopted the American Conference of Governmental Industrial Hygienists' (ACGIH) threshold limit values (TLVs) for the n-hexane and acrylamide standards. ACGIH documented its derivation of each TLV (l), but the relationships between the TLVs and the underlying documentation were not explicitly stated. EPA's standards were stated more clearly.

A detailed evaluation of the risk assessment information used in the development of the standards for lead, EPN, acrylamide, and n-hexane confirmed that the safety factor approach has been used for neurotoxicity risk assessment in diverse circumstances. The safety factor approach (based on a NOAEL) is commonly used in the U.S. pharmaceutical industry, where neurotoxic effects sometimes limit the dose (10).

To date, there have been few instances in which neurotoxicity was the *principal* basis for regulation. There are perhaps three reasons for this. First, toxicity tests currently used by regulatory agencies are generally not specifically designed to identify neurotoxic agents. Histopathological analyses may identify some neurotoxic agents, but pathological analyses alone are of limited use in identifying adverse effects on the function of the nervous system (e.g., behavioral effects). Second, the risk assessment methodologies currently in use for carcinogenesis assume the absence of a threshold, whereas those used for other toxic effects assume a threshold. The practical consequence of this dichotomous system is that whenever a toxic agent exhibits both carcinogenic and other-than-carcinogenic effects, concerns about the carcinogenic risks tend to override concerns about other risks that may be associated with the agent at low doses. As indicated earlier, however, these assumptions regarding thresholds for carcinogenic and other toxic chemicals are the subject of debate. Third, in some cases other, noncancer health effects may occur at lower levels than neurotoxic effects, and regulations may have been based on these concerns.

Concerns about carcinogenicity have dominated discussions about the risks posed by toxic substances. However, the adverse effects on organs and organ systems (the nervous system, liver, immune system, cardiovascular system, and so on) may pose an equal or greater threat to public health. Consequently, it is important to devise risk assessment strategies to address noncancer health risks.

Limitations of Current Approaches

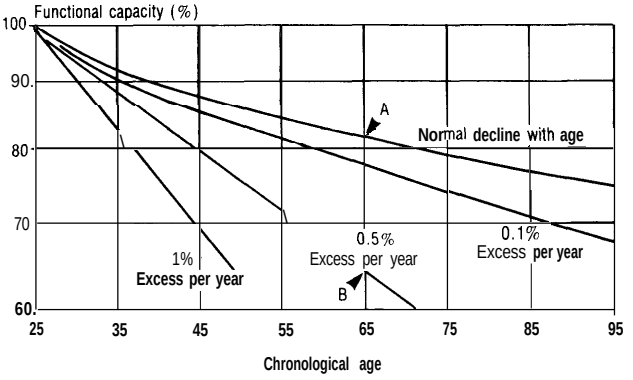
The nervous system is perhaps the most complex organ system of the body. Consequently, evaluating the neurotoxic potential of environmental agents is a particular challenge. For example, testing for a toxic effect on one component of the nervous system (e.g., hearing) may or may not reveal a toxic effect on another component (e.g., vision); furthermore, an effect on one nervous system function is not necessarily predictive of an effect on another nervous system function. Other factors that complicate risk assessment of neurotoxic substances include the apparent reversibility of many neurotoxic effects and the possibility of "silent," or latent, adverse

effects, which become apparent only late in life (27) (see box 7-G).

An important difference between neurotoxicity and carcinogenicity is the extent to which the effects are reversible. The endpoint of carcinogenicity is considered to be irreversible (although some persons argue that, strictly speaking, a "cure" would render the effect reversible), whereas the endpoints of neurotoxicity may be either reversible or irreversible, depending on the specific effect, the duration and frequency of exposure, and the toxicity of the substance (see box 7-G). Reversibility requires the introduction of a new variable into the risk assessment equation. Consequently, it has been proposed that it may be useful to specify a reversible effect level (27). Yet, determining whether or not an effect is truly reversible can be difficult. For example, exposure to a neurotoxic substance early in life could appear to give rise to a short-term, reversible effect, but later in life an irreversible effect (e.g., a neurological disease) could become apparent.

The age at which neurotoxic effects are evaluated can strongly influence the outcome of a risk analysis. For example, mice exposed to methylmercury during prenatal development may not exhibit adverse effects until late in their lives (23). Similarly, humans exposed to a toxic substance early in life may not suffer adverse effects until decades later. With age, the functional capacity of the brain declines significantly, and chronic exposure to some neurotoxic substances is thought to accelerate this process (27). As indicated in the hypothetical example in figure 6-4, a small acceleration in the loss of functional capacity may, with time, have very significant effects. For example, in this model, the postulated functional capacity of the brain that has not been chronically exposed to neurotoxic substances through age 65 is more than 80 percent of the capacity at age 65 (see figure 6-4, point A). However, even a modest acceleration of 0.5 percent per year results in a functional capacity of 65 percent (see point B), a more than 15-point reduction in this theoretical example. As figure 6-4 suggests, an acceleration of 1.0 percent per year could result in a large reduction in functional capacity over time. Hence, many scientists and regulatory officials believe that risk analyses should consider adverse effects over a range of ages and should take into account possible latent effects (27). More research is needed to understand the actual relationship between decline in functional capacity and the impact of toxic substances on the nervous system.

Figure 6-4-Postulated Decline in Brain Functional Capacity With Age and Exposure to Neurotoxic Substances



The heavy line (top) shows the rate posited to occur without added variables. The lighter lines show accelerations of 0.1 percent, 0.5 percent, and 1.0 percent annually, as might be produced by chronic exposure to neurotoxic substances.

SOURCE: B. Weiss and W, Simon, "Quantitative Perspectives on the Long-Term Toxicity of Methyl Mercury and Similar Poisons," ***Behavioral Toxicology,*** B. Weiss and V. Laties (eds.) (New York, NY: Plenum Press, 1975).

Issues in Hazard Identification

Neurotoxicological assessment of environmental agents is not uniform among Federal regulatory agencies (1 1,20,24). Although hazard identification through general toxicity testing (described inch. 5) can identify substances with *obvious* neurotoxic properties, substances producing more subtle effects are generally not detected. One exception is EPA's Office of Toxic Substances, which has included a battery of more sophisticated neurotoxicity tests in its regulatory requirements (see ch. 7). Until recently, however, EPA has not imposed these specific test requirements on many substances.

As discussed in chapter 5, neurotoxicity tests (and toxicity tests in general) should meet certain criteria such as sensitivity, specificity, and reproducibility before being adopted for routine use in hazard identification or dose-response assessment. Currently, there is a consensus among scientists that several neurotoxicological tests meet the necessary criteria and could be used for routine testing of potentially neurotoxic substances (14,18,22). A question that remains is precisely how EPA will use test data in the regulatory decisionmaking process.

Issues in Dose-Response Assessment

Thresholds and the RfD Approach-Toxic agents are conventionally classified into two groups: those that exert adverse effects only after a threshold dose is exceeded and those that theoretically increase risk at all doses greater than zero (no-threshold agents). This classification system, which has important consequences for risk assessment, has the practical effect of grouping all carcinogens into the no-threshold category and all other forms of toxicity into the threshold category. As indicated earlier, there is uncertainty about whether all carcinogens belong in the no-threshold group and all noncarcinogens, including neurotoxic agents, belong in the threshold group (19).

One consequence of this dichotomous system is that different models for risk assessment are used for the two groups. Typically, noncarcinogenic risk is modeled under the assumption that risk declines with dose and that the mathematical model that describes this relationship applies even below the region of observed effects. The model used for carcinogens yields zero risk (zero probability of developing cancer) only when the dose becomes zero. On the other hand, the consequence of assuming a threshold model is the development of RfDs by applying safety factors to NOELs or NOAELs.

NOAEL v. NOEL-The objective of using a NOAEL as opposed to a NOEL, as described above, is to establish a threshold dose such that no *adverse* effect would be likely to occur at exposures at or below this dose. Implicit in the establishment of a NOAEL is the understanding that any effects that occur below this dose would have no known biological relevance, whereas effects occurring above this dose would be harmful. A NOEL, on the other hand, reflects a dose below which no observable effect of any type occurs. An effect might be measurable, yet not be deleterious to human health; in fact, the effect might be beneficial or might not be biologically meaningful.

Due to limits in scientific understanding of the biological relevance of measurable effects, regulatory standards are often based on NOELs and not NOAELs. This reflects the intent to err on the side of caution and to be overprotective rather than underprotective of public health. When regulating pharmaceuticals, NOAELs are used because *adverse* effects must be distinguished from positive pharmacological effects. Also, recent draft developmental toxicity testing guidelines (54 FR 13472; 53 FR 5932; 51 FR 17890) are based on the NOAEL. Developmental testing is discussed in chapter 5.



Photo credit: United Automobile, Aerospace, and Agricultural Implement Workers of America-U4VPublic Relations Department

Safety Factors—A safety factor, as described above, is generally applied to the NOEL or NOAEL to estimate the RfD. However, the use of such factors creates an uncertainty in itself. Safety factors are generally derived not from chemical-specific data, but from *a priori* estimations of the ranges of variation in extrapolations used to determine an RfD (from animals to humans and within the human population). The limited research done on the topic of safety factors needed to account for intraspecies variability indicates that the tenfold factor used for this purpose tends to be more rather than less protective of a diverse human population (7,26).

What is unclear at the present time is the actual degree of protection against toxic effects that is associated with the RfD. It is likely that different safety factors are necessary for different chemicals; thus the RfD may be highly protective for one neurotoxic substance (i.e., one associated with an extremely low risk) but insufficiently protective for another.

Issues in Risk Characterization

Uncertainty-An important component of risk characterization that often receives inadequate attention is the delineation of uncertainties in the various stages of the assessment. The greater the total uncertainty, the less likely it is that the calculated risk represents the true risk. Every risk characterization should include a thorough discussion of all the uncertainties (50 FR 10372-10442, 51 FR 33992-34003).

There are uncertainties inherent in every risk assessment. Some are fundamental scientific questions common to all risk assessments. Questions that often arise include:

- How useful are animals as predictors of human toxicity?
- How well do responses at high doses predict responses at low doses?
- What is the relative importance of individual v. social risk? (See box 6-A.)

These questions are often difficult to answer; indeed, at times they cannot be answered. In the meantime, assumptions must be made and mathematical and interpretational conventions must be devised. In some areas, such as high to low dose extrapolation, there is no consensus among scientists. Regulatory agencies deal with such situations by adopting science policy assumptions (15). These assumptions tend to favor overstatement of risk, a practice that agencies justify on public health grounds.

Other types of uncertainties arise because the data available for any given risk assessment are incomplete or imperfect. Examples of these kinds of uncertainties include the following questions: Are toxic responses resulting from different experimental exposure routes comparable? What environmental concentrations of a contaminant are people actually exposed to? Is the toxic substance chemically modified in the environment or metabolized in the body to a more or less active form? What quantity of the chemical actually reaches and causes the toxic effect in the target organ?

Assumptions must be made to fill these gaps in information. The risk assessor usually tries to be conservative by making a worst probable case assumption. This results in a final risk number that, although uncertain, is highly likely to overestimate the true risk.

SUMMARY AND CONCLUSIONS

Toxicology and risk assessment have traditionally dealt with effects that can be characterized by *physical* changes, including morphological or biochemical abnormalities. Functional impairment of the organism, such as a chemically induced change in behavior, is now also considered a direct and measurable consequence of these types of abnormalities. The relationship between pathological changes and functional impairment needs to be further correlated, however.

Determining the biological mechanisms underlying behavior is a frontier of basic research. Research aimed at defining adverse effects at the cellular and systems levels is being actively pursued in tandem with the development of toxicity testing methods. Several tests already developed in the academic, regulatory, and private sectors can be used in routine preliminary or secondary screening of neurotoxic substances. Regulatory agencies will most likely adopt a tiered testing approach[2] whenever specific neurotoxicity tests as well as general toxicity tests are required.

With respect to identifying neurotoxic hazards and developing standardized methods of predicting them, several approaches might be pursued simultaneously. Research to improve the utility of structure-activity relationships in predicting neurotoxicity is critically needed. Strong, continuing research programs are needed to further refine and validate neurotoxicity tests. To guide the direction of this research, specific epidemiological surveillance programs could be developed to follow subpopulations that are exposed to high concentrations of neurotoxic substances (e.g., certain occupational groups). Also, weight-of-evidence approaches for classifying neurotoxic hazards, similar to EPA's weight-of-evidence classification scheme for carcinogens, might help guide regulatory decisionmaking. EPA has recently proposed such a scheme for neurotoxicity.

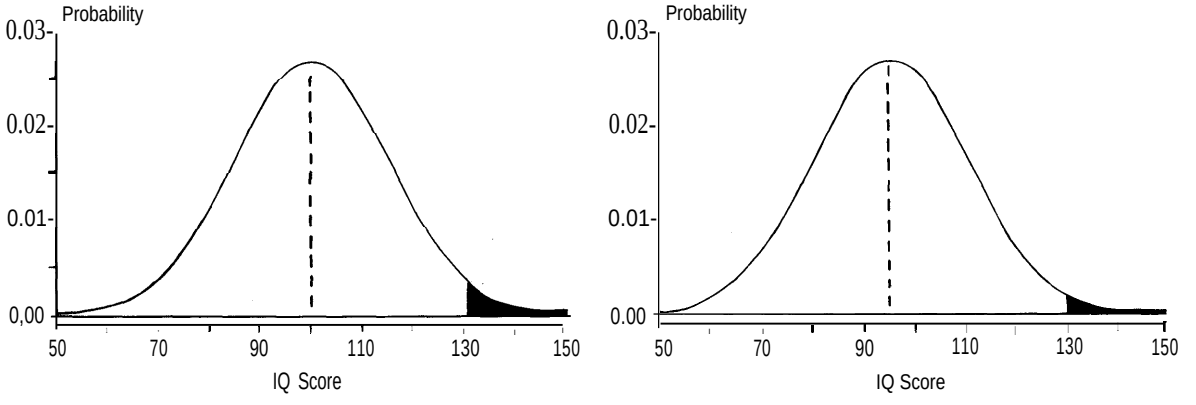
Further exploration of the scientific basis for the threshold assumption now adopted for all noncarcinogens is needed. The desirability of adopting nonthreshold dose-response relationships for some agents

[2]The tiered testing approach is described in ch. 5.

Box 6-A—Individual v. Social Risks

Risk, particularly as it relates to carcinogenicity, is typically evaluated in the context of the individual, but evaluations of this kind may underestimate the overall risk to society. A useful example is levels of lead in children. A recent analysis of lead levels in newborns grouped concentrations of lead in the umbilical cord into three categories: low (1.8 micrograms of lead per deciliter of blood, ug/dl), medium (6.5 ug/dl), and high *(14.5* ug/dl). Even though children in the high exposure group fell just below the 15 ug/dl level considered to be hazardous (according to the Centers for Disease Control), at age 2 these children score 8 percent lower than nonexposed children on a standard mental development index (the Mental Development Index of the Bayley Scales of Infant Development).

Although individual children do not display adverse neurotoxic effects, the impacts on society can be very significant. As shown in the figure below, a 5 percent reduction in the mean scores can result in a significantly different distribution of IQ scores.



Distributions of intelligence test scores. Left: standardized mean 100; standard deviation 15. Right: mean 95.

The graph on the left indicates a typical distribution, in which the mean IQ score is 100 (the standardized average). In a population of 100 million, 2.3 million individuals would be expected to score above 130. In the distribution on the right, based on a mean score of 95, about 1 million individuals score above 130, a reduction of 1.3 million individuals. Clearly, what may appear to be small differences in lead leve1-differences that are not apparent in individual evaluations-can translate into a major social problem, detectable only through statistical analysis of data from exposed and unexposed children.

SOURCE: Adapted from B. Weiss, ''Neurobehavioral Toxicity as a Basis for Risk Assessment,'' ***Trends in Pharmacological Sciences 9:59-62, 1988.***

producing delayed, irreversible neurotoxic effects might be considered. Alternative means of modeling dose-response relationships for neurotoxic agents need to be investigated and developed into practical tools. If the safety factor approach is to be maintained, empirical verifications of its adequacy are desirable, not only for neurotoxic agents but for other toxic agents as well. In addition, methods are needed to identify relatively weak neurotoxic chemicals that can cause adverse effects in humans after low-level exposures over long periods of time. Facilitating and maintaining coordination among researchers and scientists in the various regulatory programs will be crucial to ensure efficient and consistent integration of research findings into regulatory decisionmaking.

CHAPTER 6 REFERENCES

1. American Conference of Governmental Industrial Hygienists, *Documentation of the Threshold Limit Values and Biological Exposure indices, Acrylamide and Hexane* (Cincinnati, OH: 1986).
2. Barnes, D. G., and Dourson, M., "Reference Dose (RfD): Description and Use in Health Assessments," *Regulatory Toxicology and Pharmacology 8:471-486, 1988.*
3. Bass, B. F., and Muir, W. R., Summary *of Federal Actions and Risk Assessment Methods Relating to Neurotoxicity,* EPA Contract No. 68-02-4228 (Arlington, VA: Hampshire Research Associates, Inc., 1986).
4. Byrd, D., and Lave, L., "Narrowing the Range: A Framework for Risk Regulators, " *Issues in Science and Technology* (Summer) :92-100, 1987.
5. California Department of Health Services, "A Policy for Chemical Carcinogens: Guidelines on Risk Assessment and Their Scientific Rationale, " draft Berkeley, CA, 1984.
6. Conservation Foundation, *Risk Assessment and Risk Control* (Washington, DC: 1985).
7. Dourson, M. L., and Stara, J. F., "Regulatory History and Experimental Support of Uncertainty (Safety) Factors," *Regulatory Toxicology and Pharmacology 3:238-244, 1983.*
8. ENVIRON Corp., *Elements of Toxicology and Chemical Risk Assessment* (Washington, DC: 1988).
9. ENVIRON Corp., "Assessing Human Risks Posed by Neurotoxic Substances, " prepared for the Office of Technology Assessment, December 1988.
10. Gad, S., Searle Research & Development, personal communication, May 23, 1989.
11. Hampshire Research Associates, Inc., *Expert Neurotoxicity Assessment Report: Neurotoxicity Risk Assessment Guidelines* (Arlington, VA: 1985).
12. Kimmel, C. A., "Regulatory Issues and Risk Assessment for Neurotoxicology, " Neurotoxicology, Feb. 27, 1989.
13. Klaassen, C. D., "Principles of Toxicology," *Casarett and Doull's Toxicology,* C.D. Klaassen, M.O. Amdur, and J. Doull (eds.) (New York, NY: Macmillan, 1986), p. 25.
14. McMillan, D. E., "Risk Assessment for Neurobehavioral Toxicity, ' *Environmental Health Perspectives 76:155-161, 1987.*
15. National Research Council, *Risk Assessment in the Federal Government: Managing the Process* (Washington, DC: National Academy Press, 1983).
16. National Research Council, *Neurotoxicology and Models for Assessing Risk* (Washington, DC: National Academy Press, in preparation).
17. Preuss, P. W., and Ehrlich, A. M., "The Environmental Protection Agency's Risk Assessment Guidelines," *JAPCA 37(7):784-791, 1987.*
18. Reiter, L. W., "Neurotoxicology in Regulation and Risk Assessment," *Developmental Pharmacology and Therapeutics 10:354-368, 1987.*
19. Rodricks, J. V., Frankos, V., Turnbull, D., et al., "Risk Assessment for Effects Other Than Cancer, " *Food Protection Technology,* C.W. Felix (cd.) (Chelsea, MI: Lewis Publishers, 1987).
20. Sette, W. F., "Complexity of Neurotoxicological Assessment" *Neurotoxicology and Teratology 9:411-416, 1989.*
21. Silbergeld, E.K., "Developing Formal Risk Assessment Methods for Neurotoxins, " Neurobehavioral *Methods in Occupational and Environmental Health* (Washington, DC: Pan American Health Organization, 1988).
22. Spencer, P. S., and Schaumburg, H.H. (eds.), *Experimental and Clinical Neurotoxicology* (Baltimore, MD: Williams & Wilkins, 1980).
23. Spyker, J. M., *Behavioral Toxicology,* B. Weiss and V.G. Laties (eds.) (New York, NY: Plenum Press, 1975), pp. 311-375.
24. Tilson, H. A., "Symposium: Screening for Neurotoxicity: Principles and Practices, " *Journal of the American College of Toxicology 8(1):13-17, 1989.*
25. U.S. Congress, General Accounting Office, *Health Risk Analysis: Technical Adequacy in Three Selected Cases, GAO/PEMD-87-14* (Washington, DC: 1987).
26. Weil, C. S., "Statistics v. Safety Factors and Scientific Judgment in the Evaluation of Safety for Man, " *Toxicology and Applied Pharmacology 21:454-463, 1972.*
27. Weiss, B., ''Neurobehavioral Toxicity as a Basis for Risk Assessment, " *Trends in Pharmacological Sciences 9:59-62, 1988.*
28. World Health Organization, *Principles and Methods for the Assessment of Neurotoxicity Associated With Exposure to Chemicals,* Environmental Health Criteria 60 (Geneva: 1986).

Chapter 7

The Federal Regulatory Response

"The workplace should not be a test tube and company employees should not be guinea pigs. We cannot tolerate stone-age protections for space-age dangers. "

Senator Harry Reid
Committee on Environment and Public Works
March 6, 1989

"There are substances commonly used in the home that make our lives easier. We use these substances in good faith, seldom questioning the fact that they could cause peripheral nerve or brain damage. Consumers rely on the Government's and industries' judgment on health dangers associated with the use of chemicals and pesticides.

Representative Harold L. Volkmer
Committee on Science and Technology
October 8, 1989

"The industrial laboratory will always outpace the regulatory agency in providing substitutes for banned chemicals, and some of those substitutes in field use may prove as troublesome as the ones they replace. "

William D. Ruckelshaus
Issues *in Science and Technology*
Spring 1985

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Chapter 7
The Federal Regulatory Response

Over the years, Congress has enacted many statutes that apply directly or indirectly to the regulation of neurotoxic substances. Some of these statutes are framed in broad terms to protect human health in general; others address specific adverse health effects, such as carcinogenicity, teratogenicity, and in rare cases behavioral changes and neurotoxicity (25). Some statutes provide broad authority for requiring that substances be tested for potential toxic effects; others require the implementing agency to prove that substances may be harmful before any regulatory action can be taken. Some statutes call for absolute protection of health and safety; others allow for balancing risks, costs, and benefits.

Not surprisingly, Federal agencies have promulgated equally diverse regulations. Some regulatory programs require substantial testing of chemicals to screen for toxic effects; others are not empowered to require any such testing. Some call for screening substances before they are allowed to enter the marketplace; others are reactive, taking effect only when evidence indicates that an existing chemical can, or does, cause harm.

Federal laws governing toxic substances can be divided into three general categories:

1. licensing and registration laws for new and existing chemicals, which entail an explicit review process and may include a requirement for toxicity testing;
2. standard-setting laws for chemicals used in specific situations, under which regulatory agencies determine recommended or required limits on toxic substances in various environmental media (air, water, or soil) or emitted by a given source, or dictate appropriate labeling of products that contain toxic substances; and
3. control-oriented measures for dealing with chemicals, groups of chemicals, or chemical processes that are explicitly identified in the laws. [1]

Distinctions among the three categories are not absolute—there is more of a continuum than a discrete grouping in the legislative language—but this classification indicates the basic types of approaches that have been developed to protect the public and the environment from the adverse effects of toxic substances. Table 7-1 presents key features of 18 Federal laws regulating the use of toxic substances (14).

The approach to regulation embodied in a statute largely determines the Federal response. Licensing programs are externally driven and must respond to petitions or applications from manufacturers or other outside parties; standard-setting and control-oriented programs may have to respond to deadlines set by Congress (for control-oriented programs, however, these deadlines generally affect regulation of sites rather than specific chemicals). Application and notification procedures under the licensing statutes require the regulatory agencies to review however many chemicals per year are submitted, whereas agencies charged with setting standards can control the scheduling and priorities of review to a greater degree.

Although some of the standard-setting and control-oriented programs have the ability to pursue research into the adverse effects of chemical substances, it is the licensing statutes that generally grant authority to require that chemicals be tested for toxic effects. As a consequence of these and other differences, implementation of licensing statutes has tended to be more active and, accordingly, more controversial than that of standard-setting or control-oriented statutes.

It is necessary to keep in mind that regulatory activities may be curtailed, expanded, or otherwise affected by various nonregulatory factors. The appropriations process determines the resources available to an agency to carry out its regulatory activities. Oversight by the Office of Management and Budget may require an agency to restrict or modify regulatory implementation. Abundant litigation challenging environmental laws and regulations has created a large body of court decisions that further interpret and clarify agencies' regulatory rights and responsibilities (see box 7-A); product

[1] Others have classified the regulatory response differently; one environmental law treatise, for example, suggests only two categories—product controls and pollution emission controls. The scheme proposed here is not definitive but is meant to emphasize how chemicals are singled out for attention and review in the legislative and regulatory processes.

Table 7-l—Key Features of Federal Laws Regulating Toxic Substances

Statute	Regulatory authority (regulatory agency)[a]	Toxic substance or effect of concern	Approach to risk
Part1-Licensing Laws			
Federal Food, Drug, and Cosmetic Act	Control levels of added substances (FDA)	"any poisonous or deleterious substance which may render it injurious to health"	No explicit consideration of benefits
	Control levels of natural components of food (FDA)	"poisonous or deleterious . . . does not ordinarily render it injurious to health"	Balance risk against need for plentiful and affordable food
	Control levels of environmental contaminants (FDA)	"poisonous or deleterious . . . does not ordinarily render it injurious to health"	Balance risk against whether required, unavoidable, or not measurable
	Set (EPA) and enforce (FDA, USDA) tolerances on pesticide residues for food and feed crops	"poisonous or deleterious . . . not generally recognized as safe for use . . . to the extent necessary to protect the public health"	Ensure adequate, wholesome, economical food supply; other ways pesticide affects consumers; usefulness
	Regulate introduction of new drugs and biologics (FDA)	"substantial evidence that safe and effective"; no "imminent hazard to public health"	Balance risks against efficacy and need
	Report on adverse reactions to drugs (FDA)	"any adverse experience ., . includes any side effect, injury, toxicity, or sensitivity reaction"	Balance risks against drug benefits
	Label cosmetics (FDA)	"poisonous or deleterious . . . may render it injurious"	No explicit consideration of benefits
Federal Insecticide, Fungicide, and Rodenticide Act	Register pesticides (EPA)	"will not generally cause any unreasonable risk to man or the environment"	Pesticide must not only be safe under conditions of use, but also effective
Toxic Substances Control Act	Require testing of existing chemicals where data are inadequate to assess risk (sec. 4); prohibit introduction into commerce of chemicals that will present an unreasonable risk (sec. 5); restrict or prevent production, use, or disposal of existing chemicals that present unreasonable risk (sec. 6) (EPA)	"unreasonable risk of injury to human health or the environment. . . including] carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects, and any other effect. . ."	Risks posed by chemical must be balanced against benefits it provides (i.e., risk must be unreasonable)
Part II-Standard-Setting **Laws**			
Clean Air Act	Conduct research on air pollution (EPA)	"adverse effects on health, including, but not limited to, behavioral physiological, toxicological, and biochemical effects"	NA
	Set air quality standards; regulate emissions of hazardous air pollutants; set standards for vehicle emissions, fuels, and fuel additives (EPA)	"endanger public health"	"Adequate margin of safety"
Federal Water Pollution Control Act; Clean Water Act	Set effluent standards for water; establish water quality criteria (EPA)	"identifiable effects on health and welfare"	Water quality criteria do not consider economic or technological feasibility
Safe Drinking Water Act	Set MCLs and MCLGs for public drinking water supplies (EPA)	"may have an adverse effect on the health of persons"	MCLGs do not consider feasibility, but MCLs do
Consumer Product Safety Act	Promulgate consumer product safety standards (CPSC)	"an unreasonable risk of injury"	Balance risks against product utility, cost, and availability
Federal Hazardous Substances Act	Ban hazardous substances for household use (CPSC)	"toxic. . . may cause substantial personal injury or substantial illness"	"the public health and safety can be adequately served"

Table 7-l—Key Features of Federal Laws Regulating Toxic Substance-Continued

Statute	Regulatory authority (regulatory agency)[a]	Toxic substance or effect of concern	Approach to risk
Federal Mine Safety and Health Act	Set standards for airborne contaminants in mines (MSHA)	"protection of life and prevention of injuries. . . material impairment of health or functional capacity"	Attain highest degree of health and safety protection; latest available scientific data; feasibility; and experience gained with health and safety laws
Occupational Safety and Health Act	Set standards for airborne contaminants in the workplace (OSHA)	"material impairment of health or functional capacity"	Attain highest degree of health and safety protection; latest available scientific data; feasibility; and experience gained with health and safety laws
Part III-Control-Oriented Laws			
Comprehensive Environmental Response, Compensation, and Liability Act; Superfund Amendments and Reauthorization Act	Fund cleanup of hazardous waste sites; designate reportable quantities for environmental release; report on community preparedness and release; prepare toxicity profiles on contaminants (EPA)	"substantial danger to the public health or welfare"	Focus on highest-risk chemicals
Controlled Substances Act	Control drugs that have potential fo rabuse (USDJ, FDA)	"substantial and detrimental effect"	Define list of substances to be controlled
Lead-Based Paint Poisoning Prevention Act	Determine, if possible, a safe level of lead in paint (CPSC)	Poisoning of children by lead-based paint	Determine whether any safe level could be established above 0.06°/0
Marine Protection, Research, and Sanctuaries Act	Regulate ocean dumping (EPA)	"adversely affect human health, welfare or amenities"	Consider appropriate alternative locations
Poison Prevention Packaging Act	Promulgate standards for packaging substances that could produce effects of concern (CPSC)	"serious personal injury or serious illness"	Determine degree and nature of hazard to children
Resource Conservation and Recovery Act	Regulate the handling of hazardous wastes; list hazardous wastes on basis of constituents (EPA)	"protect human health . . . serious irreversible or incapacitating reversible illness substantial present or potential hazard"	Control handling to minimize risks

[a]**List of acronyms** is **given** in app. F.

SOURCE: Office of Technology Assessment, 1990.

litigation may further modify the regulatory process. Furthermore, regulations may incorporate direct or indirect economic incentives in attempting to motivate industry to control pollutants (see ch. 9), adding another dimension to regulatory implementation. Clearly, the regulatory processes described herein are not rigidly circumscribed but are part of a larger regulatory dynamic (14).

LICENSING AND REGISTRATION LEGISLATION AND REGULATIONS

Three statutes govern most aspects of the licensing and registration of drugs, food additives, pesticides, and industrial chemicals: the Federal Food, Drug, and Cosmetic Act; the Federal Insecticide, Fungicide, and Rodenticide Act; and the Toxic Substances Control Act. All of these statutes require submission of applications for use of, or notification of intent to use, new chemical substances; they also authorize reviews of previously registered chemicals. The review processes followed under these acts have four basic steps:

1. manufacturer's submission of data;
2. evaluation of data by the responsible regulatory agency;
3. requests for additional data (if necessary); and
4. agency determination (which may or may not involve a formal rule-making procedure).

The extent to which neurotoxicity is addressed in the process varies among and within statutes according

Box 7-A—Toxic Substances Laws Go To Court: *The Judicial Role in Interpreting Legislative Language and Regulatory Implementation*

The passage of a statute by Congress establishes overarching boundaries for regulatory implementation, but translating Congress' goals, as stated in the legislative language, into regulatory action is by no means a simple process. Environmental laws abound with general phrases calling for protection of "public health and the environment' or for protection from 'adverse effects' some laws require that standards incorporate a' 'margin of safety. " The definition of these phrases often depends on the ever-changing forefront of scientific research into what levels of toxic substances may cause adverse effects—what, indeed, should be defined as an adverse effect—and, based on the often uncertain conclusions of preliminary research, what constitutes a margin of safety. Congress leaves the interpretation of its mandates to the discretion of the Federal regulatory agencies.

Thus, regulatory agencies get the first opportunity to interpret what Congress meant, but their responses are modified by many factors: the appropriations process; oversight by the Office of Management and Budget; requirements of the Administrative Procedures Act that the agency notify and obtain comments from the public on any proposed regulations and that it respond to all significant comments; recommendations of scientific or technical advisory panels; recognition that standards and regulations may have a profound effect on product litigation; and other internal and external pressures and requirements. It typically takes from 2 to 8 years for an agency to promulgate a rule, and the rule is then subject to further examination and interpretation through court challenges and interpretive rulings.

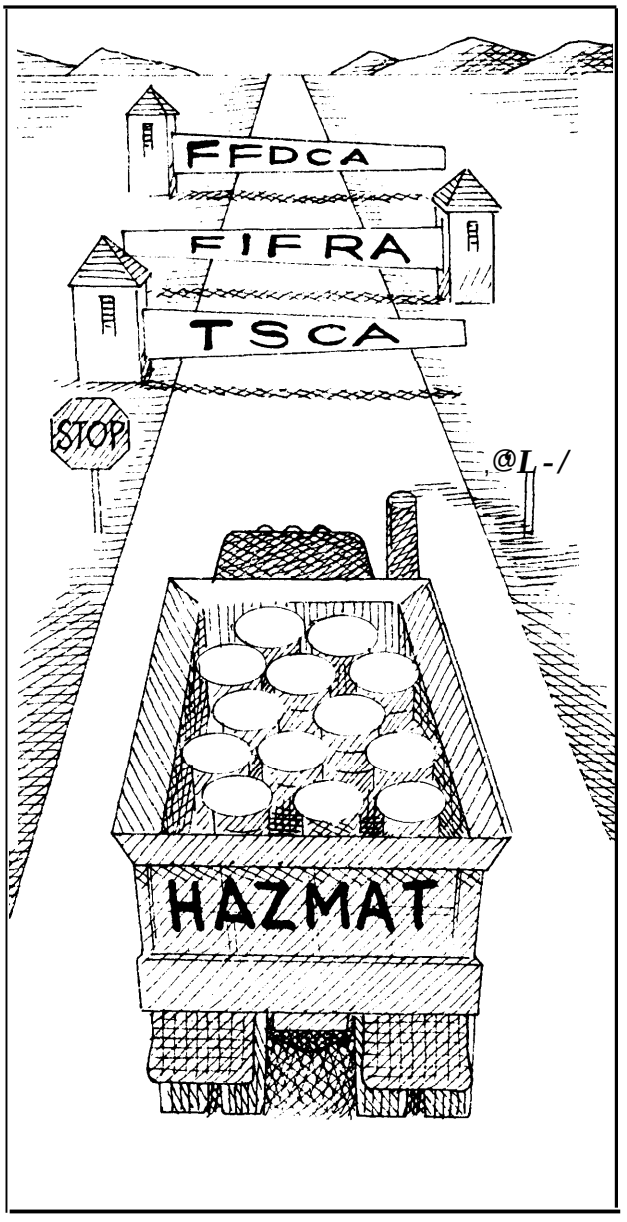
Administrative and procedural complexities have made environmental statutes the most frequently litigated of all fields of administrative law (Grad, 1985). During litigation, courts must evaluate agencies' interpretations of congressional intent, and they must often evaluate the complex underlying technical issues as well—including the definitions of adverse effects or margins of safety. The judicial interpretation may have a considerable impact on how the legislative language can be interpreted and how the regulations can be implemented.

In at least one case, the Federal district courts have upheld the use of neurotoxic effects in the setting of standards. In 1980, the Lead Industries Association, Inc., brought suit against the Environmental Protection Agency (EPA), charging that the Administrator went beyond the scope of his authority in setting standards for lead under the Clean Air Act. EPA had issued a rule setting the primary national ambient air quality standard for lead on the basis of its effects on the blood and on the nervous system (43 FR 46254). After considerable study, EPA had determined that lead's effects on the nervous system begin to appear at the level of 50 micrograms of lead per deciliter of blood (ug/dl), that anemia and other effects appear at 40 ug/dl, and that identifiable changes in the blood (though not easily diagnosed through clinical examination) begin at 30 ug/dl. To provide an adequate margin of safety, EPA set a target for the population of 15 ug/dl.

Among other arguments, the Lead Industries Association contended that the EPA's rule was not adequately supported by the finding that neurotoxic effects begin to appear at 50 ug/dl and that basing the standard on subclinical effects at 30 ug/dl went beyond the Agency's statutory authority. The courts upheld EPA's finding on neurotoxicity, stating that the record revealed ample support for the Administrator's determination of when central nervous system effects begin to occur. The decision noted that it was not the function of the court ''to resolve disagreement among the experts or to judge the merits of competing expert views. ' (" [C]hoice among scientific test data is precisely the type of judgment that must be made by EPA, not this court. That evidence in the record may also support other conclusions, even those that are inconsistent with the Administrator's, does not prevent us from concluding that his decisions were rational and supported by the record. ' The court further upheld EPA's justification for the margin of safety, noting that the legislative history of the Clean Air Act shows that margins of safety were considered essential for protecting against hazards that had not yet been identified.

Judicial interpretation is one of many factors influencing the implementation of regulations; as this case shows, it may strengthen an agency's regulatory decisions. As for neurotoxic effects, which have rarely been explicitly mentioned in statutes, the courts may play an important role in ensuring that they are considered in the process of protecting public health and the environment.

SOURCES: F.P. Grad, "A Brief Account of the Beginnings of Modern Environmental Law," Treatise on Environmental Law, sec. 1.01 (St. Paul, MN: Matthew Bender, 1985); "kid Industries Association, Inc. v, U.S. Environmental Protection Agency, " *Federal Reporter* (2d series) 647:1130-1189, 1980.



Illustrated by: Ray Driver

to the type of substance being reviewed and whether it is a new or existing substance.[2]

Federal Food, Drug, and Cosmetic Act

The earliest Federal statute governing food safety was the Food and Drugs Act of 1906 (19), which prohibited the marketing or transport of "adulterated food," that is, any food that contained "any added poison or other added deleterious ingredient which may render such article injurious to health." The Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 301-392),[3] which replaced the original Act in 1938, expanded controls to include naturally occurring as well as added toxic substances. However, it did not delineate specific toxic effects. The Act is based on a broad concept of safety as absence of injury:

> A food shall be deemed to be adulterated-if it bears or contains any poisons or deleterious substances which *may render it injurious to health;* but in case the substance is not an added substance, such food shall not be considered adulterated under this clause if the quantity of such substance in such food *does not ordinarily render it injurious to health . . . [sec.* 402(a)(l)] [emphasis added].

Thus, added substances are governed by a stricter standard than naturally occurring substances. Since its passage, FFDCA has been clarified and expanded by various amendments, but the language referring to toxic effects remains the same.

The Act grants the Food and Drug Administration (FDA) authority to regulate foods, drugs, and cosmetics in the following categories:

- food and general safety (sec. 402),
- environmental contaminants (sec. 406),
- pesticide residues (sec. 408),
- food additives (sec. 409),
- drugs and biologics (sec. 505),
- cosmetics (sec. 601), and
- color additives (sec. 706).

FDA can use this authority to require premarket submission of specific toxicity test data. It could incorporate neurotoxicity tests in the guidelines for recommended testing or require neurotoxicity testing during the application process if there is evidence of potential neurotoxic effects.

Environmental Contaminants of Food

FDA is authorized to regulate unavoidable contaminants of raw agricultural commodities under" either the general food safety provisions (sec. 402) or the specific provisions of section 406, which calls for FDA to:

[2]The information in this section is drawn primarily from personal communication with officials at the respective agencies.

[3]All United States Code (U. S. C.) citations refer to the 1982 edition, unless otherwise noted.

> . . . promulgate regulations limiting the quantity therein or thereon to such extent as. . . [is] necessary for the protection of public health, and any quantity exceeding the limits so fixed shall also be deemed unsafe . . . (21 U.S.C. 346).

In setting the limits, FDA must consider whether the substance is required or unavoidable in the production or processing of the food item and the potential effects of the substance on health. Though not included in the statute, the extent to which the substance can be detected in foods is also considered, since it would be impossible to enforce limits that could not be detected (19).

FDA asserts that it is not always appropriate to set formal tolerance levels for contaminants-e.g., when new toxicity data are being developed for a substance that previously had little or none (39 FR 42745). In addition, the formal rule-making procedure demanded for setting tolerances is elaborate and time-consuming. Given these circumstances, FDA has chosen to rely primarily on a regulatory option not explicitly established by statute—that of setting informal tolerances, called action levels. An "action level is based on the same criteria as a tolerance, except that an action level is temporary until the appearance of more stable circumstances makes a formal tolerance appropriate" (39 FR 42745).4 Action levels are not binding, nor do they have the legal force of tolerance levels, but they can be used to "prohibit any detectable amount of the substance in food" (21 CFR part 109.4). Any food that contains more than the action level dictates may be declared adulterated and be subject to further regulatory action.

In establishing either an action level or a tolerance, FDA uses available information on health effects to determine a dosage at which risk of exposure to a contaminant is acceptable. Once the action level or tolerance is established, FDA may take appropriate action to restrict food that does not meet these standards.

Pesticide Residues

The 1954 amendments to FFDCA empowered FDA to set and enforce standards for pesticide residues on raw, unprocessed agricultural commodities. More recent amendments bestowed the standard-setting responsibility on the Administrator of the Environmental Protection Agency (EPA):

> The Administrator [of EPA] shall promulgate regulations establishing tolerances with respect to the use in or on raw agricultural commodities of poisonous or deleterious pesticide chemicals and of pesticide chemicals which are not generally recognized . . . as safe for use, to the extent necessary to protect the public health [sec. 408(b), 21 U.S.C. 346a, 1976)].

Pesticides that are expected to become more concentrated during processing require separate tolerances. EPA may revoke or change tolerances if new evidence or further review indicates that a change is necessary (29).

The establishment of tolerances takes place concurrently with pesticide registration under the Federal Insecticide, Fungicide, and Rodenticide Act, described below. The manufacturer petitions EPA to set a tolerance for the pesticide residue; the pesticide cannot be registered for use on a food or feed crop until a tolerance has been set or an exemption granted (48). The FFDCA specifies that a pesticide tolerance petition include "full reports of investigations made with respect to the safety of the pesticide chemical" [sec. 408(d)(l)(C)], thus placing the burden of proof of the safety of a pesticide on the manufacturer.

Food and Color Additives

The Food Additives Amendment of 1954 (Public Law 85-929) sought to "prohibit the use in food of additives which have not been adequately tested to establish their safety. " The amendment initiated an application process for the approval of food additives that, like the pesticide tolerance provisions, shifted the burden of proof from the FDA to the producer.

Manufacturers must file a written petition before a potential food additive can be approved for use. The petition must contain "scientific data adequate to support safety" (15) and ". . . full reports of investigations made with respect to the safety for use of such additive, including full information as to the methods and controls used in conducting such investigations' [sec. 409(b)(2)(E)].

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[4]Recent court challenges, however, have resulted in a decision requiring FDA to subject proposed action levels to public notification and comment; FDA incorporated the decision in a proposed rule in April 1989 (54 FR 16128-30). It remains to be seen whether action levels will continue to offer a streamlined alternative to the setting of tolerances.

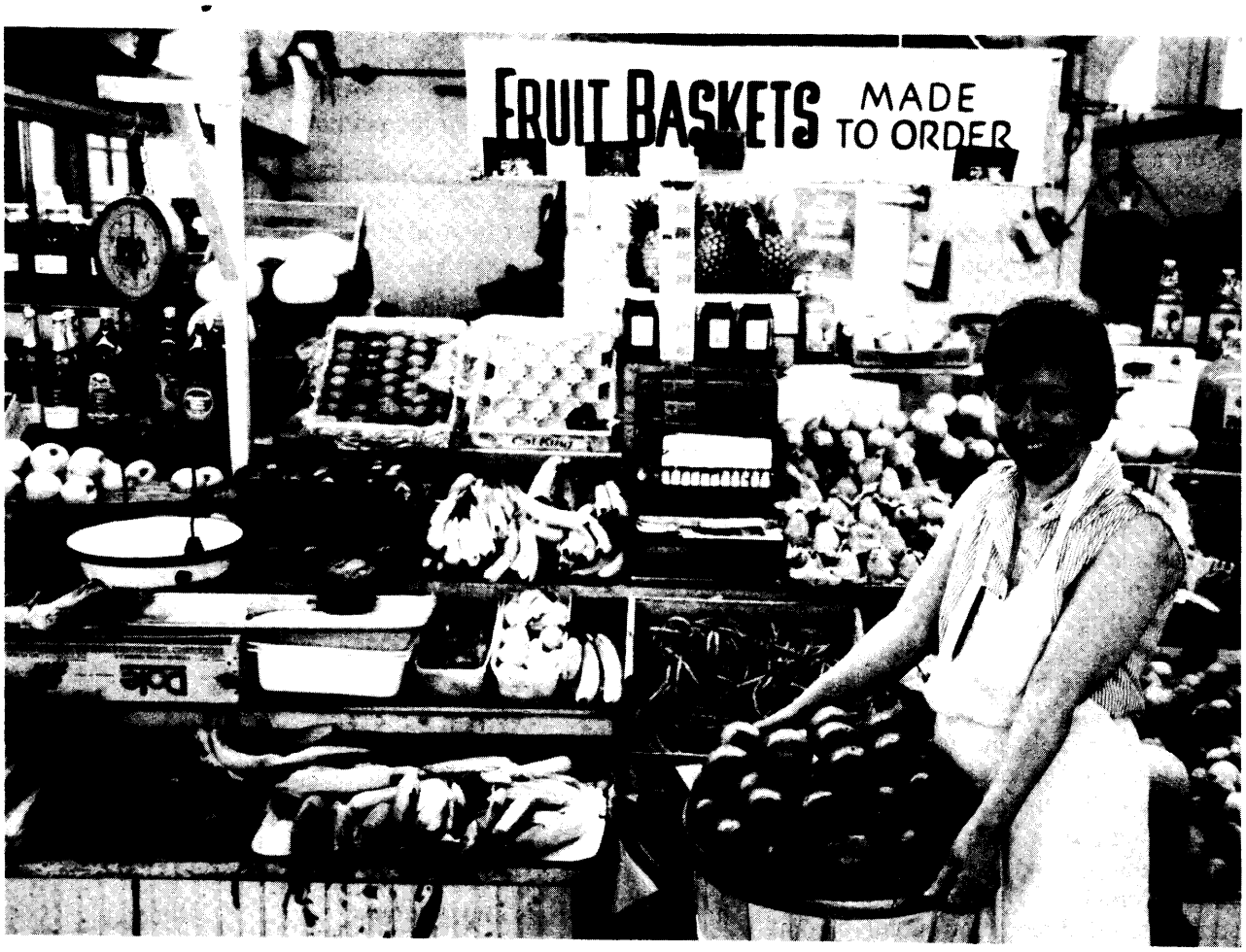

Photo credit: U.S. Environmental Protection Agency

FDA decides whether, and in what amounts, a food additive may be used on the basis of the data submitted with the application. It has drawn its interpretation of safety from the legislative history of the Act, which used the phrase "reasonable certainty of no harm," and has incorporated that standard into its regulations regarding toxicity testing (15).

Color additives to food are regulated under the Color Additive Amendments of 1960. These regulations are essentially the same as those for food additives, including a process of premarketing approval. In addition, color additives to drugs and cosmetics are regulated. A color additive may be approved for general or restricted use if it is found that "it is suitable and may be safely employed" [sec. 706(b)(2)].

Petitions for approval of food and color additives are handled by FDA's Center for Food Safety and Applied Nutrition (CFSAN). These include direct food additives (e.g., preservatives) and color additives, as well as indirect additives, such as constituents of packaging materials that might migrate into food. Although the application process officially begins with submission of the petition and supporting data, CFSAN may, and frequently does, hold informal preapplication meetings with petitioners to clarify data needs.

Each application must contain all data relevant to assessing safety. The tests required are determined on the basis of predicted exposure. For direct food additives, CFSAN test guidelines, known as the Red Book, list particular exposure levels and characteristics of chemical structure that require certain types of tests (30). Most substances must be subjected to subchronic studies in mammals as well as reproductive tests. No specific neurotoxicity tests are required, but the protocols do call for observation of

effects on animal behavior, so some prediction of adult or developmental neurotoxicity, or both, may be provided. The test requirements are negotiable, but the petitioner must present sufficient data to ensure a reasonable certainty that no harm will result from the use of the additive.

The Red Book is currently being revised, and the new version may contain specific tests for neurotoxicity. The precise nature of these tests is still under review. In order for FDA to impose any additional testing requirements, it must show that further tests are necessary.

Petitions must be reviewed within 90 days of submission, although FFDCA permits extensions to 180 days. Each petition is evaluated by senior scientists from CFSAN's Division of Toxicological Review and Evaluation. Most reviewers are general toxicologists; the division has had neurotoxicologists directly involved in reviewing petitions in the past, but few in 1988 or 1989. If the data indicate neurotoxic effects, the division may call on the Neurobehavioral Toxicology Team-neurotoxicologists who are not generally members of the review team-for further research. This team has been asked to review three chemicals in the last 5 years; the total number of chemicals reviewed by CFSAN during that period is uncertain, but the center annually reviews approximately 60 indirect food additives, 10 direct food additives, and 10 color additives.

If the toxicological data submitted with a petition are insufficient for reaching a conclusion on whether a substance poses unreasonable risks, CFSAN negotiates with the petitioner to conduct additional tests. New data must be submitted within 180 days, although extensions may be given for reasonable cause. (Time spent on developing new data is not counted in the time limit by which FDA must act on the application, and if the necessity for new information is a result of the petitioner's failure to submit all data that were clearly required, the FDA may reset the clock to day 1 when the additional data are submitted.)

If CFSAN determines, on the basis of toxicological data and potential exposure patterns, that a substance may be harmful, the food or color additive petition may be denied. Alternatively, FDA may impose limits on the amount of additives that will be allowed in foods. If the petition does not contain enough evidence for CFSAN to make a determination on the safety of a substance[a], and if the petitioner is unable or unwilling to develop the necessary data, CFSAN requests that the petition be withdrawn or the petition is denied approval.

To date, CFSAN has reviewed the neurotoxic potential of a variety of direct food additives, indirect food additives, and color additives, including:

- acrylamide (as a contaminant of polymer food contact surfaces),
- acrylonitrile (as a contaminant of polymer food contact surfaces),
- aspartame (artificial sweetener),
- chlorofluorocarbons (Freon 12),
- cyclamates (artificial sweeteners),
- erythrosin (FD&C Red No. 3),
- methyl chloride (as solvent for hop extract),
- methyl tin compounds (as stabilizers for plastics),
- organophosphites (antioxidants in food packaging):
  -di-tert-butylphenyl phosphite,
  --octadecyl phosphite, and
  —Tris phosphite.

As noted above, the Neurobehavioral Toxicology Team does not regularly participate in such reviews.

Drugs and Biologics

Drugs are regulated under various categories, including new drugs (for humans), biologics (biological products such as vaccines), and animal drugs. The statute requires submission of a new drug application (NDA) before a drug can be approved for market. The NDA must contain "substantial evidence" that the drug is both safe and effective:

> . . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed . . . [sec. 505(d)(7)].

This is generally considered to be the highest standard for drug approval in the world.

The statute also provides that FDA shall not approve a drug if it finds deficiencies in the safety tests conducted or if the test data indicate a lack of

safety. If clinical investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof or if "the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions,' FDA is directed to refuse the application [sec. 505 (d)(1) and (2)].

FDA may deny approval of a new drug on the finding of "an imminent hazard to the public health" [sec. 505(e)]. If the application is approved, FDA specifies how the drug is to be packaged, labeled, and so on. New drugs that are identical to previously approved drugs are subject to an abbreviated application process.

Biologics, including "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, allergenic product, or analogous product" (42 U.S.C. 262), are under the purview of a complex regulatory mechanism combining provisions of both FFDCA and the Public Health Service Act. Because they are also defined as drugs, most biologics must be tested and approved by the same process FDA uses for new drugs (29).

Animal drugs are approved under essentially the same process as human drugs, with the additional provisos that FDA must consider "the probable consumption of such drug and of any substance formed in or on food because of the use of such drug' and the 'cumulative effect on manor animal of such drug" [WC. 512(d)(2)(A)].

FFDCA also requires reporting of adverse drug reactions, both during the application process [sec. 505(i)] and after a drug has been approved [sec. 505@]. "Adverse reactions" are defined by FDA as

> any adverse experience associated with the use of a drug, whether or not considered drug-related, and includes any side-effect, injury, toxicity, or sensitivity reaction, or significant failure of expected pharmacological action" (21 CFR 310.301). This requirement for reporting adverse reactions could be used to gauge the effectiveness of the drug approval process.

Applications for approval of new or investigational prescription drugs are handled by FDA's Center for Drug Evaluation and Research; biological products are handled by the Center for Biologics Evaluation and Research. The approval process for a new drug generally takes about 3 years, but it can take up to 7 years. (The shortest approval time to date, for azidothymidine (AZT), used to treat AIDS, was 7 months.)

An NDA must contain data from all prior preclinical (animal) and clinical (human) studies. Clinical studies are conducted in three phases. Phase 1 consists of short-term tests designed to elucidate how the drug is metabolized in humans, to obtain basic pharmacological and toxicological data in humans, and, if possible, to find evidence that the drug is effective in humans. Phase 2 tests are the initial controlled clinical trials and studies of short-term side-effects. Phase 3 generally consists of controlled and uncontrolled clinical trials in a larger group of subjects. These trials are intended to provide the additional information on safety and effectiveness needed to determine the risk-benefit ratio of the drug and to draft appropriate labeling.

All drugs that have not been previously tested in humans, or for which additional clinical data are required before NDA submission, must submit an investigational new drug (IND) application before the sponsor can initiate clinical trials. New drugs that have previously undergone clinical trials, such as drugs that have been approved in other countries, may skip the IND application (if they have already been subjected to adequate, well-controlled clinical trials).

FDA has developed guidelines for the types of nonclinical studies that are needed to support approval of different types of clinical trials. The guidelines do not, for the most part, call for specific tests for toxic effects (the prevailing view at the Center for Drug Evaluation and Research is that rigid test guidelines rapidly become obsolete and may lead to false assurance of the safety of a drug). Instead, the guidelines allow for considerable latitude in the selection of test protocol. The final selection of test protocols requires that the petitioner convince FDA that the data are adequate and that FDA convince the petitioner that its requirements are not unreasonable.

An IND is reviewed by a general toxicologist. Drugs that are not designed to cause neuropharmacological effects are not necessarily reviewed separately for neurotoxicity, although behavioral effects are evaluated in animal reproduction studies and neuropathology is conducted as part of the sub-

chronic studies required for the IND. A specific review for neurotoxicity is initiated only if there is cause for suspicion. Outside experts may be called in for such reviews through mechanisms such as standing committees and special review committees. Drugs that are designed to act on the nervous system—i.e., neuroeffective substances—are reviewed separately by neurotoxicology specialists from the Division of Neuropharmacological Drug Products of the Center for Drug Evaluation and Research's Office of Drug Evaluation I.

After the phase I tests have been concluded, the applicant must conduct appropriate additional nonclinical toxicity tests. The data required hinge on the particular clinical trial under consideration. A l-year animal study incorporating ophthalmological examinations and behavioral observations is required for all drugs. (For a drug to be prescribed to women of childbearing age, reproductive toxicity studies are routinely conducted; the reproductive studies may provide some evidence regarding the potential teratological effects of the drug.)

Positive evidence of toxic effects can lead to termination or modification of the clinical trials, depending on the nature of the evidence, the seventy of the effects, and the disease that the drug is intended to treat. If the animal data included in either the IND application or NDA are inadequate, FDA will issue a "clinical hold" order to delay further clinical testing until the appropriate preclinical data are developed.

Postmarked monitoring of drugs occurs through FDA's spontaneous adverse report monitoring system. Any person observing an adverse reaction associated with the use of a drug may submit a Drug Experience Report (form FDA-1639) directly to FDA or to the drug's manufacturer, who, in turn, is required to report the information to FDA (21 CFR 1989 ed. 314.80). About 90 percent of the adverse reports FDA now receives are obtained through manufacturers and 10 percent through direct reports. Analysis of these reports constitutes FDA's device for monitoring the adverse effects of prescription drugs, including effects not noted during premarket tests or clinical trials. However, as described in box 7-B, the system is limited in many respects.

No specific neurotoxicity tests are required for drugs that are not expected to be neuroeffective. Some FDA scientists believe that it is more appropriate to conduct general preclinical toxicological tests than to focus on specific tests. FDA scientists do not appear to have reached a consensus regarding the validity of preclinical neurotoxicity tests as predictors of clinical effects. They argue that it is difficult to design clinical trials that test specifically for neurotoxic effects.

Cosmetics

Substances used in cosmetics are subject only to the "may render it injurious" clause (sec. 601 of FFDCA). FDA cannot require any toxicity testing. It can, however, require that any cosmetic product that has not been adequately tested be packaged with a warning label stating that 'the safety of this product has not been determined" (21 CFR ed. 740.10). FDA has restricted or prohibited the use of fewer than 20 ingredients on the finding that they were "poisonous or deleterious" (21 CFR ed. 700.11,21 CFR ed. 250.220) (29).

Proposed Amendments

Among the proposed amendments to the FFDCA that have been introduced during the 10lst Congress, the Food Safety Amendments of 1989 (identical versions were introduced in the House and Senate as H.R. 1725 and S. 722, respectively) are potentially relevant to toxic substances regulation. A key provision of these bills is an attempt to define a standard of "negligible risk" that would apply to pesticide residues on food without regard to balancing costs and benefits. This definition would replace the current approach, under which pesticide tolerances for both raw commodities and processed foods are set at a level to protect the public's health unless the pesticide is a carcinogen, in which case no detectable amount is allowed in processed foods. Hearings have been held on the bills, but neither has been voted on by the full assembly.[5] If passed, the negligible risk provisions—and the absence of authority for cost-benefit analyses-could have far-reaching consequences in the regulation of pesticide residues.

Federal Insecticide, Fungicide, and Rodenticide Act

FIFRA was enacted in 1947 to replace the 1910 Federal Insecticide Act. FIFRA expanded the con-

[5] As of February 1990.

Box 7-B—Limitations of FDA's Postmarked Monitoring System for Adverse Drug Reactions: Halcion, A Case Study

Halcion, the most widely prescribed sleeping medication in the United States, was first approved for use in late 1982 with a recommended usual adult dose of 0.25 to 0.50 mg. Its package insert included mentions of amnesia, confusion, agitation, and hallucinations as possible side-effects. Over the next few years, FDA's adverse reaction monitoring system recorded an excess of adverse reports for Halcion in comparison to other benzodiazepine hypnotics-even after correcting for market share of the drug. In 1987, as a result of the reports and the apparent dose-relatedness of some adverse effects, several labeling and marketing changes were made. The usual adult dose was changed to 0.25 mg, two paragraphs mentioning the apparent dose-relatedness of some side-effects were added to the package insert and a "Dear Doctor" letter was issued detailing the labeling changes. In early 1988, Upjohn, the manufacturer, discontinued the 0.50 mg tablet.

Following these changes, public concern about possible problems associated with Halcion use increased, largely because of a September 1988 article in *California Magazine* and a story on the ABC television program 20/20 in February 1989. The number of adverse reports received, which was expected to decline as a result of the labeling changes and Halcion's status as an "older" drug (the number of adverse reports associated with a drug normally decreases over time), rose. In September 1989, FDA convened an expert panel to review the reporting data on Halcion and to discuss whether further changes should be made in the labeling or marketing of the drug.

Discussion at that meeting illustrates the difficulties of drawing conclusions from the spontaneous adverse reporting process. In a comparison of adverse reports for Halcion (45 million prescriptions written since 1982) with adverse reports for Restoril (35 million prescriptions written since 1980), a drug prescribed to patients with similar sleeping problems, the following data were presented:

	Total number of reports received by FDA	
Adverse event	*Halcion*	*Restoril*
Amnestic events	267	4
Hallucinations, paranoid behavior	241	12
Confusion and delirium	304	17
Hostility and intentional injury	48	2

Overall, an average of 38 adverse reports per million prescriptions was received for Halcion, while 7.5 adverse reports per million prescriptions were received for Restoril.

These seemingly dramatic results, however, were tempered by myriad complicating variables, The influence of publicity, differences in reporting rates by manufacturers, lack of dosage information in about one-half of the adverse reports for Halcion, and "new drug" v. ''older drug' effects all obscured the significance of differences between the sets of data, The 4-week period following the 20/20 episode, for example, produced twice as many adverse reports for Halcion as the 4-week period preceding the show. The FDA panel finally concurred that the data were too unreliable to warrant action, except possibly in the case of amnesia.

The unreliable data generated by the postmarketing monitoring system now in place effectively limit FDA review to premarket trials. Unexpected interactions with other medications or long-term side-effects may easily be missed. This is particularly disturbing from the standpoint of neurotoxicity, since drugs not expected to have neuropharmacological effects are not necessarily subjected to specific neurotoxicity testing. Changes which could improve the present system might include a requirement that all adverse report forms be sent directly to FDA as well as a requirement that physicians submit reports for all ''serious" adverse reactions observed.

Because of the inherent limitations in FDA's drug approval and adverse reaction monitoring systems, it is important that physicians and patients be aware of the possible adverse effects of the medications they prescribe and consume. Drugs are approved for use under certain conditions and at certain doses, and complicating factors such as age, other medications, or illness may significantly alter the effects of these drugs. In most cases, the decision to take any medication is a personal choice for the patient; an individual cannot make an informed decision without access to information about potential adverse effects.

SOURCES: U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, *Transcript of Proceedings, Thirty-First Meeting* (Rockville, MD: September 1989); "When Sleep Becomes a Nightmare," 20/20, ABC, Feb. 17, 1989; Pharmaceutical Data Services, ''Top 200 Drugs of 1989,' *American Druggist,* in press.

sumer protection aspects of the earlier statute by instituting a premarket registration procedure for all pesticides in interstate commerce. The 1972 amendments—the Federal Environmental Pesticide Control Act (Public Law 92-516)—shifted the emphasis from consumer protection to the protection of public health and the environment (47). Amendments in 1975 (Public Law 94-140), 1978 (Public Law 95-396), 1980, and 1988 refined the regulatory procedures embodied in the legislation but maintained the focus, namely, to govern pesticide use to prevent "unreasonable adverse effects. " FIFRA uses a broad standard for adverse effects:

> . . . *any unreasonable risk to man or the environment,* taking into account the economic, social, and environmental costs and benefits of the use of any pesticide [sec. 2(bb)] [emphasis added].

The statute prohibits the sale or distribution of any pesticide in the United States unless it is registered or exempt from registration under FIFRA. It gives EPA considerable authority to require submission of data, including neurotoxicity tests, as part of the registration process for new and existing chemicals. The statute places the burden of proof of safety on the manufacturer, although in the case of existing pesticides, EPA may have to go to considerable lengths to prove the inadequacy of data before it can call for further data or regulatory action.



Photo credit: National Archives

New Pesticide Registrations

FIFRA calls for premarket review and registration of both new pesticides and pesticides with new active ingredients.[6] A pesticide may be registered if EPA determines that, when considered with any restrictions on use:

- its composition is such as to warrant the proposed claim for it;
- its labeling and other material required to be submitted comply with the requirements of the Act;
- it will perform its intended function without unreasonable adverse effects on the environment; and
- when used in accordance with widespread and commonly recognized practice, it *will not generally cause unreasonable adverse effects on the environment [sec. 3(c)(5)]* [emphasis added].

The 1972 amendments enabled EPA to require that manufacturers submit whatever data EPA specifies for approval or continuation of the registration:

> The Administrator shall publish guidelines specifying the kinds of information which will be required to support the registration of a pesticide . . . [sec. 3(c)(2)(A)].

Applications for pesticide registration are submitted to EPA's Office of Pesticide Programs (OPP). The applicant must demonstrate that anew pesticide will be both safe and effective under the proposed conditions of use. In order to demonstrate efficacy, applicants must obtain an Experimental Use Permit (EUP) to conduct field studies. (An EUP application

[6]Inert ingredients—those parts of the pesticide formulation not claimed to have anypesticidal activity-have not traditionallybeen included in the registration process. EPA has recently begun to review and evaluate them, however. Although EPA believes that FIFRA provides the authority to require testing of inert ingredients of known toxicity, it is not clear how inert ingredients of unknown toxicity should be handled (l).

requires less extensive toxicity data than the registration application, but the applicant must provide enough information to establish that the field test itself is safe.) EUPs are also obtained for new uses of a pesticide, such as application on a new crop. If the pesticide is intended to be used on food or feed crops, the applicant submits a petition for the setting of tolerances, which is done in tandem with the registration process.

The toxicity data in each application are reviewed initially by a toxicologist from OPP's Hazard Evaluation Division. The division has a neurotoxicologist on its staff who may be consulted if necessary, but the neurotoxicologist does not automatically participate in application reviews. Under division procedures, a single toxicologist is responsible for reviewing each application. The review is conducted in accordance with procedures codified in OPP's Standard Evaluation Procedures or Risk Assessment Guidelines, or both. Limited neurotoxicity testing is required only for organophosphorous pesticides, but subchronic tests include a limited evaluation of behavioral and pathological effects on the nervous system.

If data provided with an application are determined by EPA to be inadequate for a reasonable evaluation of potential hazards, the Agency will require additional toxicity testing. EPA may require tests in addition to those specified in the test guidelines, if necessary, to clarify issues raised by the data presented.

If OPP finds that a new pesticide presents an unreasonable risk of adverse effects, EPA may deny the registration altogether, restrict use of the pesticide to certain crops or to certain geographical areas, or require that it be applied under the supervision of certified applicators or that protective equipment be worn during application. In addition, EPA may impose specific labeling requirements (see box 7-C).

The FIFRA test guidelines (40 CFR ed. 158) contain very limited recommendations for neurotoxicity testing. At the present time, only organophosphates must be tested for neurotoxic effects, and they are subject to just a single type of test—a hen test for delayed neuropathy (see ch. 5 for more information on test procedures). Current guidelines require limited neuropathological examinations and observations for behavioral effects as part of acute and subchronic toxicity studies. However, the test guidelines are now under revision, and new neurotoxicity test requirements are likely to be added (the development of new guidelines is described below in the section on "new initiatives"). A review of new active ingredients registered in the past 5 fiscal years revealed that out of 54 pesticides, including 20 insecticides, only 3 were organophosphates.

Reregistration of Existing Pesticides

Because many pesticides were registered on the basis of toxicity data that might now be considered inadequate, EPA is reexamining the safety of registered pesticides. EPA may call for the registrant to develop new data for evaluating toxic effects of the pesticide. Section 3(c)(2)(B) of FIFRA states:

> . . . If the Administrator determines that additional data are required to maintain in effect an existing registration of a pesticide, the Administrator shall notify all existing registrants.

In conjunction with the FIFRA reregistration process, EPA is also mandated by FFDCA to set tolerances for the maximum pesticide residues allowed in or on various food and animal feed crops. EPA may periodically review previously set tolerances, which are enforced by FDA and the U.S. Department of Agriculture (USDA) (48 FR 39499). As pesticides go through the reregistration process, EPA may decide that the tolerance levels need to be reassessed.

Reregistration of existing pesticides does not require the submission of applications or data. Rather, OPP initiates the process by reviewing available data from its internal files and, on rare occasions, from the published literature. In the past, EPA has selected and scheduled reviews of chemicals with few restrictions, producing approximately 25 registration standards (the document which specifies the conditions that a registrant must meet to maintain the registration of a pesticide) per year. The 1988 amendments to FIFRA mandated that EPA review 600 active ingredients of existing pesticides by 1997 (i.e., more than 60 registration standards per year-a considerably faster rate than current operating procedures have fostered). EPA, therefore, is developing procedures for conducting reregistration reviews more quickly and is determining whether additional personnel will be required.

The evaluation process is similar to that for new chemicals and the test guidelines for re-registration are the same as those for registration. OPP may consult with outside experts about what kinds of

Box 7-C—Regulatory Requirements for Labeling: How Effective Are They?

Labeling requirements are a common regulatory tool for dealing with toxic but useful substances. Pesticides, prescription and over-the-counter drugs, household substances, and all commercial poisons are subject to labeling provisions incorporated in statutes such as the Federal Insecticide, Fungicide, and Rodenticide Act; the Federal Food, Drug, and Cosmetic Act; the Federal Hazardous Substances Act and the Consumer Product Safety Act.

Labels are intended to reduce the risks of exposure to, or harm from, toxic substances by alerting consumers to the dangers of a substance and providing instructions for its safe and proper use. When regulators make decisions contingent on specific labeling requirements, they rely on at least three tacit assumptions: 1) that consumers will read the label; 2) that they will understand and believe it; and 3) that they will obey its instructions. Clearly, all three must happen in order for labels to be effective in preventing dangerous exposures. But is it realistic to rely on labels?

Increasing evidence suggests that it is not. An Environmental Protection Agency (EPA) draft report on the effectiveness of pesticide labeling finds several weaknesses in current schemes. The report which includes a survey of representatives from the pesticide industry, State regulatory agencies, environmental organizations, and household users, found that few people read an entire label and that many people may not even read the parts of the label that relate specifically to their intended use of the chemical. Labels maybe redundant and too technical; the information is often crowded and difficult to read; and the instructions may be vague or contradictory. (For example, the label on one rat poison instructed users to keep the poison away from wildlife.) Furthermore, there are few guidelines on how to label for specific toxic effects, such as neurotoxicity, EPA concluded that many labels are not well designed for their audiences and must be improved if they are to have any real effect.

What is the solution? EPA suggests measures such as greater use of hazard symbols, more readable and perhaps standardized formats, and a uniform system of designating hazards so that consumers can recognize them more easily. EPA is developing criteria for the labeling of specific categories of toxic effects, including neurotoxicity; guidelines may be issued by early 1990.

Labeling requirements have often been central in product litigation cases. Court decisions have stressed the need for labeling to protect humans from injury, and one State court ruled that even ''compliance with Federal labeling requirements will not prevent the finding that the manufacturer had not fully disclosed the risks of a product" (Grad, 1985), It appears, then, that industry also stands to benefit by working with regulators to develop adequate and effective labels.

SOURCES: U.S. Environmental Protection Agency, "Pesticide Label Utility Project Report, " unpublished draft, April 1986; F.P. Grad, ''Pesticide Pollution-Labeling and Misbranding,' *Treatise on Environmental Law*, *sec. 8.03.4* (St. Paul, MN: Matthew Bender, 1985).

additional data should be developed. If additional data are needed, EPA issues a data call-in, either through publication in the Federal Register or by sending letters to affected registrants. FIFRA grants EPA the authority to request any additional data that are determined to be necessary.

If EPA determines during the reregistration process that an existing pesticide ingredient may pose an unreasonable risk, the chemical may undergo a special review as described below. If registrants do not respond to the data call-in (as is generally the case for pesticides that are no longer being manufactured), the registration is canceled. If, in the course of reregistering a pesticide, EPA finds that it poses an unreasonable risk, the Agency may cancel or suspend the chemical without initiating a special review.

EPA has requested specific neurotoxicity test data in a number of cases. While the Agency's database on registration standards does not enable investigators to determine all chemicals for which neurotoxicity data call-ins have been issued, it does include a data call-in (under consideration) to evaluate nervous system lesions that may be induced by thiocarbamates and a developmental neurotoxicity study protocol on N, N-diethyl-m-toluamide (Deet), the active ingredient in many mosquito repellents.

Active ingredients of existing pesticides undergo special review if EPA finds that they may pose an unreasonable risk of adverse effects. The special review is a formal procedure; accordingly, a notice of the initiation of the review and of each subsequent step in the process must be published in the Federal Register.

The review begins with an evaluation by EPA staff similar to that conducted for the registration of a new pesticide. In addition, EPA's independent Science Advisory Panel examines each case, and the Agency seeks public comment as part of the rule-making process. If a data call-in has not already been issued, EPA may issue one at this time. EPA can request all data relevant to the question of whether a chemical poses unreasonable risks of adverse effects.

If EPA determines that the risks of a pesticide outweigh the benefits of its continued use, it may cancel or suspend registration of the pesticide or impose restrictions on its registration. Registration may be suspended during the time it takes to complete the cancellation proceedings if EPA determines that the risks of use during that time outweigh the benefits. A suspension may be appealed and public hearings requested. EPA may also issue an emergency suspension, which is immediate and absolute and cannot be appealed. Other potential restrictions are the same as listed above for new pesticide registrations. Until 1988, EPA was required to indemnify all manufacturers and consumers for any amounts of the pesticide they possessed, which made cancellation proceedings extremely costly for pesticides that were being marketed in significant quantities. Now, however, EPA must reimburse only endusers (usually farmers).



Photo credit: U.S. Environmental Protection Agency

About 14 special review decisions are made each year, one-third of which are final decisions to initiate special review. Five active ingredients are known to have been reviewed for neurotoxicity. On further review, three of these, dichlorvos, tributyl phosphorotrithioate, and S, S, S-tributyl phosphorotrithioate, were returned to the registration process and two, acrylonitrile and EPN (phenylphosphonothioic acid, o-ethyl, o-p-nitrophenyl ester), were not (9). Registration of acrylonitrile was voluntarily canceled; EPA imposed restrictions (protective clothing and new labeling requirements) on the use of EPN (phenylphosphonothioic acid, o-ethyl, o-p-nitrophenyl ester), and subsequently all registrations were voluntarily canceled. Aldicarb, which has well-documented neurotoxic effects, is subject to special review, but the principal focus of the special review is the potential of Aldicarb to contaminate groundwater. No chemical has undergone full special review for neurotoxicity.

Approximately 75 active pesticide ingredients are on EPA's restricted use list (i.e., they may only be used under the supervision of a certified applicator), some of which are restricted because of concern about their neurotoxic effects. While there are certainly active ingredients whose use is restricted based on their neurotoxic effects (48 FR 39496), determining which ones was not feasible within the limits of this survey.

Toxic Substances Control Act

The Toxic Substances Control Act (TSCA) (Public Law 94-469) was enacted in 1976 to "regulate commerce and protect human health and the environment by requiring testing and necessary use restrictions on certain chemicals. " Congress intended to create "adequate authority" to test and regulate chemicals in commerce that are not subject to other statutes:

> [A]dequate authority should exist to regulate chemical substances and mixtures which present an

> *unreasonable risk of injury to health or the environment,* and to take action with respect to chemical substances and mixtures which are *imminent hazards. . . [sec.* l(b)(2)] [emphasis added].

TSCA defines several health and environmental effects of concern, including neurotoxic effects that are exhibited as behavioral disorders:

> The health and environmental effects for which standards for the development of test data may be prescribed include carcinogenesis, mutagenesis, teratogenesis, *behavioral disorders,* cumulative or synergistic effects, and any other effect which may present an unreasonable risk of injury to health or the environment [sec. 4(b)(2)(A)] [emphasis added].

The statute, which is one of the most procedurally complex pieces of legislation in the area of human health and the environment, sets forth a framework that authorizes EPA to review the safety of existing chemicals, to receive premanufacture notices (PMNs) for new chemicals, to regulate hazardous substances, and to call for the reporting of data on health and environmental effects and substantial risks. EPA may, in some cases, require that manufacturers conduct health and safety studies, but the burden of proof is on the Agency to find that a chemical substance or mixture may or will present an unreasonable risk to public health or the environment.



Photo credit: U.S. Environmental Protection Agency

New Chemicals

TSCA requires manufacturers to notify EPA in advance of the intended introduction into commerce of a new chemical (through PMNs) or the intended manufacture or processing of any chemical for a significant new use. (The Act does not require PMNs for the production of small quantities of chemicals for the purpose of research and development.) Submitters are required to present all test data that indicate whether "the manufacture, processing, distribution in commerce, use, and disposal of the chemical substance or any combination of such activities will not represent an unreasonable risk of injury to health or the environment" [sec. 5(b)(2)(B)(i)].

EPA has 90 days (extendable under certain circumstances to 180 days) to review the PMN. If EPA determines that the chemical may present an unreasonable risk, it may prohibit or limit the use of the chemical in commerce until data are developed to permit a further evaluation of the chemical's effects. If EPA decides that a substance "presents or will present" an unreasonable risk, it may restrict or prohibit the production, use, or disposal of the substance.

The PMN contains data on a chemical's identity and structure, proposed use, byproducts, and impurities and is submitted to EPA's Office of Toxic Substances (OTS). Certain chemicals are also subject to reporting under a significant new use rule (SNUR); EPA must be notified if such a chemical is to be used in a way that differs significantly from that proposed in the original PMN (usually because the evaluation of the PMN depended on a specific pattern of use).

Because TSCA does not require that manufacturers carry out any specific program of toxicity testing in order for new chemicals to be approved, PMNs are rarely submitted with toxicity data—fewer than 50 percent of all PMNs and fewer than 65 percent of PMNs for nonpolymers contain any toxicity data(5). PMNs that do include toxicity data generally provide results from a minimal set of studies, perhaps two or three acute tests and maybe a test for irritation (see ch. *5* for details on testing). **The requirement for manufacturers to submit all data in their possession may act as a disincentive to testing, in**

that evidence of toxicity could lead EPA to conclude that there may bean unreasonable risk, whereas the absence of data will not do so.

Because the PMN generally provides few data, most evaluation is performed on the basis of the structural analogues of the new chemical to existing chemicals and extrapolations from known properties of well-characterized chemical classes. Thus, the first stage of the PMN review is a computer-assisted search for structural analogues with known toxicity (or lack of toxicity). Senior OTS toxicologists with expertise in various specialty fields then review the chemical's potential toxicity. Their review is based on the structure-activity relationships revealed by the computer search and conducted by members of the review team. Until recently, neurotoxicologists were not routinely present at the initial structure-activity meetings but were called on afterward if concerns about neurotoxicity were raised. Under current OTS procedures, a neurotoxicologist is present at the initial structure-activity review and all appropriate meetings thereafter.

Unlike the public regulatory process for reviewing existing chemicals, the PMN process rarely calls on reviewers outside of OTS. In addition, because of the high proportion of confidential business information that accompanies PMNs, little of the review process is open to the public (see box 7-D).

If toxicity is predicted on the basis of structural analogues, a chemical may be submitted to standard review, a detailed examination that consumes much of the time allotted for the PMN review. From fiscal year 1984 through fiscal year 1987, approximately 20 percent of the 6,120 PMN chemicals received a detailed review. Based on the standard review, EPA has concluded that approximately 10 percent of all PMN chemicals may or will present unreasonable risks of adverse effects on human health or the environment.

EPA cannot require additional toxicity data unless it finds that a chemical mayor will present unreasonable risks. However, EPA can sometimes induce manufacturers to develop the additional data that EPA considers necessary by offering to suspend the PMN process in the meantime. In negotiating with manufacturers, EPA may request tests listed in the guidelines for testing existing chemicals or additional tests. If EPA finds that the chemical may present an unreasonable risk, it can halt the use of the chemical pending development of adequate data to resolve the issue of risk. If EPA finds positive evidence that a chemical presents or will present unreasonable risks, it can ban or limit the use of the chemical.

A neurotoxicologist is present from the early stages of a PMN review for all chemicals except polymers, which, because of their low reactivity and low potential for absorption, generally present lower toxicity hazards and are thus evaluated separately. EPA has identified at least six classes of chemicals (acrylamide derivatives, acrylates, carbamates, phosphines and phosphates, pyridine derivatives, and imidazoles) that should alert reviewers to the potential for neurotoxicity during the structure-activity review. Other chemicals likely to cause concern include quaternary ammonium compounds, glycol ethers, and miscellaneous halogenated solvents. OTS is developing a more explicit set of classification criteria for neurotoxicity in order to standardize the procedures; even so, EPA neurotoxicologists have expressed concern that accurate structure-activity predictions may not be possible without information on mechanisms of action, which is available for only a few classes of chemicals (including quaternary ammonium, organophosphate compounds, and some solvents).

Neurotoxicity concerns are one of the triggers for placing a chemical into the standard review process. However, most chemicals identified as being potentially neurotoxic do not enter that process, for a variety of reasons, including lack of adequate data to support a case, lack of a strong structure-activity relationship, data indicating that human exposure would be minimal (or inadequate data on exposure), or lack of appreciation by individuals analyzing the data of certain neurobehavioral effects.

Some 220 of the approximately 1,200 chemicals (out of 6,120 PMNs submitted) that underwent standard review during fiscal years 1984 through 1987 were identified as being potentially neurotoxic. However, neurotoxicity was not the basis for most regulatory actions taken by EPA. EPA was not able to provide precise information on the extent to which concerns about neurotoxicity did influence regulatory decisionmaking, although such an analysis is now pending (5,24).

Regulation of Existing Chemicals

Existing chemicals are regulated under several sections of TSCA. Section 4 allows EPA to rule that

Box 7-D-Confidential Business Information Under TSCA: Does It Influence Regulatory Effectiveness?

In order to assess accurately the toxic risks posed by a chemical, a considerable amount of information must be reviewed, including the identity, properties, and intended uses of the chemical. Depending on the particular chemical and its application, some of this information may represent trade secrets that, if known to a competitor, would place the manufacturer or importer of a chemical at a competitive disadvantage.

The approach taken under the Toxic Substances Control Act (TSCA) toward the protection of trade secrets has been to allow nearly all information submitted to the Environmental Protection Agency (EPA) on a premanufacture notice (PMN) for a chemical to be claimed as confidential business information (CBI). Information covered by such a claim is divulged only to EPA employees who have been granted a special CBI clearance, primarily selected staff from and contractors for the Office of Toxic Substances (OTS). CBI may be released only if the Administrator determines that it is necessary to do so to protect against an unreasonable risk, and submitters must be given 30 days' advance notice of CBI releases. EPA officials or officials of other Federal agencies may obtain access to needed CBI materials, but given the breadth of information covered by CBI claims, these officials are not in a position to know what CBI information in OTS files is relevant to the performance of their duties.

The protection of CBI offered by TSCA is considerably greater than that offered by the confidentiality provisions of some other laws. For example, under Title III of the Superfund Amendments and Reauthorization Act, only the specific identity of a chemical covered by the reporting provisions of the Act can be claimed to be confidential. Further, under TSCA, the burden of challenging CBI claims falls on EPA; PMN submitters are not required to substantiate CBI claims unless challenged.

Toxicity data per se cannot be claimed as CBI under TSCA, but much of the other information relevant to assessing toxic risks can be—including the identity of the chemical for which toxicity data are presented, its physical-chemical properties, and its intended uses. These provisions of TSCA present significant obstacles to effective regulation, not only with respect to the PMN program, but also with respect to other regulatory programs, both inside and outside EPA. Three general types of obstacles can be identified: added administrative burdens on OTS, interference with effective cooperation among regulatory programs, and prevention of public oversight of the regulatory process.

Within the PMN program, CBI requirements have required OTS not only to maintain duplicate sets of records (CBI and non-CBI), but also duplicate computer databases and even duplicate computers. Public interest groups and other interested members of the public have no access to information that would allow them to questioner to accept—EPA's actions on PMNs, Neither can members of the public take any action for self-protection, as they are frequently kept from information regarding the identity of toxic chemicals or the products that might contain them. TSCA CBI provisions also pose a serious obstacle to the involvement of regulatory, academic, and industrial scientists who could assist OTS in assessing the risks of PMN chemicals.

Because CBI has the capability to "contaminate" information systems (any document or information system that contains CBI becomes CBI itself), the impediments to regulatory effectiveness posed by CBI have spread from the PMN program to programs dealing with other aspects of TSCA. Rule-making on asbestos is a particularly egregious example, where much of EPA's supporting analysis could not be made available for public review because it was based on CBI.

Persons involved in other regulatory programs, whether inside or outside of government, are not in a position to obtain information that could make important differences in the implementation of regulations. A Resource Conservation and Recovery Act permit writer in an EPA regional office, for example, will not have access to information that might significantly influence decisions regarding the disposal of TSCA chemicals; and the Consumer Product Safety Commission may not be made aware of information regarding chemicals in consumer products.

Few persons would dispute the principle of protecting true trade secrets. There is good reason, however, to question whether the burden imposed by the liberal confidentiality provisions of TSCA on the government, the public, and even industry is justifiable. Industry has managed to adapt to the less protective provisions of other laws, and alternative strategies for protecting proprietary information (e.g., patents) are available.

SOURCE: Office of Technology Assessment, 1990.

chemicals or mixtures be tested for health and environmental effects if the Agency determines that:

> (A)(i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment (ii) there are insufficient data and experience on which the effects of. . . such activities on health or the environment can reasonably be predicted, and (iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or (B)(i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture [sec. 4 (a)(l)].

If EPA can show that there is inadequate information on the effects of a compound *and* that testing is necessary to obtain such information, it is required to write a test rule that defines what is to be tested and what particular tests are to be performed. OTS has developed guidelines that describe the general procedures for the conduct of toxicity tests (40 CFR 796), although each test rule contains specific requirements for the individual chemical involved.

In contrast to FIFRA, TSCA has mandated an explicit means of identifying chemicals that must be tested by EPA for their effects on health and the environment-namely, the Interagency Testing Committee (ITC). The ITC is a multidisciplinary advisory panel composed of one member each from EPA, the Occupational Safety and Health Administration, the Council on Environmental Quality, the National Institute for Occupational Safety and Health, the National Institute of Environmental Health Sciences, the National Cancer Institute, the National Science Foundation, and the Department of Commerce. ITC conducts an ongoing, independent review of chemicals in commerce, based on recommendations from members as well as external nominations, in order to select chemicals for testing. (ITC reviews data from the published literature and solicits information from the public and from manufacturers.) The committee recommends testing priorities based on the finding that there are insufficient data to assess the hazards posed by a substance or the finding that potential human exposures are significant. (ITC has no overarching responsibility to coordinate agency testing; it simply suggests high-priority chemicals for EPA to investigate.)

ITC publishes its findings in the Federal Register and submits to EPA all data located on the substance, as well as important gaps in data, by means of a priority list which is updated every 6 months. The committee may indicate particular effects for which it believes that a substance should be tested, or it may simply point to high exposure and a general lack of data as justification for including a chemical on the priority list.

Chemicals selected for review and testing are subjected to an extensive evaluation by ITC members, experts called onto review documents, and any persons who nominate chemicals for review. EPA then conducts its internal review, which involves a multidisciplinary team, including neurotoxicologists if indicated. The group may also request assistance from EPA research personnel.

EPA examines the concerns raised by ITC and decides whether or not to issue a test rule for a substance. EPA is not limited to the issues raised by ITC; it may decide that some concerns are unjustified, or it may identify additional issues that were not mentioned in ITC's recommendations. The main reasons for which EPA may decide not to test a chemical are the determination that adequate data for a risk decision *are* available or that the chemical is no longer used in commerce. In three cases, EPA has issued test rules on chemicals that were not nominated by the ITC. If EPA decides to pursue testing, it may require tests on the basis of hazard concerns raised in the review or a high volume of production. EPA has developed guidelines for the types of tests that may be required; these are published in the Code of Federal Regulations (40 CFR 795; 40 CFR 798).

EPA can seek additional data under section 4 of TSCA by negotiating a consent decree, which is a legally binding mutual agreement that industry will conduct specified tests and that EPA will not make additional requests. The process of negotiating a consent decree can be faster and more efficient than formal rule-making, and EPA generally prefers this option. In either case, the manufacturer must conduct additional tests and submit the data to EPA in a timely manner. Once the test data have been developed and submitted, section 6 of TSCA authorizes EPA to restrict or prohibit the production, use, and disposal of the substance if the data indicate an unreasonable risk.

Box 7-E—Regulating for Neurotoxicity v. Other Toxic Effects: The Case of Acrylamide

One of the first chemicals that the Interagency Testing Committee (ITC) considered, shortly after it began operations in 1977, was acrylamide, a chemical with a variety of commercial uses. Acrylamide was already known to cause severe neurotoxic effects, but its ability to cause other chronic effects had not been well characterized. ITC noted this state of research and recommended that acrylamide be tested for effects other than neurotoxicity. The Environmental Protection Agency (EPA) had to decide whether the known neurotoxicity of this chemical was sufficient for regulatory purposes or whether additional data documenting its effects on health were necessary.

In its response to the ITC, EPA chose not to require testing of acrylamide, for two reasons. First, EPA believed that acrylamide was so neurotoxic that regulatory restrictions would be imposed to the maximum degree possible on the basis of known effects, and additional test information would be of little regulatory significance. Second, EPA noted that a chemical company was already in the midst of performing a long-term bioassay for other effects, so if additional data were, in fact, necessary, they were already forthcoming.

When the chemical company in question learned that EPA was not going to require testing, it decided to suspend its test for toxic effects other than neurotoxicity. EPA then had to decide whether neurotoxicity would be considered the driving effect or whether to impose new testing requirements. EPA retreated from its earlier position that the neurotoxicity data were sufficient and decided that data on other effects were needed. As a result, EPA persuaded the company to resume its testing and withheld assessments and final regulatory decisions pending those additional data.

SOURCE: W.R. Muir, former director, Office of Toxic Substances, U.S. Environmental Protection Agency, and President, Hampshire Research Associates, personal communication, 1988.

Neurotoxicity is one of the specific concerns that may be identified by ITC in recommending that a substance be tested, in which case EPA must respond either by including a requirement for neurotoxicity testing in its test rule or by justifying the exclusion of neurotoxicity tests. In the 24 ITC reports to the EPA Administrator issued between October 1977 and May 1989, the ITC proposed 100 chemicals or chemical classes[7] for inclusion in the TSCA section 4 priority list for testing. Of these proposals, one-third included an expression of concern regarding possible neurotoxicity (box 7-E).

Current EPA policy is to specify neurotoxicity testing both when a chemical "may present an unreasonable risk" of neurotoxicity and when there may be substantial human exposure. Under an 'A' finding (an unreasonable risk finding), a core test battery for neurotoxicity is recommended; the core battery includes a functional observational battery (FOB), motor activity tests, and neuropathological evaluations. When appropriate, these tests can be combined with other toxicity studies. Unless otherwise specified, it is assumed that both acute and subchronic testing will be conducted using the FOB and motor activity protocols, with neuropathological tests following subchronic exposures.

It may be necessary to examine other endpoints for specific chemicals, depending on their structure or the nature of existing data. Among the additional tests specified in EPA guidelines are schedule-controlled operant behavior (SCOB), developmental neurotoxicity, peripheral nerve function, and neurotoxic esterase (NTE). For organophosphates and related compounds, study design would include a 28-day repeated exposure period (e.g., 5 days per week) and NTE, ataxia, and neuropathological tests.

Because of the wide variety of production levels and exposure patterns among chemicals, EPA has developed a three-level approach to testing under a "B" finding (significant quantity finding). Testing of level 1 chemicals (low production, low exposure) generally includes the three core tests. FOB and neuropathology are considered a minimum requirement, although a 28-day subchronic study may be used in place of the usual 90-day study. For organophosphorous compounds, acute NTE and acute delayed hen tests are required. For level 2 chemicals (medium production and exposure, consumer exposure), the core battery is required; when appropriate, these tests may be combined with other toxicity studies. Level 3 chemicals (high production, high exposure) also require the core battery, and

[7]The actual number depends on the breadth of the *class* designation used.

Table 7-2-Chemicals Subject to Neurotoxicity Evaluation Under Section 4 of TSCA

Chemical	Current status	Neurotoxicity test; notes
Aniline and substituted anilines	Enforceable consent agreement announced 8/88 (53 FR 31 804)	Not being pursued for neurotoxicity; originally proposed on basis of ability to induce anoxia
Aryl phosphates	Advanced notice of proposed rule-making 12/83 (48 FR 57452)	Proposed rule under development
Cresols	Notice of final rule-making 5/87 (52 FR 19082)	FOB, MA, and NP (subchronic) added to ongoing studies by Office of Drinking Water
Cumene	Final rule 7/88 (53 FR 28195)	FOB, MA, NP (subschronic)
Cyclohexane'	Proposed rule 5/87 (52 FR 19096)	FOB, MA, NP, (subchronic); SCOB (subchronic and acute); DN if warranted after other studies completed
Cyclohexanone*	Negotiated testing agreement 1/84 (49 FR 136)	DN
1,2-Dichloropropane	Final rule 9/86 (51 FR 32079); test standard 10/87 (52 FR 37138)	FOB, MA, NP (subchronic)
Diethylene glycol butyl ether (and corresponding acetate)	Final rule 2/88 (53 FR 5932)	FOB, MA, NP (subchronic)
Diisodecyl phenyl phosphite (PDDP)	Consent order, 2/89 (54 FR 81 12)	NTE, delayed neurotoxicity (subchronic)
Ethyltoluenes, trimethylbenzenes, and C9 aromatic fraction	Final rule 5/85 (50 FR 20662); test standard 1/87 (52 FR 2522)	FOB, MA, NP (subchronic)
Commercial hexane	Final rule 2/88 (53 FR 3382)	SCOB (acute), FOB (subchronic), MA, NP
Hydroquinone and quinone	Final rule 12/85 (50 FR 53145); 5/87 (52 FR 19865)	FOB, NP (subchronic); existing data on motor activity
Isopropanol	Proposed rule 3/88 (53 FR 8638)	FOB, MA, (acute); FOB, MA, NP (subchronic); DN
2-Mercaptobenzothiazole	Final rule 9/88 (53 FR 34514)	FOB, MA, NP (subchronic)
Methyl ethyl ketoxime	Proposed rule 9/88 (53 FR 35838)	FOB, MA (acute and subchronic); NP (subchronic)
Methyl-tert-butyl ether (MTBE)	Consent order 3/88 (53 FR 10391)	FOB, MA, (acute and subchronic); NP (subchronic) testing begun
Oleylamine	Final rule 8/87 (52 FR 31962)	No neurotoxicity testing in final rule, although was in proposed rule
Unsubstituted phenylenediamines (o,m,p)	Extension of comment period 1/88 (53 FR 913)	Revised notice includes FOB, MA (acute, all three isomers, subchronic triggered from acute)
Tributyl phosphate	Proposed rule 11/87 (52 FR 43346)	FOB, MA (acute and subchronic);NP (subchronic)
1,1,1 -Trichloroethane	Consent order in preparation 8/87 (52 FR 31445)	FOB, electrophysiology (acute and subchronic)
Triethylene glycol ethers	Consent order 4/89 (54 FR 13470); final rule for DN (54 FR 13473)	FOB, MA (acute and subchronic); NP (subchronic); DN
Urea-formaldehyde resins	Advanced notice of proposed rule-making	No rule issued

KEY:
DN-developmental neurotoxicity tests
FOB-functional observational battery
MA-motor activity test
NP-directed neuropathological studies
NTE-neurotoxic esterase
SCOB-schedule-controlled operant behavior
Rule-making began prior to issuance of neurotoxicity test guidelines.

SOURCE: Office of Technology Assessment, 1990.

developmental neurotoxicity tests may be required in the near future. EPA neurotoxicologists may add tests to any of the above requirements if existing data indicate the need.

To date, test rules or consent decrees for 19 chemicals or chemical classes have included neurotoxicity testing (table 7-2). In four cases, a test protocol for developmental neurotoxicity was also considered, either as a definite requirement or in the event that other tests indicated neurotoxic effects in adults.

In the event that testing conducted under TSCA section 4 indicates that a chemical poses an unreasonable risk, section 6 gives EPA the authority to regulate production, distribution, use, or disposal of chemicals in commerce, if there is "a reasonable basis' to conclude that any of these activities "presents or will present an unreasonable risk of

injury to health or the environment" [sec. 6(a)]. In order to take a regulatory action, the burden of proof again falls on EPA to show that the listed activities "will present" a risk. EPA may then promulgate rules "to the extent necessary to protect adequately against such risk using the least burdensome requirements" [sec. 6(a)]. This provision has been used for the regulation of a very limited number of chemicals, among them PCBs, dioxin, and, most recently, asbestos.

Finally, TSCA authorizes EPA to require that new information regarding harmful effects of chemical substances be reported:

> . . . any person who manufactures, [imports,] processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment shall immediately inform the [EPA] Administrator of such information . . . [sec. 8(e)].

STANDARD-SETTING LEGISLATION AND REGULATIONS

These statutes authorize regulatory agencies to set standards for chemicals in specific situations or environments. Emissions from smokestacks, automobile exhaust, and sewage pipes, as well as chemicals found in the workplace and in consumer products, are subject to restrictions mandated by various standard-setting statutes. Some of the major standard-setting statutes—the Clean Air Act, the Federal Water Pollution Control Act as amended by the Clean Water Act, and the Safe Drinking Water Act-are pollution control measures. Others focus on the safety, labeling, and packaging of consumer and household products, including the Consumer Product Safety Act, the Federal Hazardous Substances Act, and the Poison Prevention Packaging Act. A third type of standard-setting statute, characterized by the Federal Mine Safety and Health Act and the Occupational Safety and Health Act, addresses issues of workplace safety. (See table 7-1 for key features of these statutes.)

In contrast to the regulatory activity mandated by licensing statutes, regulatory programs charged with setting standards cannot require that chemical substances be tested for toxicity. For the most part, standard-setting programs must base their decisions on reviews of existing literature on toxicology,

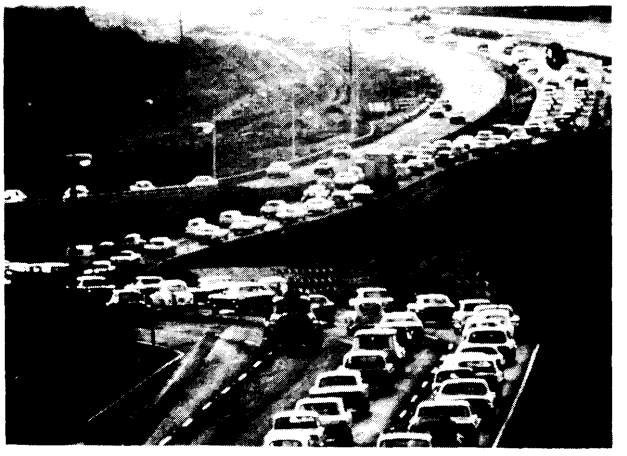

Photo credit: National Archives

although some of them have limited research capabilities as well (see ch. 4). Once a standard is set, the primary regulatory activity is enforcement—making sure that standards are not exceeded.

Clean Air Act

The Clean Air Act (CAA) (Public Law 159) was passed in 1955 "to provide research and technical assistance relating to air pollution control. The Act cited "dangers to the public health and welfare" as an adverse effect of concern. The 1970 amendments (Public Law 91-604) defined more specific effects and authorized an accelerated research program:

> . . . to improve knowledge of the contribution of air pollutants to the occurrence of adverse effects on health, including, but not limited to, *behavioral,* physiological, toxicological, and biochemical effects . . . and the short- and long-term effects of air pollutants on welfare [sec. 2(f) (l)] [emphasis added].

The 1970 amendments also called for EPA to set standards limiting hazardous air pollutants based on their effects on the public health and welfare. Recent amendments have refined the standard-setting procedures further and have revised the schedule for meeting standards. The air pollution control framework set forth by the Clean Air Act calls for EPA to establish standards for ambient air, emissions of hazardous substances, and emissions from automobiles, including fuel and fuel additives.

EPA regulates air pollutants by setting National Primary and Secondary Ambient Air Quality Standards as necessary to protect public health, with 'an adequate margin of safety" [sec. lo]. EPA

has interpreted the requirement for "an adequate margin of safety' as intending:

> . . . to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It is also intended to provide a reasonable degree of protection against hazards that research has not yet identified (50 FR 37484).

The primary standard is to be based solely on health concerns (50 FR 37484). However, a regulatory impact analysis is conducted to obtain information and provide a cost-benefit analysis for various alternative standards (22).

The Act defines a hazardous air pollutant as:

> . . . an air pollutant to which no ambient air quality standard is applicable and which in the judgment of the Administrator causes, or contributes to, air pollution which may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible illness [sec. 1 12(a)(l)].

It directs EPA to set emissions standards for such pollutants at a level that will provide "an ample margin of safety to protect the public health" [sec. 1 lo]. In its promulgation of National Emissions Standards for Hazardous Air Pollutants, EPA has interpreted "ample margin of safety" as not requiring the total elimination of risk (40 CFR 19 ed. 61).

The Act specifically prescribes that EPA set standards for vehicle emissions, fuel, and fuel additives. A fuel or fuel additive may be regulated only on the basis of endangerment of the public health or welfare and then only". . . after consideration of all relevant medical and scientific evidence . . . including consideration of other technologically or economically feasible means of achieving emission standards . . ." [WC. 21 l(c)(2)(A)].

EPA has promulgated Primary National Ambient Air Quality Standards for the following six pollutants: sulfur oxides, particulate matter, carbon monoxide, ozone, nitrogen dioxide, and lead (40 CFR 50). Standards for carbon monoxide (36 FR 8186) and lead (43 FR 46254) were set in response to neurotoxic effects caused by these compounds.

The original carbon monoxide standards were based on evidence that the ability to discriminate time intervals was impaired in humans when 2 to 3 percent of the body's hemoglobin—the oxygen-binding component of red blood cells—was bound to carbon monoxide (forming carboxyhemoglobin, COHb) and was therefore unable to bind to and carry oxygen (28). The impairment of time discrimination, a neurotoxic effect, was considered the most sensitive effect. The study from which these data were derived, however, has been discredited (45 FR 55066). On August 18, 1980, after reviewing the literature, including that published since the original standards were promulgated, EPA proposed retention of the 8-hour primary standard [9 parts of carbon monoxide per million parts of air (ppm)] and revision of the l-hour standard (from 35 ppm to 25 ppm), based on cardiotoxic rather than neurotoxic effects (45 FR 55066). In order to set an ambient air standard, the Agency used an equation to estimate the concentrations of carbon monoxide in ambient air that were likely to result in COHb levels of concern (45 FR 5506).

Since that time, an expert committee convened by EPA has determined that EPA should not rely on these data (50 FR 37484). After further review of the scientific literature, however, EPA decided to let stand the current primary carbon monoxide standards, which are based on concern for central nervous system and cardiovascular effects, the latter being considered to be the more sensitive (50 FR 37484). Effects on the central nervous system of low levels of COHb include "impairment of vigilance, visual perception, manual dexterity, learning ability, and performance of complex tasks" (50 FR 37484). The population most sensitive to the cardiovascular effects included persons with angina and other cardiovascular diseases. The standard was set at a level which was estimated to keep more than 99.9 percent of this sensitive population below 2.1 percent COHb (50 FR 37484).

The primary lead standard was based on impaired heme synthesis (heme is a nonprotein iron compound that gives hemoglobin its characteristic color and oxygen-carrying properties) and nervous system deficits, which included cognitive deficits, encephalopathy, and peripheral neuropathy (43 FR 46254). Children were considered to be the most sensitive population, and the standard was set at a level estimated to keep 99.5 percent of children below what was considered to be the maximum safe level of 30 micrograms of lead per deciliter of blood (43 FR 46254). The actual standard was calculated based on 20 percent of lead in the blood being

contributed from the air and 80 percent from other sources.[8] The lead standard is presently under review by EPA, and nervous system disturbances are still one of the most sensitive categories of effects (9).

National Emission Standards for Hazardous Air Pollutants have been promulgated by EPA for the following: benzene arsenic, beryllium, mercury, vinyl chloride, asbestos, and radionuclides. Only the standard for mercury was based on concerns about neurotoxic effects (38 FR 8820). The endpoint that was the driving force behind this standard was paresthesia (tingling, burning sensations) (45).

Automobile and other vehicle emissions are regulated by the Office of Mobile Sources. To date, carbon monoxide, nitrogen oxides, hydrocarbons, and particulate have been regulated. Of these four pollutants, carbon monoxide was regulated in part on the basis of neurotoxic concerns, the same concerns on which the Primary National Ambient Air Quality Standard for carbon monoxide was based. The standard itself varies, depending on the vehicle class and model year.

EPA regulates the lead content of gasoline on the basis of the same neurotoxic effects cited in the primary national ambient air quality standard for lead (50 FR 9386). A standard of 0.1 gram of lead per gallon of leaded gasoline became effective January 1, 1986. EPA was particularly concerned about the impact of lead on the health of preschool children and has clearly stated that its long-term objective is to eliminate the use of lead in gasoline (50 FR 9386).

Proposed Amendments

Efforts to amend the CAA during the IOOth Congress were not successful. More than 30 different bills proposing amendments to CAA, including an Administration proposal, have been introduced in the House and Senate during the 10lst Congress, and hearings have been held on many of them. Although the issue is being actively debated and the CAA will almost certainly be amended, it is too early to tell what form the amendments will take and what direct effect, if any, the amendments will have on the regulation of neurotoxic substances.

Federal Water Pollution Control Act and Clean Waler Act

The Federal Water Pollution Control Act (FWPCA) (33 U.S.C. 466) and amendments to it, including the Clean Water Act (CWA), established a framework for the control of water pollution based on human health and environmental concerns. The 1972 amendments (Public Law 92-500), which completely revised earlier versions of FWPCA, authorized EPA to set effluent standards for a designated list of hazardous substances (40 CFR 116). Further amendments to the FWPCA, including the 1977 Clean Water Act, authorized EPA to develop and periodically review water quality criteria that accurately reflect ''the latest scientific knowledge" on "the kind and extent of *all identifiable effects on health and welfare' [sec.* 304(a)(l)] [emphasis added]. The criteria are not regulations and, as such, carry no enforcement authority. However, they provide guidance for the derivation of regulatory standards, including general effluent limitations and toxic pollutant effluent limitations authorized by the FWPCA (45 FR 79319).

EPA is authorized to establish water quality criteria to protect human health and the environment. The criteria to protect human health are "based solely on data and scientific judgments on the relationship between pollutant concentrations and environmental and human health effects. . . and do not reflect considerations of economic or technological feasibility" (45 FR 79319).

EPA's Office of Water Regulations and Standards has established three types of water quality criteria for pollutants where sufficient data are available: 1) to protect freshwater aquatic life, 2) to protect saltwater aquatic life, and 3) to protect human health. Derivation of criteria to protect human health was based on three endpoints: carcinogenicity, adverse noncarcinogenic effects, and organoleptic effects (45 FR 79347). (Organoleptic effects refer to taste or odor characteristics of a compound and have no demonstrated adverse effects on human health.) Criteria were based on organoleptic effects when the organoleptic threshold was lower than that calcu-

[8]The Lead Industries Association, Inc., challenged the standard in court, arguing that EPA could only regulate based on "clearly adverse effects'' and that the nervous system effects had not been adequately documented at the levels cited by EPA (17). The court upheld EPA's standard, however, noting that the EPA Administrator's actions were reasonable, that EPA did, in fact, have sufficient evidence suggesting nervous system effects, that the statute allows the EPA Administrator considerable discretion to determine adverse effects, and that in any event the standard was based in part on providing an "adequate margin of safety,' which is required by the Clean Air Act.

lated from toxicity data or when there were insufficient toxicity data.

Water quality standards set to protect human health and based on toxicological data have been established for 86 compounds (45 FR 7931 8; 49 FR 5831). For four of these, lead, mercury, thallium, and toluene, neurotoxic effects were of major concern (34-44). A brief survey of the water quality criteria documents (34-44) indicates that at least eight other chemicals are noted as causing neurotoxic effects, even though the standards for these chemicals were based on other endpoints (9).

Safe Drinking Water Act

The Safe Drinking Water Act (SDWA) of 1974 amended the Public Health Service Act ''to assure that the public is provided with safe drinking water" (Public Law 93-523). SDWA and its amendments instituted a framework of primary and secondary water regulations designed to control contaminants in public drinking water supplies that EPA determines 'may have any adverse effect on the health of persons" [sec. 1401(1)(B)].

Under the Act, EPA was to establish Revised National Primary Drinking Water Regulations, using a two-stage process. First, EPA was to establish recommended maximum contaminant levels (RMCLs), which are nonenforceable health goals. RMCLs were to be set "at a level [at] which. . . no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety" [sec. 1412(b)(l)(B)]. For carcinogenic pollutants, the RMCL was to be set at zero. Once an RMCL had been promulgated, EPA was to establish a maximum contaminant level (MCL) for that pollutant. An MCL was an enforceable standard and is to be set:

> . . . as close to the recommended maximum contaminant levels. . . as is feasible. . . [i.e.], with the use of the best technology, treatment techniques, and other means, which the Administrator finds are generally available taking costs into consideration [sec. 1412 (b)(3)].

A treatment technique maybe established instead of an MCL if "it is not economically or technologically feasible to . . . ascertain the level of . . . [a] contaminant [in drinking water]" [sec. 1401 (C)(ii)].

When the Act was amended in 1986, the two-step process was retained, with EPA to specify nonenforceable goals [RMCLs were renamed maximum contaminant level goals (MCLGs)], on which MCLS were to be based. EPA was required to propose and promulgate MCLGs and MCLs simultaneously for any chemical. Another key feature of the amendments, from a neurotoxicological perspective, was the imposition of a ban on the use of lead pipe, solder, or flux in plumbing for drinking water after June 19, 1986.

The Office of Drinking Water of EPA has set MCLGs for carcinogenic pollutants at zero. MCLGs for noncarcinogenic agents are set by establishing the dose at which harmful effects may be observed and then compensating for uncertainties in the process (50 FR 46946). EPA then predicts exposures from food and air sources and sets the MCLGs accordingly (50 FR 46946).

Since the revision of the Act, MCLGs have been set for fewer than 15 inorganic chemicals under the National Primary Drinking Water Regulations (48 FR 45502). Of the 10 MCLs issued, three were based partly or entirely on nervous system effects: 1) barium, 2) lead, and 3) mercury. For one, arsenic, the nervous system was mentioned as one of several organ systems affected with more severe intoxication, but the MCL was not based on this (33).

The National Primary Drinking Water Regulations also contain MCLs for 10 organic chemicals: four pesticides, two herbicides, and four trihalomethanes. It is difficult to ascertain the effects of concern for the four pesticide and two herbicide MCLs. According to one EPA document, the severity of the symptoms of the pesticides (endrin, lindane, methoxychlor, and toxaphene) is related to the concentrations of the compounds in the nervous system (33). Specific effects of concern for the two herbicides [2,4-D and 2,4,5-TP (Silvex)] are not mentioned (33). The standard for the four trihalomethanes was based on chronic low-level effects (primarily cancer), although these compounds do have an acute effect on the nervous system.

In addition to setting drinking water standards, the Office of Drinking Water publishes health advisories describing levels of contaminants. These advisories cover l-day, 10-day, long-term (approximately 7 years, or 10 percent of an individual's lifetime), and lifetime exposures. The advisories are not federally enforceable but describe levels of contaminants in drinking water that are associated with adverse health effects. The advisories do not

clearly indicate the effects that are of primary concern, but one or more of the advisories for seven contaminants appear to have been based on neurotoxic effects (50 FR 46936).

Consumer Product Safety Act and Federal Hazardous Substances Act

The Consumer Product Safety Act (Public Law 92-573) of 1972 established the Consumer Product Safety Commission (CPSC) as an independent regulatory commission charged with protecting the public from "unreasonable risks of injury associated with consumer products" [sec. 2(a)(3)]. Risk of injury is defined as "risk of death, personal injury, or serious or frequent illness" [sec. 3(a)(3)].

The Act authorizes CPSC to promulgate consumer product safety standards, including performance requirements and warning or instructional labels, necessary to 'prevent or reduce an unreasonable risk of injury associated with such product" [sec. 7(a)]. The determination of whether or not a particular risk of injury is unreasonable involves balancing ". . . the probability that the risk will result in harm and the gravity of the harm against a rule's effects on the product's utility, cost, and availability to the consumer" (42 FR 44198). The Consumer Product Safety Act's broad authority could cover products with neurotoxic effects, but toxic substances in general are more likely to be regulated under the Federal Hazardous Substances Act because the former prohibits the regulation of a risk that can be adequately regulated under the latter [sec. 30(d)].

The Federal Hazardous Substances Act (Public Law 86-613) was passed in 1960 to protect the public health by requiring that hazardous substances be labeled with various warnings, according to the nature of the hazard. The Act defines a ''hazardous substance' as:

> *Any* substance or mixture of substances which (i) is toxic, (ii) is corrosive, (iii) is an irritant. . . if such substance or mixture of substances *may cause substantial personal injury or substantial illness* during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children [sec. 2(f)(l)] [emphasis added].

A toxic substance is defined as "any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface" [sec. 2(g)].

The Act directs CPSC to issue regulations clarifying which categories of substances fit the various definitions of hazardous, if there is any uncertainty [sec. 3(a)(l)], and to ban substances through a formal rule-making procedure:

> . . . on the basis of the finding that, notwithstanding such cautionary labeling as is or may be required under this Act for that substance, the degree or nature of the hazard involved in the presence or use of such substance in households is such that the objective of the public health and safety can be adequately served only by keeping such substance . . . out of the channels of interstate commerce . . . [sec. 2(q)(l)].

The Act calls for banning substances that are too dangerous for household use.

Because of the interrelatedness of concerns embodied in the Consumer Product Safety Act and the Federal Hazardous Substances Act and because both are administered by CPSC, regulatory actions under the two statutes have been closely intertwined. CPSC has responded to its mandate by setting standards for various consumer products. Its actions based on neurotoxicity concerns have been to ban products with paint or other surface material containing lead in excess of 0.06 percent (42 FR 44199). This standard was designed "to reduce or eliminate the unreasonable risk of injury associated with lead poisoning in children' (42 FR 44198) and addressed consumer products that bear lead-containing paint, including toys and other items used by children and furniture used by consumers (42 FR 44199). The Commission cited the following as adverse effects of lead on the nervous system: hyperactivity, slowed learning ability, withdrawal, and blindness (42 FR 44200).

CPSC has been involved in working out a voluntary consensus on the labeling of various consumer products containing organic solvents such as n-hexane. Concern about these compounds was based on the association between repeated exposure to solvents and permanent neurological damage. CPSC recently hired a staff neurotoxicologist but has not undertaken any specific neurotoxicity product evaluations lately. The Commission does, however, plan to draft criteria for classifying, evaluating, and labeling products that warrant concern for neurotoxic effects (under the authority of both Acts).

Federal Mine Safety and Health Act

The Federal Mine Health and Safety Act of 1969 (Public Law 91-173), as amended in 1977 (Public Law 95-173), grew out of congressional concern over the:

> . . . urgent need to provide more effective means and measures for improving the working conditions and practices in the Nation's coal or other mines in order to prevent *death and serious physical harm,* and in order to prevent *occupational diseases* originating in such mines [sec. 2(a)] [emphasis added].

Although no specific toxic effects are singled out for consideration, the concern about physical harm and occupational diseases could encompass neurotoxic effects.

The Act established the Mine Safety and Health Administration (MSHA) in the Department of Labor and authorized it to "develop, promulgate, and revise, as may be appropriate, improved mandatory health or safety standards for *the protection of life and prevention of injuries* in coal or other mines' [sec. 10l(a)] [emphasis added]. MSHA is to ensure that miners will not ''suffer material impairment of health or functional capacity even if such miner has regular exposure to the hazards dealt with by such standard for the period of his working life" [sec. l o] .

MSHA initially fulfilled its standard-setting mandate by adopting standards for airborne contaminants recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) (box 7-F), and the American National Standards Institute (30 CFR 57.5). In 1981, MSHA began a comprehensive review of its safety standards, including those for air (46 FR 57253,46 FR 10190); since then, it has moved to update its regulations by incorporating more recent threshold limit values (see ch. 6).

Occupational Safety and Health Act

The Occupational Safety and Health Act (OSH Act) was enacted in 1970 to improve workplace safety. The Act established the Occupational Safety and Health Administration (OSHA) in the Department of Labor and directed it to promulgate health and safety standards, defined in the Act as:

> . . . conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment and places of employment [sec. 3(8)].

The Act also authorizes OSHA to promulgate new standards for toxic materials and to modify or revoke existing ones, to ensure ". . . that no employee will suffer *material impairment of health or fictional capacity* even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life" [sec. 6(b)(5)] [emphasis added].

In 1971, OSHA adopted existing Federal standards, most of which had been adopted under the Walsh-Healy Act, and approximately 20 consensus standards of the American National Standards Institute as permissible exposure limits (PELs) (39 FR 23540).

In addition to initiating a standard-setting framework, the OSH Act established the National Institute for Occupational Safety and Health (NIOSH) as a research agency "authorized to develop and establish recommended occupational safety and health standards" [sec. 22(c)(l)] and to set criteria for such standards. Although the Act directed that the standards and criteria be used by OSHA in the promulgation of new or revised health and safety standards, OSHA has acted on few of NIOSH's recommendations. NIOSH is also responsible for assessing work-related diseases and injuries, including those caused by toxic substances.

Since the adoption of initial standards, OSHA has issued complete health standards for 25 substances (27). Of these, the one concerning lead was based, in part, on nervous system effects (43 FR 52952). Four other compounds, inorganic arsenic, acrylonitrile, ethylene oxide, and 1,2-dibromo-3-chloropropane, were cited as causing various disturbances in the nervous system, but the standards for these were driven by concerns about carcinogenic effects (29 FR 1910).

OSHA recently published a far-reaching revision and update of existing standards (54 FR 2332). The rule affects standards for 428 chemical substances: it lowers PELs for 212 substances, establishes them for 164 substances that were not formerly regulated, and maintains unchanged the existing levels for 52 substances. The regulation addressed only chemicals that were covered by the most recent ACGIH recommendations and whose threshold limit values (TLVs) differed from current PELs. No new stand-

Box 7-F—The American Conference of Governmental Industrial Hygienists

The American Conference of Governmental Industrial Hygienists (ACGIH) is a professional society organized in 1938 by a group of governmental industrial hygienists. Its recommendations have played a major role in setting standards under both the Occupational Safety and Health Act and the Federal Mine Safety and Health Act. ACGIH membership consists of government or industrial hygienists involved in occupational safety and health programs who seek to establish a consensus among industrial toxicologists on the levels of chemicals that might reasonably be considered safe in the workplace.

Over the years, ACGIH has set threshold limit values (TLVs) for hundreds of occupational substances and publishes its recommendations annually. These values refer to airborne concentrations of substances that the majority of workers maybe repeatedly exposed to on a daily basis without adverse effect (ACGIH, 1985).

ACGIH sets three types of TLVs for chemical compounds: time-weighted average concentrations, which are for an 8-hour workday and a 40-hour workweek; short-term exposure limits, which are 15-minute time-weighted average exposures not be exceeded at any time; and ceiling limits, which are not to be exceeded even for an instant (ACGIH, 1985).

There are no set guidelines for the establishment of TLVs. Rather, the values are based on the TLV committee's professional judgment, after they have reviewed information from industrial experience, from experimental human and animal studies, and, when possible, from a combination of all three. The basis on which the values are established may differ from substance to substance: protection against impairment of health maybe a guiding factor for some, whereas reasonable freedom from irritation, narcosis, nuisance, or other forms of stress may form the basis for others (ACGIH, 1985).

The TLVs are not legally enforceable but are meant to be used as guidelines. The 1968 ACGIH chemical substance TLVs and the 1969 noise TLV, however, were adopted as Federal standards under the Walsh-Healy Act prior to enactment of the Occupational Safety and Health Act. In the early 1970s, these standards were adopted as permissible exposure limits by the Occupational Safety and Health Administration, as mandated by the Act (OTA, 1985).

As of 1985, ACGIH had set 605 TLVs covering a wide range of compounds (ACGIH, 1985); TLVs for 202 of these substances were set in whole or in part to protect individuals from nervous system effects ranging from drowsiness to nerve damage. (This number does not include effects such as eye, nose, and throat irritation, although these effects might be broadly construed as neurotoxic.)

OSHA recently published a revised standard that increased the protection of workers by implementing new or revised PELs for 428 toxic substances (53 FR 20960-20991). The final standard was published in January 1989. The new rule established lower exposure limits for approximately 212 substances already regulated by OSHA. PELs would be established for the first time for another 164 substances. A large number of these are established to prevent adverse effects on the nervous system. The regulation addressed only chemicals that were covered by the most recent ACGIH recommendations and whose TLVs differed from current PELs. No new standards were promulgated for chemicals for which NIOSH had specified recommended exposure levels, unless those chemicals were also on the ACGIH list.

Critics of ACGIH argue that the TLVs are essentially industry consensus standards arrived at through a limited review of available toxicological information. Nevertheless, TLVs are widely used by both industry and government officials.

SOURCES: American Conference of Governmental Industrial Hygienists, *Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH for 1985-1986* (Cincinnati, OH: 1985); U.S. Congress, Office of Technology Assessment, Preventing *Illness and Injury in the Workplace, OTA-H-256* (Washington, DC: U.S. Government Printing Office, 1985).

ards were promulgated for chemicals for which NIOSH had specified recommended exposure levels, unless those chemicals were also on the ACGIH list. This issue is discussed in more detail in chapter 10.

Tables in the Federal Register notice announcing the rule listed the explicit toxicological concerns behind 410 of the standards. Of those, PELs for 20 compounds were based on the avoidance of direct neuropathic effects. An additional 19 were based on the avoidance of narcosis. A total of 79 chemicals were regulated to prevent irritation, an effect that does not necessarily imply neurotoxicity but may include some neurotoxic effects. Methanol, a chemical that adversely affects the optic nerve, was one of

the five substances listed because of ocular concerns. Finally, 26 chemicals were listed under the category of avoidance of metabolic effects. This category contained several substances that cause neurotoxic effects, including carbon monoxide and some types of cholinesterase inhibitors (cholinesterase inhibition is discussed in chs. 3 and 10).

The rule sets standards for an additional 73 chemicals on the basis of structural analogies to other compounds with known effects. Of the 73, 18 were selected because they are analogous to compounds that induce neurological effects, narcosis, or cholinesterase inhibition. PELs for 26 chemicals were based on no observed adverse effect levels (NOAELs). For six of these, the adverse effects noted in the rule were neurological.

Although the chemicals discussed above have been regulated explicitly on the basis of neurological concerns, it should be remembered that other neurotoxic chemicals may have been regulated on the basis of other undesirable effects they induce. For example, the PEL for carbon disulfide, a well-known neurotoxicant, is based on avoidance of cardiovascular effects.

In addition to specifying PELs, OSHA has issued, and subsequently expanded, a hazard communication standard (52 FR 3 1852). This requires manufacturers and importers to assess the hazards of the chemicals they produce or import, requires employers to provide information to their employees concerning hazardous chemicals (using training, labels, material safety data sheets, and access to written records), and requires distributors of hazardous chemicals to provide information to their customers (via proper labels and Material Safety Data Sheets). It should be noted that many such data sheets contain very limited information on toxic hazards.

CONTROL-ORIENTED LEGISLATION AND REGULATIONS

Hazardous chemical substances in the environment and in consumer products are the subject of control-oriented statutes such as the Comprehensive Environmental Response, Compensation, and Liability Act, the Controlled Substances Act, the Lead-Based Paint Poisoning Prevention Act, the Marine Protection, Research, and Sanctuaries Act, the Poisoning Prevention Packaging Act, and the Resource Conservation and Recovery Act. These statutes, which are founded on a recognition of the problems caused by predetermined or specified sets of hazardous chemicals, are focused on developing procedures to control existing situations (see table 7-l). Regulatory implementation under these laws consists primarily of setting allowable levels or reporting requirements and enforcing the limits that have been set.

Comprehensive Environmental Response, Compensation, and Liability Act

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), also known as Superfund, was enacted in 1980 to provide authority for EPA to clean up hazardous waste sites. CERCLA defined hazardous substances as either compounds that have already been designated under other Acts or compounds designated by EPA" which, when released into the *environment may present substantial danger to the public health or welfare or the environment" [sec.* 102(a)] [emphasis added]. In addition to identifying hazardous substances, CERCLA directs EPA to "promulgate regulations establishing that quantity of any hazardous substance the release of which shall be reported" [sec. 102(a)], essentially supplanting a similar process established under the Clean Water Act. These reportable quantities (RQs) are used to trigger the appropriate response "necessary to protect the public health or welfare or the environment" [sec. l o] .

Initially, all RQs were set at 1 pound, unless other RQs were assigned under section 311 of the Clean Water Act. As authorized under section 102 of CERCLA, EPA has adjusted RQs for approximately 440 of the 717 substances on the list (40 CFR 302; 51 FR 34534), based on "scientific and technical criteria which correlate with the possibility of hazard or harm on the release of a substance in a reportable quantity" (48 FR 23560). The criteria EPA used were aquatic toxicity, mammalian toxicity, ignitability, reactivity, chronic toxicity, and potential carcinogenicity. Of the 245 hazardous substances evaluated by EPA's Environment Criteria and Assessment Office, 64 were reviewed for chronic toxicity. Of those 64, 22 could not be ranked due to insufficient data. Of the 42 that were ranked, 5 were ranked on the basis of effects on the nervous system (11).



Photo credit: U.S. Environmental Protection Agency

The Superfund Amendments and Reauthorization Act (SARA) (Public Law 99-499) passed in 1986 called for the development of a list of 100 high-risk chemicals from the chemicals on the Superfund list for which available data were inadequate. SARA established a research program at the Agency for Toxic Substances and Disease Registry to conduct the necessary research and to develop toxicology data profiles on the 100 chemicals. Thus, although CERCLA as amended is not a testing program, it does sponsor research. The toxicological profiles being prepared under SARA provide an explicit discussion of health effects for various routes of exposure to a chemical (oral, inhalation, dermal). The specific effects considered include systemic effects, immunological effects, neurological effects, developmental effects, reproductive effects, genotoxic effects, cancer, and death.

Controlled Substances Act

Congress passed the Controlled Substances Act in 1970 as Title II of the Comprehensive Drug Abuse Prevention and Control Act (Public Law 91-513). Finding that ". . . the illegal importation, manufacture, distribution, and possession and improper use of controlled substances have a substantial and detrimental effect on the health and general welfare of the American people' [sec. 101(2)], Congress set forth a framework for restricting a defined list of substances, many of which are drugs with beneficial as well as harmful uses.

The Act established five categories, or schedules, of controlled substances based on potential for abuse, severity of possible harmful effects, likelihood of dependence, and accepted medical uses [sec. 202; 28 CFR]. The Act grants the Attorney General and the Department of Justice authority to regulate and enforce the control of scheduled substances and to add to, remove from, or amend the schedules as appropriate.

The Controlled Substances Act calls for cooperation between FDA and the Justice Department in determining which drugs should be controlled. In addition, FDA is directed to notify the Justice Department whenever "a new drug application is submitted . . . for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, [and] it appears that such drug has abuse potential" [sec. 201(f)]. Thus, the primary scientific and pharmacological investigations, including evaluations of toxicity or of effects on the central nervous system, are handled under the FDA procedures described under FFDCA.

Marine Protection, Research, and Sanctuaries Act

Finding that "unregulated dumping of material into ocean waters endangers human health, welfare, and amenities, and the marine environment" [sec. 2(a)], Congress enacted the Marine Protection, Research, and Sanctuaries Act (MPRSA) (Public Law 92-532) in 1972 to:

> . . . regulate the dumping of all types of materials into ocean waters and to prevent or strictly limit the dumping into ocean waters of any material which would *adversely affect human health, welfare, or amenities,* or the marine environment, ecological systems, or economical potentialities [sec. 2(B)] [emphasis added].

Materials are defined as:

> . . . matter of any kind or description, including, but not limited to, dredged material, solid waste, incinerator residue, garbage, sewage, sewage sludge, munitions, radiological, chemical, and biological warfare agents, radioactive materials, chemicals, biological and laboratory waste, wreck or discarded equipment



Photo credit: U.S. Environmental Protection Agency

rock, sand, excavation debris, and industrial, municipal, agricultural, and other waste [sec. 3(c)].

The Act prohibits dumping of the defined materials in U.S. territorial waters and 12 miles beyond U.S. boundaries unless the dumper obtains a permit.

MPRSA does not establish any program or requirement for ascertaining the toxic effects of materials nor any mechanism by which specific, newly identified toxic materials may be added to the list. EPA has restricted or prohibited the dumping of several categories of substances because of toxic or radioactive effects or persistence. Mercury and mercury compounds—known neurotoxicants—are among the compounds specifically restricted (40 CFR 227.6), although the regulations do not mention neurotoxic effects in particular.

. EPA's primary regulatory responsibility under MPRSA has been control of ocean dumping sites through the permitting process (40 CFR 220-31). EPA has delegated this authority to regional EPA administrators (52 FR 25009). EPA considers the impact of the proposed dumping on ''aesthetic, recreational, and economic values, " including the "[presence in the material of toxic chemical constituents released in volumes which may affect humans directly" (40 CFR 227.18). Apart from restrictions on mercury, however, there is no clear record of how or whether specific neurotoxic effects have been regulated under MPRSA.

Lead-Based Paint Poisoning Prevention Act and Poison Prevention Packaging Act

The Lead-Based Paint Poisoning Prevention Act (LBPPPA) (Public Law 91-695) is the only statute based primarily on concerns for neurotoxic effects (see ch. 10). The purpose of the Act-to eliminate lead-based paint poisoning—was to be accomplished by screening and testing children, removing lead-based paint from buildings, and banning the use of lead-based paint in Federal construction or rehabilitation of residential housing. The 1973 amendments (Public Law 93-151) defined lead-based paint as any paint which contains 0.06 percent lead. That 0.06 percentage was based on studies indicating the permissible daily intake of lead to be 300 micrograms, which the U.S. Public Health Service and the American Academy of Pediatrics



Photo credit: U.S. *Environmental Protection Agency*

Household substances that pose a risk to children are regulated under the Poison Prevention Packaging Act.

then calculated to be a limit of no more than 0.06 percent lead by weight.

The Act was amended again in 1976 by the National Consumer Health Information and Health Promotion Act, which instructed the CPSC:

> . . . to determine, by December 23, 1976, whether a level of lead in excess of 0.06 percent but not over 0.50 percent, was safe. If the Commission were unable to determine a safe level of lead in this range, paint manufactured after June 22, 1977, containing more than 0.06 percent would be considered ''lead-based paint" (42 FR 44193).

The CPSC later ruled that available data did not support the establishment of a level in this range as being safe (42 FR 44193), so the 0.06 percent level remained in effect.

The Poison Prevention Packaging Act (PPPA) (Public Law 91-601) was enacted in 1970 to prevent inadvertent poisoning of small children by hazardous household substances. Packaging of these substances was to be done in such a way as to make it "significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance therein within a reasonable time' [sec. 2(4)]. The Act authorizes the CPSC to promulgate standard-setting rules for special packaging if the Commission determines that:

> . . . the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children *from serious personal injury or serious illness resulting* from handling, using, or ingesting such substance [sec. 3(a)(l)] [emphasis added].

The Act encompasses hazardous substances as defined in the Federal Hazardous Substances Act; foods, drugs, and cosmetics as defined in the FFDCA; and fuels packaged for household use.

Because LBPPPA and PPPA are designed to control acknowledged problems, most regulatory actions undertaken by the CPSC under these two statutes are aimed at enforcement. Under LBPPPA, the Commission may conduct periodic measure-

ments to ensure that lead in paints does not exceed the mandated level. Under PPPA, the only regulatory option is for CPSC to require protective packaging of hazardous household substances that are identified or designated as toxic by other statutes or agencies; PPPA has little impact on the substantive regulation of toxic substances.

Resource Conservation and Recovery Act

The Resource Conservation and Recovery Act (RCRA) directs EPA to identify and list hazardous wastes. Generators, transporters, and facilities that treat, store, or dispose of such wastes are then subject to regulations promulgated by the Administrator as necessary *to protect human health and the environment" [sec.* 3002(a)] [emphasis added]. A hazardous waste is defined as a:

> . . . solid waste, or combination of solid wastes, which because of its quantity, concentration, or physical, chemical, or infectious characteristics may:
>
> (A) cause, or significantly contribute to, an increase in serious *irreversible, or incapacitating reversible, illness;* or
>
> *(B) pose a substantial present or potential hazard to human health* or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed [sec. 1004(5)] [emphasis added].

EPA classifies a solid waste as hazardous based on ignitability, corrosivity, and reactivity, as well as on various toxicity criteria, including fatality at low doses or the capability of "causing or significantly contributing to an increase in serious irreversible, or incapacitating reversible, illness' (40 CFR 261). Toxic wastes are designated on the basis of the nature of the toxicity of the constituent, its concentration, and its persistence (40 CFR 261.1 1). The statute allows for direct measurement of waste toxicity in some cases.

EPA has adopted standards based on the chronic health limits defined under the National Primary Drinking Water Standards; consequently, the same eight chemicals that were identified for neurotoxic concerns under the SDWA are regulated under the Resource Conservation and Recovery Act.

NEW INITIATIVES IN REGULATING NEUROTOXIC SUBSTANCES

A primary issue in regulating potentially neurotoxic substances is the adequacy of the data on which evaluations are based. Representatives of Federal regulatory agencies disagree on whether or how well current toxicity tests predict neurotoxic effects of chemicals on humans. Consequently, new initiatives for regulating neurotoxic substances have emerged in agencies dissatisfied with existing approaches.

The first tangible result of attempts to improve regulatory testing for neurotoxic effects was the publication in 1985 of a set of neurotoxicity test guidelines by EPA's Office of Toxic Substances. The primary purpose of these guidelines was to aid development of test rules under section 4 of TSCA (50 FR 39458). The significance of the guidelines is demonstrated by the fact that, since they were introduced, experimental protocols based on them have been incorporated into a substantial number of test rules and consent agreements. Studies to validate the scientific utility of the guidelines are now under way.

The two most notable ongoing regulatory initiatives concerning neurotoxicants are also centered on development of test guidelines. These initiatives, one by EPA and one by FDA, are discussed in the sections that follow. A third new initiative, which is less a change in neurotoxicity regulation than an attempt to obtain international consensus on changes already made by EPA, is an EPA proposal to the United Nations Organization for Economic Cooperation and Development (OECD) to add a mammalian neurotoxicity screening battery to OECD's test guidelines.

Revision of EPA's Neurotoxicity Test Guidelines for Pesticides

Recent efforts at EPA to coordinate evaluations of neurotoxicity under TSCA and FIFRA highlight some of the differences that have existed between the regulatory programs of the Office of Toxic Substances and those of the Office of Pesticide Programs (OPP). When OTS published its neurotoxicity guidelines in 1985, its Health and Environmental Review Division had been employing neurotoxicologists for several years, reflecting OTS's approach of having chemicals reviewed by several

scientists with different areas of toxicological expertise. In contrast, OPP's Hazard Evaluation Division has traditionally assumed equivalency of training among its toxicologists, which may have fostered some reluctance on OPP's part to focus on specific organ system tests, including neurotoxicity tests, in its evaluations. Since 1986, OPP has consulted OTS neurotoxicity test guidelines when requesting data on the neurotoxicity potential of pesticides. In that year, OPP also hired two neurotoxicologists previously employed by OTS.

Adoption of neurotoxicity testing guidelines by OPP was delayed by uncertainties regarding revision of FIFRA by Congress in late 1986, but plans to add neurotoxicity guidelines to those specified in 40 CFR 158 continued in 1987. Work on the guidelines received further impetus in February 1987, when a coalition including the Center for Science in the Public Interest (CSPI) and 11 other groups and individuals petitioned EPA to develop methods for assessing neurotoxic effects of active and inert ingredients in pesticides (10). OPP submitted its response to a subpanel of the FIFRA Science Advisory Panel (SAP) for review in October 1987, but SAP's approval of those guidelines was superseded by a decision to revise all of the part 158 guidelines, eliminating tests that are outmoded or uninformative and adding tests in several areas, including neurotoxicity and immunotoxicity.

In May 1988, the director of OPP met with representatives of CSPI and other groups who had signed the petition. In August 1988, CSPI sent a letter to EPA's administrator for pesticides and toxic substances suggesting several modifications of the revised guidelines approved by SAP. CSPI called for routine conduct of chronic neurotoxicity studies (rather than just when acute and subchronic studies indicated neurotoxic effects) and for inclusion of schedule-controlled operant behavior and developmental neurotoxicity tests on a regular basis (see ch. 5 for descriptions of these tests). CSPI also pressed for revision of the pesticide assessment guidelines (46) rather than promulgation of a regulation to add new data requirements to 40 CFR 158.

EPA responded with a letter to CSPI in November 1988, stating that the Agency intended to adhere to the guidelines recommended by the SAP subpanel and that it was still considering appropriate criteria for initiating tests beyond the base set of tests. EPA agreed to modify the pesticide test guidelines but stressed the need to coordinate OPP and OTS guideline revisions through an intra-agency work group. Draft EPA guidelines were supposed to be completed by February 1990 and made available for public comment in May 1990.

Meanwhile, efforts to improve neurotoxicity testing requirements through the 1988 amendments to FIFRA resulted in changes in the principal report accompanying these amendments. Section 219 of S. 1516 (reported by the Senate Agriculture Committee in May 1988) would have required the EPA Administrator to "develop methods for testing to accurately detect neurotoxic and behavioral effects of pesticides, and their ingredients," and "as such methods are developed, require to the extent appropriate and necessary that data from such testing be submitted by persons seeking to obtain or maintain pesticide registrations." This provision was not included in the amendments finally enacted, but the House Agriculture Committee's report on the bill that became law noted the deficiencies of EPA's current neurotoxicity testing and called for improvements:

> In light of recommendations made by a number of scientific and public health organizations urging expanded neurotoxic and behavioral testing, the Committee requests that EPA intensify the degree of such testing in its pesticide program, including testing related to chronic exposure, prenatal, and neonatal effects (26).

At present, scientists in OPP and OTS are working together to produce a set of revised neurotoxicity test guidelines (see ch. 5). The test guidelines will be accompanied by risk assessment guidelines to direct the scientific review of the data they provide (box 7-G).

Revision of the FDA's Red Book for Food and Color Additives

FDA's Center for Food Safety and Applied Nutrition has been considering the utility of specific tests for neurotoxic effects for several years. In

[9]The co-petitioners were the State of New York, the Wisconsin Public Intervener's Office, the Natural Resources Defense Council, the National Coalition Against Misuse of Pesticides, the Northwest Coalition for Alternatives to Pesticides, the American Psychological Association, the American Public Health Association, the Association of Children and Adults with Learning Disabilities, the U.S. Public Interest Research Group, and Drs. Philip J. Landrigan and Richard E. Letz, Mount Sinai School of Medicine.

Box 7-G-Flexibility in Neurotoxicological Testing

One controversy that has arisen with the introduction of neurotoxicity test guidelines by the Environmental Protection Agency (EPA) is the assertion by some scientists that test guidelines impose excessively rigid limitations on toxicological testing. These scientists, both inside and outside regulatory agencies, have stated that test guidelines result in testing that may ignore important parameters influencing a chemical's toxicity, preclude the effective use of expert scientific judgment, and stifle innovation in testing.

While acknowledging the validity of some of these objections, scientists favoring test guidelines have observed that the purpose of most toxicological testing in the regulatory context is not elucidation of mechanisms of toxicity, but rather clarification of the relative toxic hazards posed by various chemicals. (FDA's preclinical studies of drugs represent an exception to this generalization.) If toxicity test protocols are designed independently for each chemical under review, it becomes nearly impossible to compare chemicals.

Scientists with opposing views on this issue have also advanced arguments on practical grounds. Those opposed to test guidelines have stated that few contract laboratories have the capabilities to perform all of the neurotoxicological tests specified in the current EPA Office of Toxic Substances' guidelines. (However, scientists at contract testing laboratories have stated that they can implement any test procedures that are supported by an adequate market.) Opponents of test guidelines have also noted that the laboratories frequently lack an adequate set of control data to demonstrate the validity and reliability of tests. Regulatory scientists have noted that the requirements of Federal rule-making procedures would make designing new studies for each chemical of concern an extremely protracted process. (In practice, regulatory agencies have sometimes negotiated the performance of tests that differ substantially from those specified in the guidelines.)

One compromise (which has received extensive discussion but apparently little effort toward implementation) is the specification of test guidelines in terms of sensitivity. Sensitivity could be defined as the detection of effects of known toxicants (positive control studies) or as the detection of a specific decrease in neurological function (e.g., a 30-degree narrowing of the visual field). Such a specification would provide for both scientific judgment and consistency across tests of different agents.

In some areas of neurotoxicity testing, either form of sensitivity specification appears to be workable. This is the case for tests of basic sensory functions, because there is wide agreement among scientists on functional definitions, and probably also for various tests of motor function. It may also be possible to achieve consensus on the sensitivity of various approaches to neuropathological examinations. Tests of more complex neural function, such as learning, while amenable to specification in terms of positive control studies, provide much greater challenges to other forms of validation. There is still considerable debate concerning the validity of various measures of complex neural function (see ch. 5), and debates over the relative merits of test strategies are likely to persist for some time.

SOURCE: J.S. Young and W.R. Muir, ''Survey of Major Toxicology Testing Laboratories on the Use of Organ Function Tests in Toxicology,' prepared for the U.S. Environmental Protection Agency, EPA contract No. 68-024228, work assignment No. 121415, Washington, DC, September 1986.

September 1985, it sponsored a conference on ''Predicting Neurotoxicity and Behavioral Dysfunction from Preclinical Toxicologic Data, " administered by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology. At this conference, a panel of scientists from academia, industry, and government recommended a two-tiered approach to neurotoxicological evaluations: the first was a screening test, which included either a functional observational battery or a motor activity test, or both, with the use of structure-activity information as appropriate; the second contained more detailed tests, to be conducted on substances that produced neurotoxic effects during any of the fret-tier tests. (These tests are described in more detail inch. 5.) This approach is comparable to the screening required by EPA's OTS guidelines, although the FDA panel did not request direct neuropathological examination.

Since the 1985 meeting, CFSAN has continued to consider revision of the Red Book guidelines for testing of food and color additives. CFSAN scientists considered including some neurotoxicity tests but perhaps not the full range of tests specified in the OTS guidelines. FDA believes that, in order to impose additional testing requirements on industry, it must demonstrate that the tests would increase the

ability to detect neurotoxicants. CFSAN is seeking to demonstrate the utility of proposed neurotoxicity tests by supporting extramural research efforts that focus on neurochemical measures, animal behavior, and measurements of human performance.

The proposed CFSAN guidelines differ from the OTS guidelines in several respects. For example, FDA is reluctant to recommend screening tests that require specific instrumentation, because agency officials believe that requiring industry to procure potentially expensive new instruments would be difficult to justify if less expensive methods would produce adequate data. FDA is also reluctant to require specific neuropathological examinations as screening tests, instead reserving such studies, and behavioral studies requiring instrumentation, as second-tier tests for compounds that give indications of being neurotoxic. Finally, CFSAN is unlikely to include any structure-activity considerations in its proposed neurotoxicity guidelines. CFSAN has yet to develop a specific proposal for a set of neurotoxicity tests or for indicators requiring the performance of such tests.

Suggested Revisions of OECD Toxicity Testing Guidelines

In 1986, EPA, as the designated U.S. representative to the OECD committee for updating toxicity testing guidelines, suggested adding a mammalian neurotoxicity screening battery, which includes elements of the OTS functional observational battery, motor activity test, and neuropathology evaluation (see ch. 5). The new battery would be more generally used, while the OECD's current neurotoxicity guidelines, which specify hen tests, would be used for delayed organophosphate toxicity. In accordance with OECD updating procedures, the proposal was circulated to member countries for review. EPA subsequently revised the guidelines, and the complex OECD procedure for convening expert panels was begun.

CONSISTENCY OF FEDERAL REGULATION OF NEUROTOXIC SUBSTANCES

General Toxicological Considerations

There are numerous differences in regulatory practice under different laws, even within the group of licensing laws (FFDCA, FIFRA, and TSCA). For the most part, these differences do not apply specifically to the regulation of neurotoxic effects, but rather to regulation of all toxic effects. Thus, consistency of regulation for specific neurotoxic effects hinges on consistency of regulation in general (14).

Consistency of Regulatory Requirements

Statutory requirements for chemical regulatory programs differ in several important respects, among them the number of chemicals evaluated, the time available for review, the amount and type of data available at the beginning of the review process, the ability of the reviewer to acquire additional data after review has begun, and the burden of proof regarding safety. For example, the premanufacture notice process under TSCA necessitates review of hundreds of chemicals every year; each review is allotted only 90 days (although an extension is possible), and substantive toxicity data are rarely submitted. EPA can obtain additional data or impose controls on chemicals only if it finds that there may be an unreasonable risk associated with use of the chemical. Indeed, critics charge that the procedural complexities of TSCA incorporated in the statute impose a considerable administrative burden on EPA and render any action under the law difficult. In contrast, under FIFRA, applicants for registration of a pesticide must submit extensive toxicological data and follow specified test protocols, the review process extends over a period of years, the applicant is required to submit additional data if the basic data set raises concerns, and the applicant must establish that the pesticide will be both safe and effective under the proposed conditions of use. Thus, legislation is the root of some regulatory inconsistency, although there is little in legislative language that would preclude a significant increase in intra- and interagency cooperation and coordination.

Consistency of Protection

That there are differences in the degree of scrutiny under different regulatory programs is widely acknowledged. What is less certain is that these differences correspond to differences in the degree of protection offered by the laws and regulations. Often, these disparate requirements reflect real differences in the potential risks posed by the chemicals each program regulates. It maybe that the more intense scrutiny reserved for some types of chemicals is an appropriate reflection of the likeli-



Photo credit: U.S. Environmental Protection Agency

hood that they will harm human health or the environment.

Current laws are generally based on the premise that chemicals for which there is a greater probability of exposure should meet a higher standard of safety. This is most clearly illustrated by explicit prohibition of carcinogenic substances as direct food additives and of pesticides that become concentrated in foods [FFDCA Delaney clause, sec. 409(c)(3), 706(b)(5)(B)]. No such blanket prohibition applies to general industrial or commercial chemicals (regulated under the OSH Act and TSCA), in part because there is less certainty concerning the likelihood of human exposure to many of these chemicals. Some critics of the mechanisms by which industrial and commercial chemicals are regulated argue that these laws do not adequately protect the public's health.

The case is similar for chemicals causing noncarcinogenic toxic effects, which can be divided into chemical classes on the basis of both inherent hazard and expected level of exposure. Chemicals in commerce make up a vast universe—more than 60,000 identifiable chemicals are in EPA's inventory. Many of these chemicals may be present in industrial settings, and a large subset of them is present in consumer products. Pesticides, broadly defined, form a slightly smaller universe, but the number of active ingredients used on foods is much smaller (approximately 600). These differences in the size of chemical classes are reflected in the number of new members of each class introduced each year.

The stringency of the evaluation process for new chemicals under the various laws generally matches the presumption of risk-the combination of hazard and exposure potential-posed by each class and the number of new class members introduced each year. Thus, drugs are not to be permitted to enter the market until proven safe and effective in clinical trials. New pesticides and food additives are evaluated nearly as stringently; however, human trials are not performed. Commercial chemicals, whether intended for industrial or consumer use, receive the least scrutiny.

There are two exceptions to these trends, one minor and one significant. Consumer chemicals

have not received any procedurally different scrutiny than those intended for industrial use, despite the fact that larger numbers of persons may be exposed as consumers than as industrial workers. (EPA does take exposure patterns into account in evaluating chemicals in commerce.) Of much greater potential importance is the fact that cosmetics are not required to undergo premarket toxicity testing. Industry voluntarily tests cosmetics and cosmetic ingredients for acute toxic effects, but few are examined for chronic toxicity. Some have been found to have acute and chronic neurotoxic effects on laboratory animals.

While many scientists find some comfort in the observation that the stringency of review of a chemical matches its presumptive risk (except for cosmetics), public interest groups and others have voiced concerns over such odds playing. The transition of chemical regulation in general from "assurance of safety" to "acceptable risk" remains a source of contention (16). A less comforting observation, even to scientists, is that the stringency of review of a chemical is often inversely proportional to the size of the class of chemicals to be reviewed. For example, chemicals under TSCA make up the largest chemical class, yet they receive relatively little scrutiny under the normal premanufacture notice process. Critics of EPA argue that regulatory resource considerations and a desire not to burden industry, rather than presumptive risk, are in fact driving chemical review criteria. (Economic considerations in regulating toxic substances are discussed in ch. 8.) They raise the question of whether the minimal screening given the majority of chemicals is adequate to deal with high-risk chemicals that are not members of known risk categories (see box 7-H).

Regulation of New v. Existing Chemicals

Existing chemicals in each of the classes considered above are subject to varying degrees of review and reevaluation. In contrast to procedures for reviewing new chemicals, however, procedures for reexamining existing chemicals do not reflect the inherent risks of the chemical classes involved.



Photo credit: U.S. Environmental Protection Agency

EPA attempts to ensure the adequacy of data supporting continued pesticide registration through a regular review process. The registration standards program, which examines 25 chemicals per year, has thus far addressed only a small portion of the active ingredients of registered pesticides. At the present rate, active pesticide ingredients would be reviewed on an average of only once every 12 years. The 1988 FIFRA amendments mandated that the review schedule be accelerated so that *all* active ingredients are reviewed by 1997. To meet this goal, EPA will need to streamline its existing review process. Pesticides suspected of being associated with unusually high risks are examined through a separate special review program. EPA conducts special reviews of 12 to 15 chemicals per year, reaching final decisions on a third of them. Thus, it addresses only a small fraction of the (presumably) high-risk pesticides.

Under section 4 of TSCA, existing chemicals are ranked for probable risk or high exposures before they enter the test rule or consent decree process. In the period from 1977 to 1988, final rules were issued on only 25 chemicals or related sets of chemicals, and consent decrees were reached on three, with nine proposed rules pending. Clearly, these rules address only a very small fraction of the 60,000 chemicals in the TSCA inventory. Evidence that a chemical poses a significant risk must be reported to EPA under section 8(e), but no data need be developed to evaluate the risks of most chemicals. Further evidence comes from sections 8(c) and 8(d) provisions, which require that manufacturers maintain and make available to EPA records of adverse reactions and the results of unpublished toxicological investigations.

Box 7-H—TSCA's Premanufacture Notice Program: Is More Toxicity Testing Feasible?

The thousands of new industrial and consumer chemicals manufactured each year are typically subjected to far less toxicity testing and evaluation under the Toxic Substances Control Act (TSCA) than the smaller number of new pesticide, food additive, and pharmaceutical chemicals registered under other Federal laws. Although TSCA does require a premanufacture notice (PMN) process—all manufactures must notify the Environmental Protection Agency (EPA) before they can begin the commercial manufacture or importation of a new chemical-the statute does not demand that toxicity tests be conducted prior to notification. Consequently, few PMNs include any toxicity information, much less data from specific tests for neurotoxicity. EPA must review PMNs for nearly 2,000 new chemicals each year, and notwithstanding a paucity of data, EPA has only 90 or 180 days (depending on the type of chemical) to examine each PMN and determine whether the new chemical presents a significant risk.

TSCA does grant EPA the authority to require additional testing or to impose restrictions on the use of a new chemical if the Agency determines that the chemical will present an unreasonable risk. EPA has intervened in 10 to 20 percent of the PMNs reviewed annually to restrict the use of the chemicals; most of these actions have been aimed at lowering potential human exposure. In some cases, chemicals were withdrawn from consideration. In other cases, EPA has been successful in requiring manufacturers to conduct significant additional testing.

Critics have decried the lack of more comprehensive testing for this large set of chemicals. They argue that the public health cannot be adequately protected by the minimal testing conducted under TSCA. Why, they ask, doesn't EPA require more testing for toxic effects? It is not because the statute has proven defective: whenever EPA has intervened during PMN review, the Agency has prevailed. Nor is it because scientists in the Office of Toxic Substances (OTS)—the scientists responsible for reviewing PMNs—have substantially different views than their counterparts in other regulatory programs of what constitutes adequate testing.

Testing policies under TSCA are defended on the basis of practical reality: TSCA program officials rebut the charge of insufficient toxicity testing by arguing that the amount of testing being pursued under TSCA is all that can reasonably be required under the circumstances. They note that most new industrial and consumer chemicals have small, uncertain markets and that significant additional testing would cost more than the market for the chemical could cover—in effect banning the chemical based solely on a lack of information about it rather than on any concern or even suspicion about it. Furthermore, OTS scientists point out that EPA does take action against chemicals with high anticipated production volumes (and thus with substantial potential for human exposure) and chemicals suspected of causing adverse effects. Thus, they view the amount of testing of new chemicals being sought under TSCA to be the only feasible amount unless (or until) less expensive, reliable testing methods are developed that could reasonably be sought for a wider number of chemicals.

SOURCE: Office of Technology Assessment, 1990.

FDA's procedures for reviewing existing drugs and food and color additives are less formal than those for pesticides or toxic substances. The Center for Drug Evaluation and Research tracks physicians' reports of adverse drug reactions and relays them to the original evaluators of the drugs. Food and color additives have been notable exceptions to the review of existing chemicals. Until recently, there was no formal monitoring of adverse reactions after an additive was registered. For aspartame, CFSAN established voluntary reporting programs and subsequently requested that physicians and other health professionals inform it of any severe, well-documented reactions associated with foods, food additives, or dietary practices.

Although CFSAN does not require reporting on the use of approved food and color additives, it could track such information and use it to assess the risks associated with approved uses. Under the Priority-Based Assessment of Food Additives Program, a database on uses, levels in food, toxic effects, and chemical structure was created. This system should enable CFSAN personnel to compare new toxicity data to current use patterns or proposed changes in use and to search for predictive trends (e.g., correlations of particular functional groups with toxic effects). Without the ability to actively update information, however, this system may be of limited use for regulatory purposes.

Redundancy of Effort Among Agencies

The definitions of the classes of chemicals addressed in the various statutes have minimized redundancy of regulatory effort. While some chemicals have multiple uses and may be regulated under two or more different laws-e. g., pesticide compounds that also have industrial applications—the different uses dictate different risk evaluations. Under standard-setting and control-oriented laws, toxicity and risk evaluation are usually driven by considerations of probability of exposure; and differences in exposure potential probably preclude redundancy in the evaluation process. Although greater coordination among the standard-setting and control-oriented programs might be worthwhile, available evidence suggests that these programs devote relatively little effort to evaluating toxic hazards and much more to evaluating the risks posed by particular patterns of exposure.

Integration of Effort

EPA is the only regulatory agency discussed in this chapter responsible for implementing a number of very different laws. Other agencies considered in this chapter address only one law or a few closely related laws. The division of labor among regulatory agencies raises the question of how well regulatory efforts are being integrated within and between agencies.

EPA, which is charged with implementing seven regulatory programs under eight of the laws reviewed, does appear to be actively engaged in integrating regulation. Although some integration efforts have been initiated by legislation, the Agency has undertaken a number of initiatives on its own in the recent past. For example, OTS issued a section 4 test rule on chemicals referred by the Office of Solid Waste Management under CERCLA; MCLGs and MCLs have been issued for hazardous waste chemicals that might affect drinking water, even if they have rarely been detected in drinking water; and the drinking water priority list for regulation explicitly includes both pesticides and chemicals listed for priority review under SARA, Another example of recent efforts in regulatory integration is the attempt to produce consistent neurotoxicity test guidelines for both pesticides and toxic substances. Also, EPA is working to consolidate all its risk assessment information into the Integrated Risk Information System (IRIS). Finally, the creation of a discrete Regulatory Integration Division in EPA's Office of Program Planning and Evaluation suggests a commitment to consistent regulation. The creation of a formal neurotoxicity working group, which would indicate an EPA commitment to regulatory integration for the specific concern of neurotoxicity, has been proposed.

There is less evidence of attempts at regulatory integration across Federal agencies than within EPA. There is some collaboration on research but little coordination of regulatory efforts (see app. B). This may be due, in part, to the different-and sometimes conflicting-statutes. Legal requirements for dealing with confidential business information pose barriers to sharing data in some cases; more important is the focus of agency personnel on internal priorities, which does not foster interagency cooperation. The apparent lack of coordination is sometimes quite striking. For example, NIOSH is required by Congress to recommend exposure limits

for OSHA, but OSHA has rarely acted on those recommendations. In its recent rule, OSHA showed a decided preference for values recommended by the ACGIH, despite the fact that NIOSH had established recommended exposure levels (RELs) for 5 of the 20 compounds listed as neuropathic and that four of the five were lower than ACGIH's TLVs. OSHA would be expected, in some cases, to set PELs that were higher than NIOSH's RELs, based on technological and economic feasibility. ACGIH TLVs, however, are derived by a completely different process. OSHA appears to be giving equal or greater weight to the views of a private organization than to those of the agency created to supply it with health assessments.

Specific Neurotoxicological Considerations

Regulatory differences in general strategies for evaluating toxicity entail corresponding differences in the evaluation of neurotoxic effects. Thus for human therapeutic drugs, preclinical toxicity tests are used only to guide observations on clinical trials and to elucidate possible mechanisms of toxicity rather than to assess toxic potential directly. For pesticides and food and color additives, in contrast, animal toxicity data are used directly in predicting human risk. However, even within programs that have essentially similar approaches to assessing toxic risks, there are differences with respect to consideration of neurotoxic risks.

Consistency of Protection

Regulatory programs have adopted one of three basic approaches to toxicity evaluation, depending on which of three underlying assumptions they hold. One approach is based on the assumption that general toxicity tests using high doses are adequate to detect neurotoxic potential and that specific neurotoxicological evaluations are needed only if general tests, data on structural analogs, or other specific knowledge about a chemical indicates a potential for neurotoxicity. Among these are FDA's preclinical testing program for drugs and its current program for approving food additives. The second approach, represented by the pesticide registration program under FIFRA, accepts more general structural information in guiding neurotoxicity testing. All organophosphorous compounds are evaluated for their potential to induce delayed neuropathy, but nonorganophosphorous compounds are not specifically evaluated for neurotoxic potential. All pesticides undergo a general toxicity screen; however, specific neurotoxicity tests are not conducted. Finally, under section 4 of TSCA, specific neurotoxicity testing is required for any chemical with high exposure potential, as well as for chemicals specifically suspected of being neurotoxic. Such testing presumes that standard toxicity tests are not adequate to evaluate neurotoxic effects.

OTA found that Federal efforts to control neurotoxic substances vary considerably between agencies and between programs within agencies. Improving the Federal response will require increased neurotoxicity testing, improved monitoring programs, and more aggressive regulatory efforts.

Whether these different testing procedures correspond to different levels of protection depends entirely on which assumption regarding the sensitivity of standard toxicological tests is correct. Scientists inside and outside of Federal regulatory agencies have expressed a range of opinions regarding the desirability of singling out neurotoxicity as an effect of concern. Many argue that neurotoxic effects cannot be identified without undertaking specific tests. Others argue that there is no more justification for including neurotoxicity tests than for including immunotoxicity (immune system), cardiotoxicity (heart), hepatotoxicity (liver), nephrotoxicity (kidney), or other organ system tests as part of a standard test battery. These scientists believe that general test protocols in which high doses are used will be sensitive *detectors,* if not elucidators, of neurotoxicity. Other scientists argue that potential noncancer health effects in general receive too little scientific and regulatory attention and believe that greater emphasis should be placed on all noncancer health risks.

There is a correlation between the opinions expressed and the actual testing approach of the program in which a particular scientist works. The wide diversity of opinions expressed by knowledgeable scientists reflects individual views on the extent to which existing regulatory programs are protecting public health and the environment from noncancer health risks.

In principle, a study to evaluate whether neurotoxicity testing detects effects that would be missed by conventional toxicity tests is easy to design. However, to be truly predictive for regulatory purposes, such a study would have to address a large number of toxicologically dissimilar compounds. No such study has yet been designed. FDA did sponsor a

review of whether conventional toxicity testing was adequate for the prediction of neurotoxic potential (18). This review consisted of the deliberations of an ad hoc expert panel and a symposium. The panel concluded that explicit neurotoxicological evaluations should be incorporated into toxicity testing, using a tiered-testing scheme. However, its report did not present objective evidence of improvements in test sensitivity as a result of neurotoxicological testing.

As part of its effort to develop neurotoxicity test guidelines, OTS sponsored a retrospective comparison of neurotoxicity tests with standard toxicity tests for chemicals inducing narcosis, as well as a comparison of acute and chronic neurotoxicity tests that addressed a somewhat broader range of chemicals (7,8). The choice of chemicals that induce narcosis tends to bias the comparison in favor of conventional tests, because this effect is relatively easy to detect.

The OTS-sponsored studies found greater sensitivity in acute tests when specific neurotoxicological evaluations were performed-i. e., the lowest observed effect levels were lower for a majority of the 25 compounds evaluated (effects in humans were reported at even lower levels). Considerably greater sensitivity was shown by repeated-dose studies. Some compounds produced qualitatively different neurotoxic effects after repeated dosing, and others showed irreversible effects after repeated, but not acute, tests. Quantitative extrapolation from acute tests was found to underpredict toxicity from repeated exposures. The OTS studies suggest that conventional toxicity tests, especially acute high-dose tests, are not an adequate substitute for neurotoxicological evaluations. The validity of this conclusion for a broader range of compounds has not yet been established.

Coordination Among Agencies

Interviews with toxicologists and neurotoxicologists in various Federal agencies indicated that there has been, until recently, little formal coordination among agencies (see app. B). Regulatory scientists are generally aware of the views of their colleagues in other agencies. There are also several coordinated research efforts mediated by interagency agreements and by personal contact.

Contact among neurotoxicologists at different Federal agencies has not, however, fostered any unanimity of opinion on the best approach to regulating neurotoxic hazards. Real differences of scientific opinion remain, and data that would resolve these differences have not been developed by the agencies involved. Moreover, even within agencies, neurotoxicologists and other toxicologists sometimes disagree on the proper role of neurotoxicity in safety evaluations.

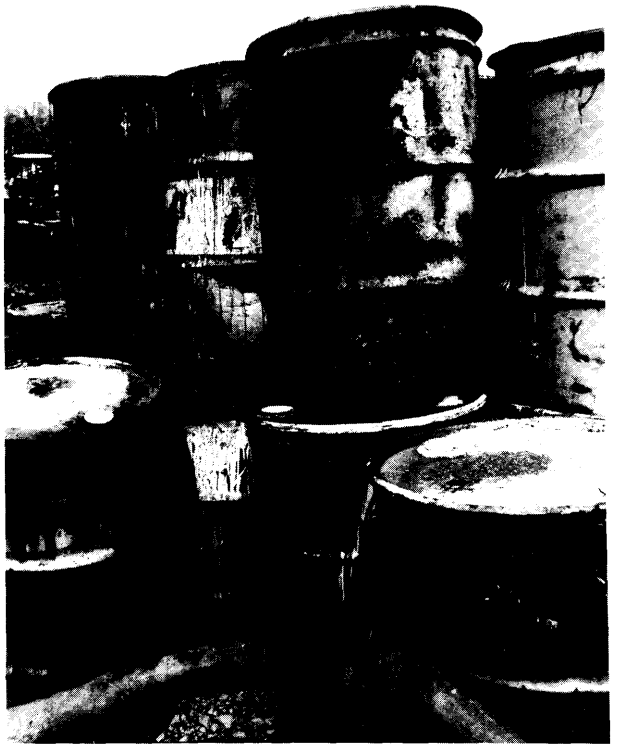

Photo credit: U.S. Environmental Protection ***Agency***

An agency's approach to evaluating neurotoxicity often corresponds to the presence or absence of neurotoxicologists on its staff. Although this presumably reflects personnel considerations-if an agency is not evaluating neurotoxicological data, it does not require people trained to do so-it does raise the question of whether persons who evaluate general toxicological data understand the contributions of directed testing to the prediction of neurotoxic effects. General toxicologists are essential to the review process, but individuals with specialized expertise are often necessary to ensure a comprehensive evaluation. Variations in the perceived need for staff neurotoxicologists reflect a more general problem of toxicological assessment, that of determining the appropriate degree of specialization required to

evaluate the many organ systems potentially affected by a toxic substance.

The Federal regulatory response to neurotoxicity is fragmented not only by differences in scientific judgment, but also by differences in regulatory responsibility. The decision to evaluate drugs, pesticides, and food additives by stricter standards than are applied to commercial chemicals is not based on the views of scientists in regulatory agencies, but on national consensus, as expressed through Congress.

The Value of Establishing a Minimal Data Set

The most striking difference in regulatory programs is between those that require routine testing of all chemicals submitted for review and those that must establish some probability of unacceptable risk in order to require the manufacturer to submit data. These differences tend to reflect both a legislative consensus regarding the hazards posed by different classes of chemicals and the sheer number of chemicals in each class that require review. If neurotoxic effects of chemicals are difficult to predict, it might follow that any regulatory scheme that does not routinely test for neurotoxicity offers diminished or insufficient protection.

If no changes are made in the laws with respect to which kinds of chemicals do and do not require premarket testing, the issue becomes one of whether there is a sound reason to require comparable tests in the several programs that already require premarket testing. Scientists charged with reviewing toxic hazard data in the various programs disagree over the desirability of standardized test guidelines in general, and standardized neurotoxicity evaluations in particular. EPA scientists have argued that standardization provides a distinct advantage for comparing the hazards posed by disparate chemicals, while FDA scientists counter that it is more appropriate to design specific tests to assess expected toxic effects.

These arguments reflect real differences between programs and the power to compel extensive testing. FDA's Center for Drug Evaluation and Research has perhaps the broadest power to compel testing, both preclinical and clinical, and is one of the strongest advocates for flexibility in testing. On the other hand, OTS must undertake arduous rule-making procedures to issue test rules and must carry out protracted negotiations to obtain consent decrees; it is, perhaps, not surprising that OTS was the first regulatory program to issue extensive neurotoxicity testing guidelines. The presence of established guidelines diminishes the number of testing issues that have to be argued in each rule-making or negotiation. The legal constraints on OTS—companies need not conduct any testing beyond what OTS explicitly rules-have favored a more rigid and explicit approach to testing requirements.

There seems to be general, if not complete, agreement among regulatory toxicologists that specific neurotoxicological evaluation is valuable, once evidence of neurotoxicity has been detected. There is also general agreement that such detailed evaluation should not be specified too rigidly but should allow for flexibility in designing tests to fit particular chemicals and to address particular questions.

ADEQUACY OF THE FEDERAL REGULATORY FRAMEWORK

It is important to bear in mind that regulations have implications reaching far beyond the letter of the law. Thus, measuring regulatory effectiveness is only one aspect of gauging the broader set of regulatory *impacts.* For example, regulations impose direct or indirect costs on industry that affect how industry conducts its business. These considerations are addressed in more detail in chapter 8.

Measurements of Effectiveness

Any attempt to measure the success of Federal regulatory agencies in evaluating and controlling the neurotoxic risks posed by chemicals depends on having an independent measure of neurotoxic risks. Finding such a measure is difficult. Two alternatives are considered here. The frost is to compare the proportion of chemicals detected and controlled as neurotoxic substances by Federal regulatory programs to estimates of the proportion of chemicals likely to have neurotoxic effects. The second is to examine evidence of regulatory failures-i. e., misses and false positives.

Expected and Detected Neurotoxicity

It is possible, for at least some regulatory programs, to estimate how many of the chemicals evaluated were reviewed for neurotoxic potential or identified as posing neurotoxic risks. Thus, in the premanufacture notice program under TSCA, approximately 220 chemicals (4 percent of the approximately 5,500 chemicals reviewed during the life-

time of the law) have raised sufficient concern regarding neurotoxicity to merit standard review. Of the 220 chemicals receiving this detailed evaluation, 180 were judged to pose neurotoxic hazards, although in many cases other hazards were judged to be more significant. Due to exposure limitations, only 120 were judged to pose neurotoxic risks. Of these, neurotoxicity was the driving concern in approximately 12 cases.

It is difficult to establish whether the PMN process is truly effective in assessing neurotoxic risk. Generally, toxicity data to confirm the PMN predictions are not available. Reports of significant risk submitted under section 8(e) could be used to identify regulatory failures resulting from inadequate review, but because chemical identities are often claimed to be confidential business information, they are open only to internal scrutiny (see box 7-D).

Of the high-hazard or high-exposure chemicals reviewed under section 4 of TSCA, 19 have been considered for neurotoxicity evaluation since the neurotoxicity test guidelines were issued; three of these were judged not to require neurotoxicity testing during the rule-making or consent decree process. Three additional chemicals were proposed for neurotoxicity testing prior to publication of the test guidelines; one was the subject of negotiated testing, a second was the subject of testing by another program office, and a proposed test rule is under development for the third. Of the chemicals for which the Interagency Testing Committee recommended neurotoxicological evaluation, EPA disagreed on the need for such testing in only two cases; in eight other cases, either testing was in progress or potential exposures were determined to be minimal.

The chemicals evaluated for neurotoxic effects represent a substantial fraction of the total number of chemicals tested under section 4 of TSCA. There are 25 final test rules, seven of which include neurotoxicity testing; nine pending proposed rules, five of

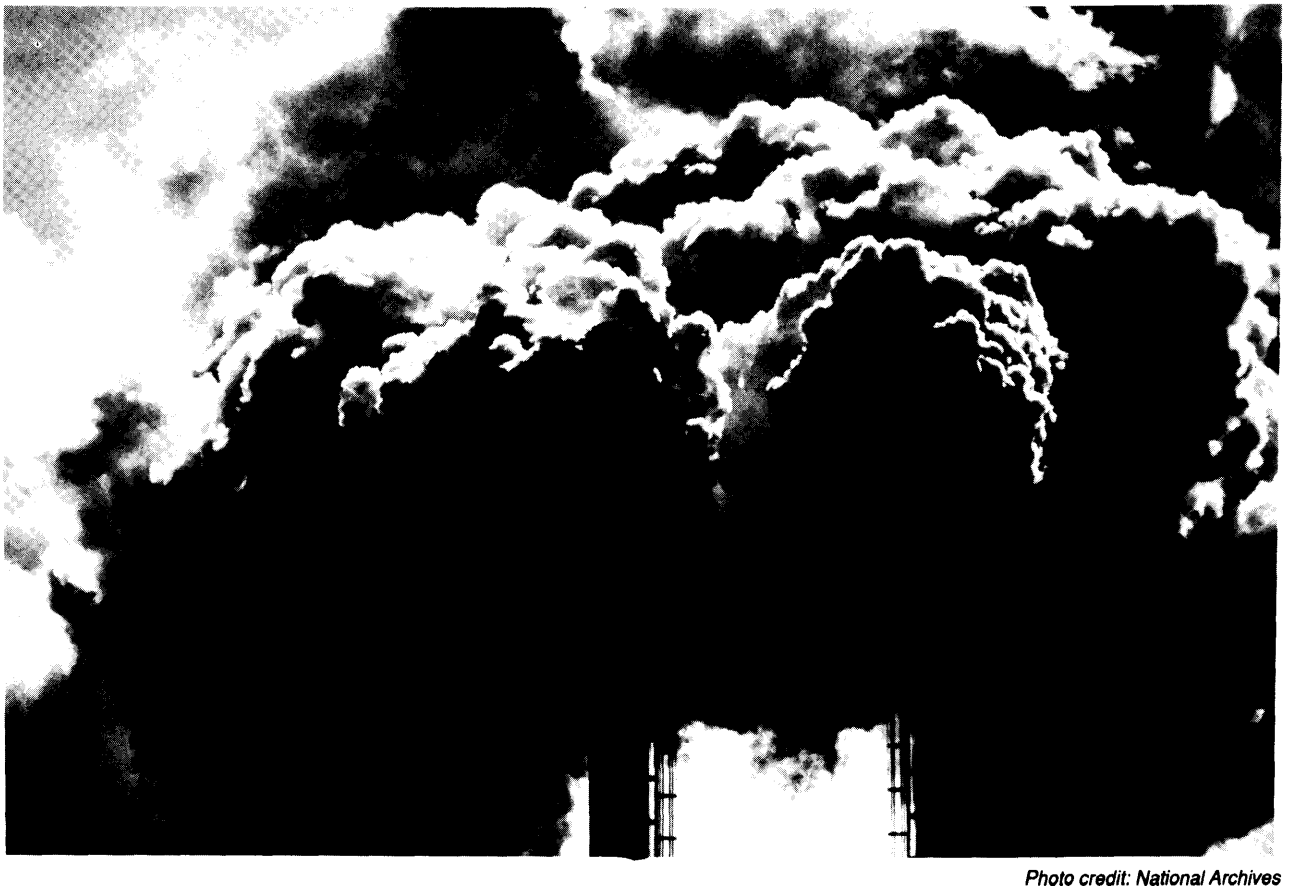

Photo credit: National Archives

which include neurotoxicity; and three consent decrees, two of which include neurotoxicity.

It is more difficult to gauge the extent of neurotoxicity testing conducted under FIFRA.While annual registration totals are available, OPP tracking systems are not yet able to determine the number of chemicals evaluated for adequacy of neurotoxicological data. Only EPN and acrylonitrile could be identified as chemicals for which regulatory action was taken on the basis of neurotoxicity. Other pesticides are being evaluated for neurotoxicity, and data call-ins have been issued, but EPA does not have any accessible record of such data call-ins.

Applications for approximately 330 commercial investigational new drugs are presented to FDA every year; approximately 20 percent of these are eventually approved. In recent years, perhaps 16 percent of the applications submitted have involved neuropharmacological agents. Of the 54 neuropharmacological agents for which FDA reviewed IND applications in 1988, nine were put on hold, two of these because of concerns regarding their toxicity. Only one of these was judged to be neurotoxic.

The FDA annually reviews approximately 60 indirect food additives, 10 direct food additives, and 10 color additives. Many of these involve potential exposures sufficiently low that only the most basic toxicity studies are performed. In the past 5 years, only three chemicals have raised sufficient concern regarding neurotoxic effects to be reviewed by the neurobehavioral toxicity team; this represents less than 1 percent of all applications received.

Under standard-setting or control-oriented legislation, it is not always possible to estimate accurately the proportion of chemicals regulated for neurotoxic concerns, both because the number of chemicals regulated is small and because these laws address chemicals already determined to pose excessive risks. The latest rule proposed by OSHA on permissible exposure limits clearly considers a large number of chemicals (more than 400). Of the approximately 300 for which a basis for a limit was explicitly stated, 20 were indicated as causing nerve damage and 19 as inducing drowsiness. Some neurotoxic chemicals (e.g., methanol) are included in lists for ocular effects, and the list of chemicals regulated for biochemical or metabolic effects includes eight chemicals (out of 26) that inhibit, either directly or indirectly, the production or activity of cholinesterase.

Interpretation of these percentages depends on the proportion of chemicals that would be expected to have neurotoxic effects. Estimates of this proportion have been made by several authors, and they vary widely. For example, Anger and Johnson estimate that there are more than 850 known neurotoxic chemicals (4). Anger (3) reported that 167 of the 588 TLVs promulgated by the ACGIH in 1982 were based at least in part on neurotoxic effects, while Bass and Muir (9) determined that 202 of the 605 TLVs promulgated in 1984-1985 met a similar criterion. In contrast, O'Donoghue (21), summarizing basic toxicity data obtained from Kodak for 448 high-volume chemicals, found only 12 to have primarily neurotoxic effects. Of the 167 chemicals listed by Anger, O'Donoghue found only 28 to have neurodegenerative effects. Differences such as these are also due in part to differing views regarding the definition of neurotoxicity. The estimates given above are not necessarily incompatible. For one thing, they reflect different starting sets of chemicals. For example, ACGIH lists all chemicals for which *some* toxic effect has been noted at or near potential levels of exposure.

Monitoring Mechanisms

An alternative approach to assessing the effectiveness of regulatory programs in controlling neurotoxic hazards is to evaluate the rate of regulatory failure. Unfortunately, while several of the licensing programs have procedures that enable them to track chemicals after approval, these programs have not generally been used to assess the adequacy of the original decisionmaking process.

The registration standards program under FIFRA is aimed at identifying deficiencies in data that resulted from earlier regulatory practice and assumes that current registration practices are appropriate. Reports of adverse reactions to drugs under FFDCA consider a wide range of adverse effects but are generally used on a chemical-specific basis.

Under TSCA, EPA receives and evaluates reports that may indicate significant risks of chemicals in commerce, some of which have been subject to PMN review. These data have not been regularly used to assess the adequacy of the PMN process. EPA has, however, acknowledged the need to review this process. Because EPA is forced to rely substantially on structure-activity analysis, rather than experimental data, in predicting the risks posed

by new chemicals, it has a particularly active interest in assessing the accuracy of its efforts. In 1984, a study was designed to obtain data on a small sample of PMN chemicals that would be representative of chemicals with the highest expected risk (those with intrinsic hazard and high exposure); of these data would be compared with the results of PMN risk assessments to yield an estimate of the accuracy of the PMN process. Unfortunately, although the study was proposed in five versions spanning a wide range of costs, not even the least expensive variant of the study was funded.

Many other statutes, including FFDCA, FIFRA, OSH Act, and the Consumer Product Safety Act, contain similar provisions for reporting adverse effects of chemicals. Any of these reporting requirements could potentially be used to track regulatory effectiveness.

Because EPA is testing chemicals with high production levels (100,000 kilograms in the third year of production) and expectations of significant human exposure, it will be obtaining some data with which to evaluate the accuracy of PMN assessments. These tests will include a functional observational battery and neuropathological measurements, but they will only be carried out for a long enough period of time to measure subchronic effects. This set of tests, taken together, may indicate how the structure-activity predictions used in PMN assessments compare to assessments that have at least a minimal data set.

SUMMARY AND CONCLUSIONS

It is the task of regulatory agencies to limit public exposure to toxic chemicals through programs mandated by law. Because of the great diversity of toxic substances, many statutes exist to control their use. These laws are administered by various Federal agencies, but primarily by EPA, FDA, and OSHA.

New and existing industrial chemicals are regulated by TSCA. Pesticides are controlled by FIFRA, and toxic substances in the workplace are regulated by the OSH Act. The FFDCA regulates food and food additives, drugs, and cosmetics. These laws address the vast majority of toxic substances, and more than a dozen other acts focus on other substances and sources of exposure. Although neurotoxicity is generally not explicitly mentioned in legislation mandating the regulation of toxic substances, it is implicitly included as a toxicity concern.

Regulatory differences in general strategies for evaluating toxicity entail corresponding differences in the evaluation of neurotoxic effects. Thus for human drugs, preclinical toxicity tests are only used to guide observations on clinical trials and to elucidate possible mechanisms of toxicity, rather than to directly assess toxic potential. For pesticides and food and color additives, in contrast, animal toxicity data are used directly in predicting human risk,

Regulatory programs have adopted one of three basic approaches to neurotoxicity evaluation, depending on which of three underlying assumptions they hold. One approach is based on the assumption that general toxicity tests using high doses are adequate to detect neurotoxic potential and that neurotoxicological evaluations are needed only if general tests, data on structural analogues, or other specific knowledge about a chemical indicate a potential for neurotoxicity. Among these are FDA's preclinical testing program for drugs and its current program for approving food additives. The second approach, represented by the pesticide registration program under FIFRA, accepts more general structural information in guiding neurotoxicity testing. All organophosphorous compounds are evaluated for the potential to induce delayed neuropathy, but nonorganophosphorous compounds are not specifically evaluated for neurotoxic potential. All pesticides undergo a general toxicity screen; however, specific neurotoxicity tests are not conducted. Finally, under section 4 of TSCA, specific neurotoxicity testing is required for any chemical with high exposure potential, as well as for chemicals specifically suspected of being neurotoxic. Such testing presumes that standard toxicity tests are not adequate to evaluate neurotoxic effects.

Critics of the regulatory framework voice concern over the odds playing they see in the current process. For example, the chemicals regulated under TSCA make up the largest classes of chemicals, yet they receive relatively little scrutiny by EPA. TSCA does offer options for selecting high-risk chemicals for further scrutiny, but the vast majority of chemicals receive only a limited review. Without significant toxicity data, predicting risk is difficult and must rely on hypothetical relations between chemical structure and biological activity. However, little is

known about structure-activity relationships with respect to neurotoxicity. Critics of EPA raise the question of whether the minimal screening given to the majority of chemicals is adequate to deal with high-risk chemicals that are not members of well-understood risk categories.

OTA found that Federal efforts to control neurotoxic substances varied considerably between agencies and between programs within agencies. This response is fragmented not only by differences in scientific judgment, but also by differences in regulatory responsibility. Moreover, the decision to evaluate drugs, pesticides, and food additives by stricter standards than are applied to commercial chemicals is based not only on the views of scientists, but also on national consensus. Thus, improving the effectiveness of Federal programs depends on many factors, including more public awareness, greater involvement by neurotoxicologists in regulatory program offices, increased neurotoxicity testing, and improved monitoring programs.

CHAPTER 7 REFERENCES

1. Aidala, J., "Pesticide Issues: Reauthorization of Public Law 92-516," Congressional Research Service Issue Brief No. IB87192 (Washington, DC: Library of Congress, Congressional Research Service, 1988).
2. American Conference of Governmental Industrial Hygienists, *Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH for 1985-1986* (Cincinnati, OH: 1985).
3. Anger, W. K., "Neurobehavioral Testing of Chemicals: Impact on Recommended Standards, " *Neurobehavioral Toxicology and Teratology* 6:147-153, 1984.
4. Anger, W. K., and Johnson, B. L., "Chemicals Affecting Behavior, ' *Neurotoxicity of Industrial and Commercial Chemicals,* J.L. O'Donoghue (cd.) (Boca Raton, FL: CRC Press, 1985), vol. 1, pp. 51-148.
5. Auer, C., Deputy Director, Health and Environmental Review Division, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, personal communication, Oct. 24, 1988.
6. Auer, C., and Gould, D., "Carcinogencity Assessment and the Role of Structure Activity Relationship (SAR) Analysis Under TSCA Section 5 *Environment and Carcinogen Reviews 5, 1987.*
7. Bass, B. F., Muir, W.R., and Young, J. S., "Neurotoxicity Science Issue Reports, Task 1: Acute Exposure Tests," prepared for the U.S. Environmental Protection Agency, EPA contract No. 68-01-6554, work assignment No. 40127, Washington, DC, February 1985.
8. Bass, B. F., Muir, W.R., and Young, J. S., "Neurotoxicity Science Issue Reports, Task 2: Acute Exposure v. Repeated Exposure Tests, " prepared for the U.S. Environmental Protection Agency, EPA contract No. 68-01-6554, work assignment No. 40127, Washington, DC, February 1985.
9. Bass, B. F., and Muir, W. R., "Summary of Federal Actions and Risk Assessment Methods Relating to Neurotoxicity," prepared for the U.S. Environmental Protection Agency, EPA contract No. 68-02-4228, Washington, DC, March 1986.
10. Center for Science in the Public Interest, 'Petition for Neurobehavioral Teratology Testing of Neuroactive Drugs, " draft of petition prepared for possible submission to the Food and Drug Administration, Washington, DC, September 1987.
11. Environmental Monitoring and Services, ''Technical Background Document to Support Rulemaking Pursuant to CERCLA, Sec. 102, Volume I,' prepared for the U.S. Environmental Protection Agency, EPA contract No. 68-03-3182, March 1985.
12. Grad, F.P., "A Brief Account of the Beginnings of Modern Environmental Law, ' *Treatise On Environmental Law, sec.* 1.01 (St. Paul, MN: Matthew Bender, 1985).
13. Grad, F. P., "Pesticide Pollution-Labeling and Misbranding, *Treatise On Environmental Law, sec. 8.03.4* (St. Paul, MN: Matthew Bender, 1985).
14. Hampshire Research Associates, Inc., "The Federal Regulatory Response to the Problem of Neurotoxicity, ' prepared for the Office of Technology Assessment, Washington, DC, Dec. 1, 1988.
15. Hattan, D. G., Henry, S. H., Montgomery, S. B., et al., "Role of the Food and Drug Administration in Regulation of Neuroeffective Food Additives, " *Nutrition and the Brain 6:31-99, 1983.*
16. Hutt, P. B., "Risk Assessment: The First Fifteen Years and the Next Fifteen Years, " lecture at The Brookings Institution, Washington, DC, Nov. 22, 1988.
17. "Lead Industries Association, Inc. v. The U.S. Environmental Protection Agency," *Federal Reporter* (2d series) 647:1130-1189, 1980.
18. Life Sciences Research Office, *Predicting Neurotoxicity and Behavioral Dysfunction From Preclinical Toxicologic Data* (Bethesda, MD: Federation of American Societies for Experimental Biology, 1986).
19. Merrill, R. A., and Schewel, M., "FDA Regulation of Environmental Contaminants of Food, " *Virginia Law Review 66:1357-1441, 1980.*
20. Muir, W. R., former director, Office of Toxic Substances, U.S. Environmental Protection Agency, and President, Hampshire Research Associates, personal communication, December 1988.

21. O'Donoghue, J.L. (cd.), *Neurotoxicity of Industrial and Commercial Chemicals* (Boca Raton, FL: CRC PRESS, 1986), vol. 2, pp. 7-92.
22. Padgett, J., and Richmond, H., "The Process of Establishing and Revising National Ambient Air Quality Standards," *Journal of the Air Pollution Control Association 33:13-16, 1983.*
23. Pharmaceutical Data Services, "Top 200 Drugs of 1989," *American Druggist, in* press.
24. Rees, C., U.S. Environmental Protection Agency, personal communication, Mar. 30, 1989.
25. Reiter, L.W., "Neurotoxicology in Regulation and Risk Assessment" *Developmental Pharmacology and Therapeutics 10:354-368, 1987.*
26. U.S. Congress, House of Representatives, Committee on Agriculture, "Report on H.R. 939," 100th Cong., 2d sess., 1988, p. 33.
27. U.S. Congress, Office of Technology Assessment, *Preventing Illness and Injury in the Workplace, OTA-H-256* (Washington, DC: U.S. Government Printing Office, 1985).
28. U.S. Department of Health, Education, and Welfare, Air Quality Criteria for Carbon Monoxide, AP-62 (Washington, DC: 1980).
29. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, *Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration,* DHHS Pub. No. (FDA) 85-1115 (Washington, DC: U.S. Government Printing Office, 1984).
30. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Food Safety and Applied Nutrition, *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food* (Washington, DC: 1982).
31. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Food Safety and Applied Nutrition, *Daily Operating Guide, HFF-2440.9* (Washington, DC: 1980).
32. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Psychopharmacological Drugs Advisory Committee, *Transcript of Proceedings, Thirty-First Meeting* (Rockville, MD: September 1989).
33. U.S. Environmental Protection Agency, "National Interim Primary Drinking Water Regulations," EPA No. 570/9-76-003, app. A (Washington, DC: Office of Water Supplies, 1976).
34, U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Chlorinated Benzenes, EPA 440/5-80-028, Office of Water Regulations and Standards, Washington, DC, October 1980.
35. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Endosulfam, EPA 440/5-80-046, Office of Water Regulations and Standards, Washington, DC, October 1980.
36. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Dichlorobenzenes, EPA 440/5-80-039, Office of Water Regulations and Standards, Washington, DC, October 1980.
37. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Halomethanes, EPA 440/5-80-051, Office of Water Regulations and Standards, Washington, DC, October 1980.
38. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Heptachlor, EPA440/5-80-052, Office of Water Regulations and Standards, Washington, DC, October 1980.
39. U.S. Environmental Protection Agency, Ambient Water Quality criteria for lead, EPA 440/5-80-057, Office of Water Regulations and Standards, Washington, DC, October 1980.
40. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Mercury, EPA 440/5-80-058, Office of Water Regulations and Standards, Washington, DC, October 1980.
41. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Toluene, EPA 440/5-80-075, Office of Water Regulations and Standards, Washington, DC, October 1980.
42. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Tetrachloroethylene, EPA 440/5-80-073, Office of Water Regulations and Standards, Washington, DC, October 1980.
43. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for Thallium, EPA 440/5-80-074, Office of Water Regulations and Standards, Washington, DC, October 1980.
44. U.S. Environmental Protection Agency, Ambient Water Quality Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin, EPA 440/5-84-007, Office of Water Regulations and Standards, Washington, DC, February 1984.
45. U.S. Environmental Protection Agency, *Mercury Health Effect Update: Health Issue Assessment,* EPA 600/8 -84-019F (Research Triangle Park, NC: Office of Research and Development, August 1984).
46. U.S. Environmental Protection Agency, Office of Pesticide Programs, *Pesticide Assessment Guidelines, Subdivision F--Hazard Evaluation: Human and Domestic Animals,* EPA Pub. No. 540/9-82-025 (Washington, DC: 1982),
47. U.S. Environmental Protection Agency, Office of Pesticide Programs, ''Pesticide Label Utility Project Report," unpublished draft, April 1986.
48. U.S. Environmental Protection Agency, Office of Public Affairs, *Pesticides Fact Book,* EPA Pub. No. A-107/86-003 (Washington, DC: 1986).
49. ''When Sleep Becomes A Nightmare,' 20/20, ABC, Feb. 17, 1989.

50. Young, J. S., and Muir, W. R., "Survey of Major Toxicology Testing Laboratories on the Use of Organ Function Tests in Toxicology, ' prepared for the U.S. Environmental Protection Agency, EPA contract No. 68-024228, work assignment No. 121415, Washington, DC, September 1986.

Chapter 8

Economic Considerations in Regulating Neurotoxic Substances

'The higher environmental issues rise on the national agenda the more important it is that we have the best possible knowledge of the economic costs of undertaking particular environmental programs *and the costs* associated with *not* undertaking them. "

Russell E. Train
Remarks at the Library of Congress
October 18, 1989

"Although conventional regulatory policies have often worked well, they have also tended to pit economic and environmental goals against each other. These goals should complement one another in the long run if either of them is to be achieved. '

Robert N. Stavins
Environment, vol. 31, No. 1
February 1989

"One of the problems in relating economic health and environmental health is that the nation has not developed a quality of life index that measures both. Environmental health factors such as morbidity and mortality, crop and forest damage, soil erosion, air and water pollution, and aesthetic degradation are given little attention compared to such economic health factors as Gross National Product (GNP) and unemployment. Much work needs to be done to develop and use more comprehensive measurements of quality of life. "

An Environmental Agenda for the Future, Island Press, 1985

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Chapter 8

Economic Considerations in Regulating Neurotoxic Substances

The fundamental economic consideration in regulating neurotoxic substances involves balancing the economic benefits of utilizing these substances commercially against their actual or potential risks to human health and the environment. The economic benefits include the reduced cost and increased productivity brought about by drugs, pesticides, and chemicals in health care, agriculture, and industry. The risks are the probabilities of increased morbidity, mortality, and environmental contamination stemming from uncontrolled or excessive uses of these substances (35).

Regulations designed to reduce or prevent neurotoxic risks can benefit society by improving public health and the environment. Inmost cases, however, government and the private sector incur costs in order to achieve these ends. The costs of regulatory compliance may give rise to a number of additional economic impacts, such as increases in market prices, reductions in industry profits, and declines in new product innovation. The problem of balancing benefits, costs, and risks of regulation is not unique to the control of neurotoxic substances; it arises in all forms of health, safety, and environmental regulation.

Many of the key Federal laws under which neurotoxic substances are regulated require agencies to ascertain the positive and negative economic consequences of regulation (see box 8-A). In implementing these laws, Congress has generally intended that agencies prepare regulatory analyses[1] and document the balancing of benefits, costs, and risks of proposed alternatives. It is important to note, however, that Congress typically has not set priorities for the various economic issues arising from regulation, nor has it specified the analytical criteria or procedures that agencies must follow in evaluating the economic impacts of regulation.

The preparation of regulatory analyses of proposals to control neurotoxic substances is a two-step process. The first step, risk assessment, involves assessing the health and environmental risks posed by various levels of exposure to these substances. Risk assessment provides a scientific basis for regulatory analyses. The second step, risk management, is the end for which risk assessment is conducted (see ch. 6).

One economic consideration in conducting risk assessments is the costs and benefits of acquiring the reliable scientific and technical data needed to regulate neurotoxic substances. Many of these data must be obtained through animal toxicity tests. Two recent evaluations of Federal efforts to regulate neurotoxic substances concluded that there is a need for more neurotoxicity testing of existing and new chemicals (30,43). To date, the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and other Federal agencies with authority to regulate toxic substances have not widely adopted or applied neurotoxicity test protocols (43). Consequently, available neurotoxicity data are insufficient to determine reasonably or to predict the health or environmental effects of all but a few of the substances in commerce that have neurotoxic potential, whether they be pesticides, industrial chemicals, food additives, or drugs.[2]

More testing of suspected neurotoxic substances will increase the chances of avoiding adverse health and environmental effects. It will also increase development and regulatory compliance costs. Industry and government incur costs in expanding the knowledge base that is essential in regulating toxic substances, but development of this knowledge theoretically improves the precision with which the benefits of regulation can be ascertained. Therefore, the question arises: What is the appropriate economic balance between the costs of neurotoxicity testing and the benefits of the resulting test data in developing regulations?

As discussed in chapter 7, the Federal Government can regulate neurotoxic substances under at least 16 laws. With the exception of regulations to

[1] In this chapter, the term "regulatory analysis" refers to analysis used in judging the desirability of a regulation. The term "regulatory impact analysis" (RIA) refers specifically to analysis performed under Executive Order 12291 (46 FR 13191-13196).

[2] A National Academy of Sciences (NAS) study examined toxicity testing results for a sample of substances that included chemicals in commerce (manufactured in both small and large volumes), pesticides, cosmetics, drugs, and food additives. From a list of 53,500 chemicals, NAS selected a ramdom sample of 675. A random subsample of 100 chemicals with at least minimal toxicity test information was examined in great detail, and conclusions were extrapolated from the review of test data on these 100 substances (30).

Box 8-A—Economic Balancing Provisions of FFDCA, FIFRA, and TSCA

The Federal Food, Drug, and Cosmetic Act (FFDCA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and the Toxic Substances Control Act (TSCA) are the primary laws under which neurotoxic substances are regulated. Each contains provisions to encourage increased testing for neurotoxicity and to control the production, distribution, and use of substances that present unreasonable risks of neurotoxicity. The following requirements for economic balancing relate to the control provisions in each of these laws.

Federal Food, Drug, and Cosmetic Act—The economic balancing provisions of FFDCA are less explicit than those of the other two Acts. The various sections of the law reflect Congress' intent both to provide for the safety of food (including substances added to food) and to maintain an economically affordable and abundant food supply. Whether regulatory analyses are undertaken depends on which section of the law is being applied and the type of regulatory action being considered. Because of amendments to FFDCA over the years, the regulation of chemicals in food is quite complex (18). Food-related substances addressed under the Act may fall into one or more categories, namely, food, direct or indirect food additives, color additives, naturally occurring environmental contaminants, inherent constituents of raw agricultural commodities, pesticide residues, and animal drug residues.

Finally, procedural considerations are important. The Bureau of Foods does not consider the process of approving and publishing a regulation that permits the safe use of a new food or color additive as formal rule-making subject to the cost-benefit analysis requirements of Executive Order 12291. Proposals to ban or limit the use of food additives that are already approved, however, are regarded as formal rule-making and are subject to the order's requirements, A proposal to establish a formal tolerance for environmental contaminants, a procedure that is rarely undertaken, is also regarded as formal rule-making and would require a cost-benefit analysis.

Federal Insecticide, Fungicide, and Rodenticide Act—In order to register a new pesticide under FIFRA, EPA must ascertain whether it will ''cause unreasonable adverse effects on the environment. ' FIFRA defines these effects very broadly, to include ''any unreasonable risk to man or the environment, *taking into account the economic, social, and environmental costs and benefits of the use of any pesticide" (7 U.S.C.* 136(bb)).

Under section 6 of FIFRA, EPA may cancel, restrict, or suspend the current registration of a pesticide if the Agency determines that the pesticide causes unreasonable adverse effects on the environment when used according to commonly recognized practice. In proposing such action, EPA must take into account the impact it will have on the prices of agricultural commodities, retail food prices, and the agricultural economy.

Toxic Substances Control Act—Section 6 of TSCA gives EPA broad authority to regulate manufacturing, processing, distribution, use, and disposal of chemical substances that present an unreasonable risk of injury to health or the environment. Section 6 states that in proposing any such regulation, EPA must consider and document: the effects of such substance or mixture on health and the magnitude of the exposure of human beings to such substance or mixture; the effects of such substance or mixture on the environment and the magnitude of the exposure of the environment to such substance or mixture; the benefits of such substance or mixture for various uses and the availability of substitutes for such uses; and the reasonably ascertainable economic consequences of the rule, after consideration of the effect on the national economy, small business, technological innovation, the environment and public health.

Congress (42) intentionally did not define "unreasonable risk," but indicated that determining whether a chemical posed such a risk should involve:

> . . . balancing of the probability that harm will occur and the magnitude and severity of that harm against the effect of proposed regulatory action on the availability to society of the benefits of the substance or mixture, taking into account the availability of substitutes for the substance or mixture which do not require regulation, and other adverse effects which such proposed action may have on society.

Congress further elaborated on the extent to which economic analysis was needed in the balancing process:

> The balancing process described above does not require a formal benefit-cost analysis under which a monetary value is assigned to the risks associated with a substance and to the cost to society of proposed regulatory action on the availability of such benefits. Because a monetary value often cannot be assigned to benefit or cost, such an analysis would not be very useful.

Congress cited the National Academy of Sciences (27) as support for the last statement.

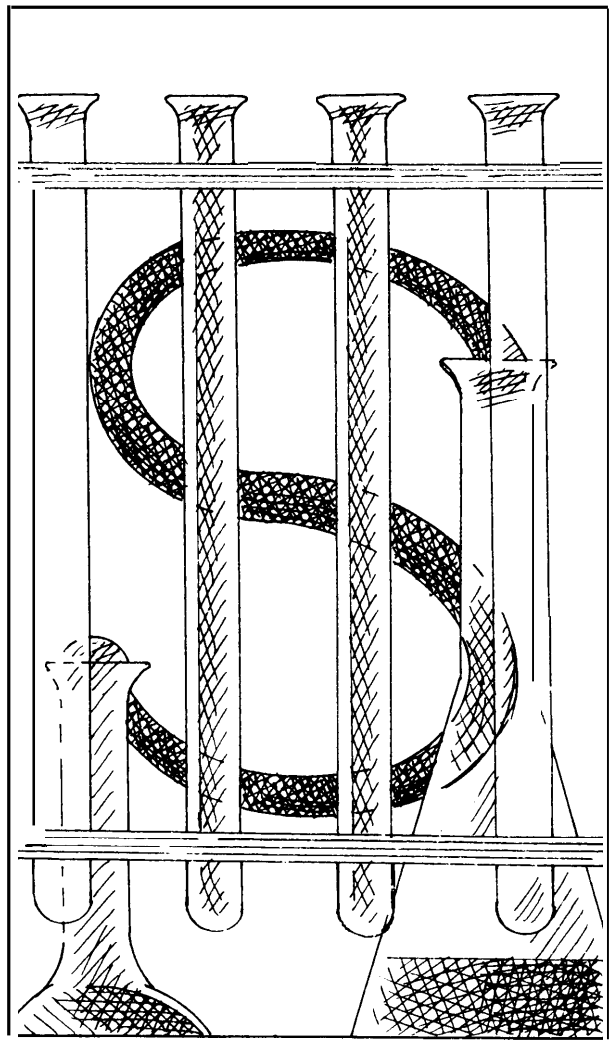
SOURCES: Office of Technology Assessment, 1990; U.S. Congress, 1976; Hattan, 1983; National Academy of Sciences, 1975.

reduce human exposures to lead,[3] the greatest amount of regulatory activity specifically directed toward neurotoxic concerns has occurred under three laws: the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended by the Federal Environmental Pesticide Control Act (FEPCA) (7 U.S.C. 135-136y); the Toxic Substances Control Act (TSCA) (15 U.S.C. 2601-2629), as amended; and the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 301-392). Each of these laws provides authority to obtain scientific and other data on which to assess risks and to control the use of toxic substances.

As with their assessments of health risks, agencies differ greatly in their approaches to evaluating and balancing the economic impacts of regulation. EPA, for example, has developed rigorous guidelines for evaluating the costs, benefits, and alternatives of regulations having major economic consequences (19). At the other end of the spectrum, FDA, in regulating food additives, carries out balancing in a less formal, more qualitative manner (22,25),[4] These differences reflect differences in legislative requirements for balancing benefits, costs, and risks (see box 8-A), as well as differences in agency views on the applicability of Executive Order 12291 (46 FR 13191), which defines current policies and requirements for the executive branch in evaluating regulatory proposals (see box 8-B).

The purpose of this chapter is to examine and evaluate several salient economic issues involved in regulating neurotoxic substances. Economic issues that arise from requirements to test for neurotoxicity as well as from restrictions on production and use of neurotoxic substances are discussed. Also discussed are the different forms of regulatory analysis that agencies have applied in addressing these issues.

Economic issues are common in the regulation of all toxic substances, regardless of the health endpoints of concern. However, since (with the exception of lead) the regulatory record for neurotoxic substances is limited, the present discussion is general in scope. No attempt has been made to present a comprehensive economic evaluation of the costs and benefits of a test rule or use regulation for a specific neurotoxic substance. Nor has an attempt been made to conduct a technology assessment of the impacts of regulating a class of neurotoxic chemicals.



Illustrated by: Ray Driver

ECONOMIC ANALYSIS OF REGULATIONS AFFECTING TOXIC SUBSTANCES, PESTICIDES, AND DRUGS

As noted above, current laws for controlling neurotoxic substances do not specify which analytical procedures Federal agencies must use in evalu-

[3] Regulations t. reduce occupational and environmental exposures to lead have been promulgated under at least 10 different Federal statute (28).

[4] An exception occurs i, the regulation of food additives that are known or suspected carcinogens. Under the 1962 Delaney amendment to FFDCA (21 U.S.C. 348(c)(3)(A)), the use of these substances in any quantity is prohibited, regardless of the impact on food costs or supply or any offsetting benefits of use (25).

Box 8-B—Requirements of Executive Order 12291

President Ronald Reagan signed Executive Order 12291 in 1981 (46 FR 13191) to increase agency accountability for regulatory actions. To achieve this goal, the order specifies that, in promulgating, reviewing, or developing regulations, all agencies, to the extent permitted by law, adhere to the following requirements:

- Administrative decisions shall be based on adequate information concerning the need for and consequences of proposed government action.
- Regulatory action shall not be undertaken unless the regulation's potential benefits to society outweigh its potential costs to society.
- Regulatory objectives shall be chosen to maximize the net benefits to society.
- Among alternative approaches to any given regulatory objectives, the alternative involving the least net cost to society shall be chosen.
- Agencies shall set regulatory priorities with the aim of maximizing the aggregate net benefits to society, taking into account the condition of the particular industries affected by the-regulations, the condition of the national economy, and other regulatory actions contemplated for the future.

The regulatory impact analysis (RIA) is the means for ensuring that agencies meet these requirements. The Order requires that agencies submit RIAs to the director of the Office of Management and Budget at least 10 days before publication in the Federal Register of a notice of proposed rule-making or final rule. For major rules, a preliminary RIA must be prepared and submitted at least 60 days before publication of a notice of proposed rule-making, and a final RIA must be submitted at least 30 days prior to publication of a final rule. A major rule is any regulation that is likely to have an annual effect on the economy of $100 million or more, to result in a major increase in costs or prices, or to have significant adverse effects on competition, employment investment, productivity, innovation, or the competitiveness of domestic firms relative to foreign counterparts.

SOURCE: Office of Technology Assessment, 1990.

ating the economic impacts of regulatory decisions. Regulatory agencies have not interpreted statutory requirements to evaluate proposed regulatory alternatives as imposing certain limits on the scope or approach of analyses that are undertaken. Instead, agencies like EPA have adapted various evaluative approaches, depending on the regulatory and economic issues involved.

The executive branch, through the Office of Management and Budget (OMB), has independently developed and implemented a requirement that agencies produce specific kinds of economic evaluations for regulatory actions that have major economic impacts. The current OMB requirement for regulatory impact analysis of such actions has evolved through a series of executive orders, and the OMB has incorporated the Regulatory Impact Analysis (RIA) requirement into its executive oversight function (see table 8-l).

This section examines four economic issues and the analytical approaches agencies have applied in addressing these issues as they have emerged in decisions to regulate toxic substances.

Costs, Benefits, and Economic Efficiency

Thus far, the terms "costs" and "benefits" have been used in a generic sense to indicate negative and positive economic impacts of regulation. Although this usage is correct, it is important to recognize that, for the purposes of analysis, these terms are narrowly defined to have specialized meanings. The precise operational definitions depend on the type and scope of analysis and the economic issue being assessed.

Accordingly, cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) have come to refer to analytical techniques in which macroeconomic analysis serves as the basis for evaluating the positive and negative economic consequences of a program or decision. For both techniques, costs refer to the resource inputs required to implement a program. Benefits and effectiveness refer to program outputs. Costs are computed in dollars, using values that the resource inputs would have had in alternative uses—their opportunity cost. In cost-benefit analysis, program consequences are also evaluated in dollar terms. In cost-effectiveness analysis, program consequences are measured in natural or physical units.

Table 8-l—The Institutionalization of Regulatory Analysis, 1971-81

Act. Executive Order	Year	Title	Type of analysis
OMB memo 10/5/71	1971	Quality of Life Review	Costs, benefits
Executive Order 11821	1974	Inflation Impacts Statement	Costs, benefits, inflationary impacts
Executive Order 11949	1976	Economic Impact Statement	Costs, benefits, economic impacts
Executive Order 12044	1978	Regulatory Analysis	Costs, economic consequences
Regulatory Flexibility Act	1980	Regulatory Flexibility Analysis	Impacts on small businesses
Executive Order 12291	1981	Regulatory Impact Analysis	Costs, benefits, net benefits

SOURCE: Office of Technology Assessment, 1990.

In the application of cost-benefit and cost-effectiveness techniques to evaluate health and safety regulations, costs and benefits are generally defined and measured from the perspective of achieving intended regulatory objectives of risk reduction. Cost-benefit or cost-effectiveness analysis is employed to evaluate whether the benefits of a regulation exceed its costs, or whether a regulation is cost-effective. That is, are the resources required to implement regulations being utilized in an efficient manner? The concept of economic efficiency refers to gains derived from resources allocated to achieve stated objectives.

In cost-benefit and cost-effectiveness analyses of toxic substances regulations (e.g., premanufacturing approvals, test rules, and use restrictions), the costs consist of those resources expended for the purposes of regulatory development, implementation, and compliance. They include expenditures by both government and the private sector. Government incurs expenses in: 1) developing regulatory procedures, including toxicity test methods, test rules, and chemical production, distribution, and use restrictions; 2) reviewing premanufacture notices (PMN), registration, and other requests by industry to produce and sell new chemical substances; and 3) carrying out necessary monitoring, inspection, and enforcement responsibilities.[5] The private sector usually bears compliance costs, which consist of labor, materials, equipment, and other expenses for: 1) obtaining premanufacturing approvals; 2) conducting animal toxicity tests,[6] keeping records, and submitting reports on chemicals of concern; and 3) altering production processes and products to conform with production, distribution, and use restrictions.

Evaluation of the benefits of controlling toxic substances involves first assessing the effectiveness of regulation in achieving risk reductions. Risk reduction is measured as reductions in mortality, morbidity, and ecological dysfunction that would occur as a consequence of changes in exposure to toxic chemicals. In cost-effectiveness analysis, benefits are measured in natural units, such as years of life saved, incidence of disease averted, and days of work loss avoided. In cost-benefit analysis, risk reductions are evaluated in monetary units.

Net efficiency refers to the difference between benefits and direct costs, or the difference between the value of reductions in health, safety, and environmental risks achieved through regulation and the value of the resources employed to achieve those reductions. It is important to note that the efficiency criterion of cost-benefit and cost-effectiveness analyses does not encompass any positive or negative impacts that regulation may have on industry employment, profits, or new product innovation. Other forms of economic analysis, some of which are discussed below, are utilized in assessing these so-called secondary economic impacts of regulation.

Under sections 4 and 5 of TSCA (15 U.S.C. 2604 and 2605), EPA typically has not conducted cost-benefit or cost-effectiveness analyses in implementing test rules or reviewing PMNs. The economic costs of complying with individual test rules for existing chemicals or production prohibitions for new chemicals are generally relatively small;[7] they are not likely to reach the $100 million per year specified by Executive Order 12291 for a major rule. Furthermore, analysis of the health and environmental benefits achieved by these actions can be

[5]In practice, it is difficult t. apportion the government's program costs to individual proposals. Consequently they are often omitted from analysis.

[6]Estimates of the costs of conducting animal toxicity tests that include certain neurological evacuations are presented later in this Chapter.

[7]Even when the total costs of complying with test rules are small, they may represent a significant portion of the sales revenues fOr low-volume, specialty chemicals. As discussed below, EPA recognizes the distributive effects of test rule costs in an analysis of impacts on market prices and profits.

speculative. To quantify these benefits, many assumptions must be made about a chemical's rate of market penetration, projected sales volume, types of uses, and likely disposal practices.

Under section 6 of TSCA (15 U.S.C. 2605), EPA considers all aspects of formal cost-benefit analysis in evaluating the impacts of a proposed regulation (48). The balancing language of section 6 (box 8-A) encourages cost-benefit analysis whether or not a regulation is likely to have major economic impacts. Since the enactment of TSCA, however, EPA has promulgated only a handful of regulations under section 6 (41).[8]

EPA's Office of Toxic Substances recently completed a preliminary risk assessment for environmental and occupational exposures to acrylamide, in which risks for carcinogenic reproductive effects and neurotoxic effects were evaluated (49). Although this assessment may lead to use restrictions that are based on neurotoxicity, further action by EPA under section 6 is contingent on reviews of the acrylamide risk assessment by the Occupational Safety and Health Administration and other agencies having potentially applicable regulatory authorities.

Under FIFRA, EPA's decisions to approve new pesticide registrations or to cancel, suspend, or alter existing registrations are not regarded as rule-making that is subject to the cost-benefit requirements of Executive Order 12291 (48). However, because of the specific balancing language of sections 3(c) and 6(b) of FIFRA (box 8-A), EPA has developed a methodology for evaluating the economic impacts of registration decisions. This procedure is discussed in the next section.

For pesticides that are applied in the production, storage, or distribution of raw agricultural commodities, part of the registration process may include an EPA review to establish a tolerance under FFDCA [21 U.S.C. 346a(b)]. EPA's granting of such a tolerance is considered rule-making, but cost-benefit analyses of these decisions are not developed, because all of the economic consequences of a tolerance are regarded as positive. Finally, the revocation of a pesticide tolerance by EPA is also considered rule-making. Although cost-benefit evaluations are developed for these decisions, they have been of limited utility in the regulatory development process.

Although few WA'S to control neurotoxic substances have been conducted, EPA has conducted cost-benefit studies of regulatory proposals to reduce human exposures to lead under other environmental statutes. Under the provisions of the Clean Air Act for regulating fuel additives [42 U.S.C. 7545(c)], EPA developed a cost-benefit analysis of several options for phasing out the use of lead additives in gasoline (39). In addition, EPA has evaluated the economic benefits of options for reducing lead in community water supplies under the Safe Drinking Water Act (42 U.S.C. 300f-j) (23). Both studies estimated the health benefits of reducing lead's neurotoxic effects in children.

Risks and Benefits

A second economic issue that arises in regulating chemicals, pesticides, and drugs concerns balancing the economic benefits of a substance that are lost through a restriction or ban on its use against the risks of continued use at unregulated levels (27,29). Risk-benefit analysis is used to address this issue.

As noted above, in a cost-benefit analysis of chemical regulation, the benefits consist of improvements in public health and environmental quality that would result from restricting the use of toxic substances. However, in risk-benefit analysis of licensing and approval regulations, in particular under FIFRA and FFDCA, the term "benefit" has acquired a different meaning. In this instance, benefits are defined in terms of the opportunity cost of switching to substitutes for the chemical in question. In registration decisions for agricultural pesticides, for example, EPA's Office of Pesticide Programs assesses benefits in terms of changes in the value of crop yields and pest control costs (29). Similarly, in approving new drugs, FDA assesses benefits in terms of therapeutic efficacy.

Risk-benefit analysis recognizes that, on the one hand, chemicals, pesticides, and drugs generate economic benefits that manifest themselves in the form of increased output and lower product prices. On the other hand, the increased use of toxic

[8]One reason for limited regulatory activity under sec. 6 is that EPA regards TSCA as the regulatory authority of last resort. Under TSCA sec. 9 (15 U.S.C. 2608(b)), for example, EPA must provide other appropriate Federal agencies with the first opportunity to regulate substances that present unreasonable risks.

chemicals may introduce more of these substances into the environment, at the time of initial use or subsequently in waste disposal. The risks to health and the environment from increased exposures to toxic chemicals, therefore, may also increase.

Risk-benefit analysis can also be used to compare the change in environmental and health risks to the change in economic benefits resulting from regulation. If the use of an existing chemical is increased, the analysis compares the potential increase in risks with the anticipated increase in benefits. If the use of a chemical is reduced, the analysis compares the expected reduction in risks with reduction in benefits.

EPA initiates risk-benefit analysis for proposed restrictions on pesticide use when it receives toxicity data that trigger questions about potential risks to human health. Although these analyses may be done when new compounds are preregistered, they are typically undertaken in response to toxicity data generated through the special review process for existing pesticides (see ch. 7). When special review leads to proposed use restrictions or suspension or cancellation of a registration for an agricultural pesticide, for example, analysts estimate the health risks and net values of crop production for projected uncontrolled and the proposed controlled applications of the pesticide. The risk-benefit ratios for these scenarios are then compared in assessing the economic impact of the proposed regulation.

The 1988 amendments to FIFRA call for an accelerated review of pesticides that were first registered under the pre-1972 FIFRA guidelines (1). Because this group includes a number of widely used agricultural insecticides that function by attacking the nervous systems of target organisms, it is likely that special reviews will trigger some risk-benefit evaluations for neurotoxicity.

In conducting risk-benefit analysis of new drugs, FDA is more qualitative in its approach. In ascertaining the benefits, FDA distinguishes between the efficacy and the effectiveness of the candidate chemical. Efficacy refers to the ability of the substance to alter the symptoms or pathological condition for which it was developed. Effectiveness refers to the degree of reduction in disease or death, and hence in health-care expenditures, a drug might achieve when optimally prescribed and taken. FDA weighs test evidence of adverse reactions to the drug (risks) against its demonstrated therapeutic properties (benefits). The 1962 amendments to FFDCA (Public Law 87-781) require that manufacturers submit sufficient data to demonstrate a new drug's efficacy but not its effectiveness.

Impacts on Market Prices and Industry Profits

A third issue of economic importance that arises in the regulation of toxic substances concerns the impact of the direct costs of regulation on market prices and industry profits. Although industry initially pays the compliance costs of regulation, it attempts to pass these increases on to customers in the form of higher product prices. Higher prices may, in turn, discourage sales and reduce industry profits. If there is a major expansion of regulations covering abroad range of industrial and commercial activities, as there was in the 1970s, the costs of regulation may contribute to the Nation's rate of inflation.[9]

TSCA stipulates that EPA consider "the relative costs of the various test protocols and methodologies" when implementing chemical test rules [section 4(b)(l); 15 U.S.C. 2603(b)(l)]. In 1980, with the first test rule issued under section 4 (45 FR 48524-48566), EPA outlined procedures for estimating the relative costs of test protocols and the projected impact of these costs on the marketability of the chemicals to be tested. These procedures remain in use today (24,40). EPA evaluates the impact of anticipated testing costs for each manufacturer or processor by estimating unit[10] test costs and then comparing these unit values to the market price of the chemical. A market analysis may be conducted to assess four key features of the market for the chemical being tested: 1) responsiveness of demand to changes in price; 2) expectations for market expansion or decline; 3) industry cost characteristics; and 4) industry structure (40).

[9]OMB and the Reagan Administration emphasized the cumulative inflationary effects of regulation in implementing Executive Order 12291.

[10]Unit test costs are estimated by first computing the annualized value of total direct test costs and then dividing by the annual supply (i.e., production and imports) of the chemical. In annualizing test costs, EPA uses the expected product lifetime for the annualization period and the estimated cost of capital in the chemical industry for the annualization rate. If available, sales volume information is used in estimating expected product lifetimes. Product lifetimes are longer for commodity chemicals (i.e., chemicals with multiple uses and large-volume sales) than for specialty chemicals. If sales volume data are unavailable, EPA uses a 15-year annualization period. The Agency currently uses 7 percent as the annualization rate (1 1).

Table 8-2-Comparison of Licensing and Notification Mechanisms

Factor affecting incentives to innovate	Licensing (FIFRA or FFDCA)	Notification (TSCA)
Burden of proof	Fails on innovating firm	Initial burden falls on regulatory agency
Agency's authority to compel testing of new products	Withhold approval until desired information is submitted	Requires agency finding that a product may pose an unreasonable risk
Burden of delay	Fails on innovating firm	Falls on public

SOURCE: Office of Technology Assessment, 1990.

EPA uses an informal rule of thumb to determine adverse economic impacts of testing. If the unit costs of testing a chemical are less than 1 percent of the price of the chemical, then the potential for adverse economic impact due to the test rule may be low. Conversely, if the unit test costs exceed 1 percent of price, then the potential for adverse economic impact may be high (24).

Regulation and Incentives for Innovation

An issue that is related to the impact of compliance costs on profitability is the effect of regulation on incentives for innovation. The development and introduction of new chemicals, pesticides, and drugs have produced benefits in virtually every area of human need: food, health, shelter, clothing, transportation, communication, and energy. On the other hand, extensive use or misuse of these substances has increased risks to public health and the environment. Hence the question, ''Does regulation to protect health and the environment alter industry's incentives to develop new drugs and chemicals?' '[11]

Companies develop and introduce new products as a means of competing in a given market and making a profit. Profitability depends on sales volumes and the cost and time required to develop, produce, and market new products. It also depends on the availability of competing products and patents and other factors that protect the market position of the innovating company. Finally, because there is uncertainty surrounding each facet of the development and commercialization of new products, innovation in the private sector will take place only if the prospective reward-risk ratio is considered favorable.

Regulation can affect each of these factors. First, the compliance costs of regulation increase the costs of developing new products. Second, the regulatory process adds to the time required to develop and introduce new products. Third, use restrictions can limit the market for a product, or in the extreme case of a ban, eliminate the market altogether. Fourth, reporting requirements may lead to the disclosure of proprietary information that may compromise the competitive position of the innovating company. Finally, because regulation can add uncertainties regarding costs, delays, protection of proprietary data, and so on, it adds to the financial risk of developing new products.

An important aspect of how a regulation affects incentives for innovation concerns the manner in which the regulatory process acts as a barrier to the commercialization of new products. In this regard there are important differences between the premarket screening requirements of TSCA versus those of FIFRA and FFDCA. The key difference is in the way the prescreening process assigns the burden of proof to demonstrate that a new product does or does not pose unreasonable risks (see table 8-2). Under the notification requirement of TSCA, the burden falls on the regulatory agency to make a finding that a product may pose an unreasonable risk. Under the licensing mechanisms of FIFRA and FFDCA, the burden falls on the innovating company. The regulatory agency can withhold approval for marketing of a new product until it is satisfied that the firm has conducted sufficient testing to establish that the product poses no unreasonable risks.

Numerous studies have sought to assess the aggregate effects of Federal regulatory changes on

11A related but analytically more complicated issue concerns whether the impact of health and safety regulations on incentives to innovate produce a net gainor loss to society. The temporal framework for analysis must be long enough to consider the positive and negative impacts of emerging chemical and drug technologies under various levels of regulatory control. Regulatory analyses usually lack this perspective. Risk-benefit analysis of proposed pesticide controls, for example, usually focuses on short-term economic impacts (3 to 5 years) and considers only currently registered chemical and nonchemical controls as alternatives (31).

innovation in the drug, pesticide, and chemical industries.[12] These studies have measured changes in an industry's innovative efforts in terms of the resource inputs and outputs of the innovative process. Measures of inputs into innovation have included: total research and development (R&D) expenditures per year; R&D expenditures as a percentage of annual sales or profits; time from initial discovery to commercialization; and development cost per new chemical entity. Typical output measures have included the number of new products registered or licensed per year and effective patent lifetimes. These measures have been examined before and after implementation of a change in a regulatory program or a change to ascertain whether there are significant quantitative differences. Although it is beyond the scope of this chapter to evaluate these studies critically, it is useful to summarize their findings and discuss some of the difficulties encountered in measuring the impact of regulation on innovation in the chemical, pesticide, and drug industries.

One difficulty in using total R&D expenditure measures has been the difficulty of distinguishing between R&D costs of truly new compounds (i.e., new chemical entities or new active ingredients for pesticides) and costs of new applications and combinations of previously discovered compounds. A second difficulty is that a substantial amount of the R&D expenditures for testing new chemicals is integral to their development. For pesticides, for example, toxicity testing and metabolism and residue studies are essential in understanding the properties and mechanisms of action on target organisms. Similar test information is needed in drug development. In other words, there is considerable overlap in the generation of test data needed to develop an application for a new substance and data needed to ensure its safety.

Drug R&D Studies

The most studied area of regulatory impact on innovation to date has been the effects of the 1962 amendments to FFDCA on R&D in the pharmaceutical industry. For the most part, studies agree that the overall rate of new drug introductions declined substantially from the 1950s to the 1960s and even more into the 1970s (see, e.g., 15,17,32,51). Studies have shown that development time and cost to manufacturers increased significantly after enactment of the 1962 amendments (see, e.g., 7,20,26,38).

Although these studies demonstrate consistent, adverse effects on drug innovation after a change to a more stringent regulatory regime, they do not agree on the relative importance of regulation as a factor in these impacts. Other influences not related to regulation, for example, declining drug research opportunities and exogenous increases in R&D costs, have been hypothesized as being partially responsible for the observed declines in drug innovation during this period. U.S. data showing that the decline in new approvals was already under way before 1962 and international data demonstrating comparable trends in other countries tend to support the conclusion that regulation has been only partially responsible for these declines (15).

Pesticide R&D Studies

Although there have been no studies of how regulatory efforts directed specifically toward neurotoxicity have affected pesticide innovation, there have been studies of the aggregate effects of pesticide regulation on R&D. A study by the Council on Agricultural Science and Technology (8) found that from 1968 to 1978—before and after enactment of the 1972 amendments to FIFRA-direct costs of bringing anew pesticide to market increased, delays from discovery to registration grew, and the composition of R&D expenditures shifted from synthesis, screening, and field testing to registration, environmental testing, and residue analysis.

Studies conducted by EPA (5) found little evidence of a reduction in pesticide innovation that could be attributed to EPA regulatory requirements. This conclusion was corroborated in an unpublished OTA study (45). OTA reported that after 1972, total pesticide industry R&D expenditures continued to grow at the same rate as pesticide sales. In addition, there was no apparent trend in pesticide registrations over the period 1966 to 1980 that could be attributed to regulation.

Chemical R&D Studies

In the late 1970s and early 1980s, prior to EPA's issuance of a final rule for premanufacturing notices

[12]For recent reviews of studies of the impact of Federal regulations on innovation in the drug, pesticide, and chemical industries, see refs. 16,19,31.

(PMNs),[13] many parties expressed concern that the major economic effect of section 5 of TSCA would be to reduce innovation by chemical companies (46,37,36). Several studies were conducted to estimate the impacts of the PMN process on the introduction of new chemicals (see, e.g., 3,37). Impacts were assessed for several alternative PMN filing formats proposed by EPA and were dependent on the direct costs of preparing and submitting the PMN as well as the indirect costs of delays and uncertainty associated with the ultimate disposition of the PMN.

One of the difficulties in assessing the impacts of the PMN rule on innovation in the chemical industry is that data on the number of new chemicals introduced annually, prior to the implementation of the PMN rule, are quite limited. It has not been possible, therefore, to establish a good baseline against which to measure the rate of chemical innovation since implementation of the rule.

EPA's estimates of direct filing costs for the final PMN rule were rather nominal ($3,000 to $18,000 in 1983 dollars per new chemical introduction) (19). However, some parties, notably the Chemical Specialties Manufacturing Association, argued that even costs in this range would have a disproportionate distributional impact on introductions of small-volume chemicals (19). Some of the smaller-volume, lower-value chemicals are not able to absorb even the relatively low compliance cost burdens represented by these estimates.

Utility of Regulatory Analyses in Devising Environmental Regulatory Policy

It is the need to document the economic impacts and potentially high costs of Federal regulatory decisions that continually motivates agencies to evaluate the effectiveness of these decisions. The goal in conducting these evaluations has been to improve regulatory decisionmaking through systematic development of information, preferably quantitative information, about the positive and negative economic impacts of proposed regulations.

From an analytical point of view, the ability of any evaluative technique to influence the selection of a particular regulatory alternative depends on the degree to which that technique can provide clear-cut distinctions among alternatives. Because of large gaps in underlying scientific information, estimates of costs, risks, and benefits are more often than not quite crude and highly uncertain. Consequently, cost-benefit and other regulatory analysis techniques are approximate and capable usually of distinguishing only between clearly superior and clearly inferior alternatives.

Improving Regulations

Despite their limitations, cost-benefit and cost-effectiveness analyses have influenced the development of regulations. In a recent assessment of impact analyses for 15 major regulations, EPA concluded that cost-benefit analysis had improved individual environmental regulations by:

- guiding the development of the regulation (i.e., showing that net benefits increase or decrease if the proposed regulation is made more or less stringent);
- leading to the specification of additional alternatives for analysis and consideration;
- eliminating alternatives that are clearly not cost-effective;
- adjusting alternatives to account for differences between industries or segments of industry; and
- supporting decisions (i.e., showing that there are net benefits for a regulatory decision that have been formulated under a different decision framework).

EPA noted that in some cases it is precluded by law from allowing the results of a cost-benefit analysis to influence rule-making.[14] In some of these instances, the Agency has prepared cost-benefit analyses anyway, to conform with the requirements of Executive Order 12291.

The General Accounting Office, in reviewing the utility of cost-benefit analysis at EPA, noted this difficulty and recommended that the Agency forward its analyses to Congress, since they could still

[13] Although the statutory requirements for premanufacture notification and review (15 U.S.C. 2604(a)(1)(A)) do not stipulate that these processes must be stated in a rule or that the information be provided in a particular form, EPA (19) determined that the issuance of a PMN rule was in the best interest of all concerned parties. Toward this end, the Agency began operating the PMN program on an interim basis in July 1979. The final rule establishing PMN requirements and review procedures was not issued until 1983 (48 FR 21742).

[14] Under the Clean Air Act, for example, primary national ambient air quality standards must be based solely on health effects, without consideration of benefits, costs, or economic impacts (42 U.S.C. 7409(b)(1).

provide useful information for congressional oversight (41). EPA supported this recommendation but noted that care should be taken in interpreting the findings because of the uncertainties and gaps in data that are likely to exist (48).

Additional Contributions

EPA noted several other contributions that cost-benefit analysis has made. As the Agency has gained experience in quantifying benefits, it has been able to transfer analytical expertise from one regulatory area to another. For example, part of what EPA learned from evaluating the health benefits of removing lead from gasoline has been applicable in estimating the benefits of reducing lead in drinking water.

Application of the cost-benefit approach has improved the consistency and comprehensiveness of regulatory analyses of proposed rules. Evaluation of regulations to control pollutants that have the same health outcome (e.g., cancer) has encouraged more uniformity in analyzing data on health effects. For multimedia pollutants, the application of cost-benefit analysis has increased awareness that regulatory action against pollution of one medium has ramifications for human exposures to pollutants in other media.

Economic Principles of Cost-Benefit and Cost-Effectiveness Analyses

As indicated above, cost-benefit and cost-effectiveness analyses seek to quantify and compare the economic inputs and outputs of a regulatory decision. If cost-benefit analysis confirms that the net benefits (i.e., the benefits minus the costs) of a regulatory proposal are positive, the regulation is said to produce an economically efficient allocation of resources. Thus, implementation of that regulation will result in a net economic gain to society.

Concepts and Definitions

In general, the concepts of cost-benefit and cost-effectiveness rest on the basic economic concept of opportunity cost: that is, the true cost of any activity consists of the value of alternative endeavors that might have been undertaken with the same resources. For example, the opportunity cost of premarket testing of a chemical is the value that resources used for toxicity testing would have had if used in production, sales, or other research activities.

The principal technical distinction between CBA and CEA, as noted earlier, is that CBA benefits are valued in monetary units, whereas CEA benefits are valued in natural, or nonmonetary, units. Because all costs and benefits are measured in the same units in CBA, this technique can be used to compare similar or widely divergent types of decisions. Thus CBA might be used to compare different regulatory options such as protective labeling, use limitations, or a total product ban. In the health area, analysts frequently prefer CEA to CBA because of the difficulty or undesirability of placing a dollar value on life. When using CEA to evaluate health programs that have both mortality- and morbidity-reducing consequences, analysts must often compare noncommensurable outcomes. How are two programs to be compared when one saves several lives but has a limited impact on morbidity, while the other saves a few lives and has a more extensive impact on illness? To address this problem, analysts have developed a measure called quality-of-life-adjusted years.

Cost-effectiveness is useful in making relative comparisons among regulatory options, and it is more meaningful when two or more alternatives are compared. For example, instead of considering the cost-effectiveness of toxicity test A standing alone, analysts examine the cost-effectiveness of test protocol A compared to protocol B or protocol C. Protocol A is cost-effective if it yields the required test data at a lower cost than protocol B or C; or A is cost-effective if it produces more useful data than B or C when the same level of resources is utilized in each test protocol. In both of these comparisons, protocol A would be regarded as the most economically efficient alternative of the three (economic efficiency is also a relative concept and refers to the alternative that provides the greatest return for a given level of resource expenditures).

THE COSTS OF NEUROTOXICITY TESTING

Animal toxicity testing and the resources expended for this purpose are now considered essential features in the development of new chemicals and drugs. FFDCA and FIFRA require demonstration of the ability of drugs and pesticides, that is, of the designed toxic properties, to attack diseases or target organisms. The relative safety of a drug (as measured in terms of unintended toxic effects) or a

pesticide (as measured in terms of morbidity or mortality to nontarget organisms) must also be demonstrated. TSCA emphasizes establishing a minimal set of information about a chemical's toxic properties before it is introduced into commerce. Under TSCA, manufacturers can also be requested to provide additional test data if there is cause to believe that a chemical may present an unreasonable risk to human health or the environment (see ch. 7).

Over the years, Federal authorities responsible for regulating chemicals have paid attention primarily to the potential carcinogenic, mutagenic, and teratogenic effects of pesticides and toxic substances. Although concerns regarding neurotoxic effects were occasionally mentioned, in most cases they were of secondary importance. With steady advances in the field of neurotoxicology and corresponding improvements in the ability to understand and to test for the neurotoxic effects of chemicals, the adverse effects that a substance may have on the nervous system have become of increasing interest and importance in regulatory decisionmaking.

In order to gauge the economic significance of requirements for increased neurotoxicity testing, this section discusses factors in the costs of animal tests for neurotoxicity. Estimates obtained by the Office of Technology Assessment (OTA) of the costs of conducting certain neurotoxicity tests are then presented. Finally, the incremental effects that the costs of neurotoxicity testing will have on total R&D costs for new chemical technologies are discussed.

Determinants of the Costs of Toxicity Tests

The costs of animal toxicity tests vary greatly from laboratory to laboratory. Many factors contribute to these variations, but they can be placed into two categories: *scientific*, or differences in protocol requirements, laboratory personnel, facilities, and so on; *and financial*, or differences in laboratory costs, rates, and fees.

Scientific Determinants

There are five major scientific considerations that determine the costs of any toxicity testing: protocol requirements, quality assurance, personnel, laboratory capabilities, and laboratory automation. Each of these is discussed below.

Protocol Requirements—The requirements of the test protocol are the single most important factor in determining the costs of toxicity testing. Of these requirements, duration of exposure has the greatest impact on costs. Tests to identify the adverse effects of acute exposures are usually completed within 1 month; tests for chronic exposures may require up to 2 years of animal dosing and observation. Because of the time difference alone, direct labor costs may differ by as much as a factor of 40.

Route of exposure is the next most important cost factor in protocol design. Because of the relative ease of dose administration, oral exposure via gavage (force-feeding) is least costly, followed by oral feeding, dermal exposure, and inhalation exposure. Dermal and inhalation exposures require special preparations and equipment. Inhalation also requires special monitoring equipment to measure the concentration of the test substance in the air breathed by the animals.

Although EPA has promulgated toxicity testing guidelines (50 FR 39397-39470), these protocols are not rigid recipes. Chemical manufacturers may exceed EPA requirements (e.g., an increased number of dosage groups or animals per group) or suggest additional testing based on previous experience and test findings.

Quality Assurance-Quality assurance affects the costs of toxicity testing in proportion to the accuracy and precision of the measurements required by the protocol. To achieve greater accuracy, more effort is needed in controlling contamination or other factors that may bias measurements. To achieve greater precision, more effort is needed in making duplicate measurements and analyses.

Federal good laboratory practice guidelines and regulations have, for the most part, required laboratories to establish in-house quality assurance units. The number of persons in these units varies by laboratory. Some laboratories do not have fill-time quality assurance personnel and rely on outside consultants or part-time personnel, whose costs may be lower. Laboratories with large quality assurance units perform functions well beyond the basic test requirements, and their costs usually are much higher.

Quality assurance personnel perform protocol evaluations, general laboratory inspections, evaluation of technical procedures, verification of raw data, interim and final report audits, and verification of the final report. The time required for these procedures

varies with the degree of automation at the laboratory, the degree of report standardization and computerization, the amount of data audited (which may range from 10 to 100 percent), and the experience and efficiency of the personnel.

Personnel—The levels of professional and technical expertise required for a particular toxicity test can significantly influence costs, particularly in acute studies. The education and experience required may be specified by the protocol, Federal regulatory requirements, or general consensus, any of which will result in cost variations. Smaller laboratories may have only limited personnel available for performing the tests (i.e., senior scientists may be performing procedures that would normally be done by technicians).

Laboratory Capabilities-Cost may also vary with mix of capabilities within a laboratory. Many laboratories do not perform the full complement of required test functions (i.e., analytical chemistry or electron microscopy) in house. Laboratories that use consultants or subcontractors to perform these functions increase costs by adding general and administrative fees. Laboratories that have extensive in-house capabilities but do not operate at full capacity incur greater overhead.

Laboratory Automation-There are major cost differences between manual and automated methods of data collection. Highly sophisticated, on-line computer systems can capture data electronically, lowering facility and animal monitoring costs. Examples include automatic control, monitoring, and recording of environmental conditions within the laboratory, as well as computerized data stations for animal body weights, food consumption, and clinical observations.

Financial Determinants

Four financial factors influence laboratory costs: 1) overhead rates, 2) general and administrative rates, 3) fees, and 4) labor rates.

Overhead Rates-Overhead costs are the indirect expenses, such as rent, heating, lighting, equipment, computer services, telephone, insurance, and so on, associated with the operation of a laboratory. Overhead costs are usually computed as a percentage—called the overhead rate-of total direct labor costs.

Overhead rates vary significantly among laboratories, for numerous reasons. Geographical location can affect overhead rates through variation in utility costs; rent, land, or construction costs; property taxes; State income taxes; and Federal corporate income taxes. The number of years the commercial laboratory has been in business may influence its overhead rate. Newer firms typically have a smaller work force, a large capital investment in new equipment, and sizable expenses in order to generate new business. Older, established firms often support a significant portion of employees on overhead, offer a better benefits package, and buy more up-to-date instrumentation.

The overall capabilities offered by a laboratory also affect the overhead rate. The more varied the capabilities, the more equipment and personnel are required. On the other hand, laboratories with more limited capabilities must hire consultants and subcontractors to perform certain tests, which may be quite expensive,

General and Administrative Rates-General and administrative costs represent the salaries of administrative and support personnel who do not engage in the study, but whose functions are essential to the operation of the laboratory. Examples include management, personnel, accounting, contracts, marketing, and legal employees. Usually, commercial laboratories have general and administrative rates of 5 to 25 percent of total direct labor costs. The more established laboratories tend to have higher general and administrative rates because of higher ratios of support to nonsupport personnel.

Fees—Fees refers to the profit expected from a study. Due to the confidential nature of such information, it is difficult to obtain data on fees received by commercial laboratories, but they range from 5 to 40 percent.

The wide range in profits may reflect marketing strategy and the volume of studies being performed. If volume is low, lower fees may be charged to attract new business. To encourage volume testing, many laboratories will also offer discounted prices for multiple testing packages. These package deals may be significantly lower than the sum of the unit costs for each of the individual tests in the package. Furthermore, acute toxicity protocols are often bid at or below actual cost in order to encourage future business.

Labor Rates-Labor rates vary substantially from one laboratory to another, depending on the mix of

individuals required to conduct a specific test. Salaries for similar types of technical positions also vary with regional economic conditions.

Cost Estimates for Neurotoxicity Testing

Because experience with neurotoxicity testing is still relatively limited, there is considerable uncertainty regarding testing costs. Recently, in support of the TSCA Test Guidelines Program, EPA (50) prepared estimates for several toxicity testing protocols that include neurotoxicity testing. These estimates were constructed by a senior toxicologist who is experienced in managing contract laboratory operations for toxicity testing. Because of the uncertainty regarding the representativeness of test cost estimates that are essentially from one source, it was decided as part of this study to obtain independent estimates of the costs of neurotoxicity testing.

To obtain these estimates, OTA surveyed researchers in several industrial, government, and contract laboratories (35). Researchers were selected on the basis of their experience in neurotoxicity testing, not the type of laboratory in which they work. Because the potential pool was small, it was not possible to obtain enough individuals to represent in a statistically valid way each of the three laboratory settings.

The chief purpose of the survey was to obtain a better understanding of the range of costs for animal tests to characterize the neurotoxicity of a specific chemical. A questionnaire was prepared to obtain cost estimates for acute, subchronic, and chronic toxicity tests of a single chemical that include various neurological evaluations. Cost estimates were requested for acute, subchronic, and chronic toxicity tests augmented with four neurotoxicity tests: functional observational battery, motor activity, neuropathologica1 evaluations, and schedule-controlled operant behavior. (See ch. 5 for a description of these tests.) Duration and route of exposure were specified for each protocol. The protocols for which cost estimates were solicited are indicated in table 8-3.

In addition to total costs for each test protocol, respondents were asked to provide separate estimates of the incremental costs for each of the four neurotoxicity tests. The purpose was to assess how much each type of neurotoxicity test would contribute to total test costs and whether neurotoxicity test requirements would lead to substantial increases in costs. This information is not available in the EPA estimates (50).

The ranges for the different test cost estimates that were obtained from this survey are presented in table 8-4. These are the highest and lowest cost estimates for the indicated toxicity tests and the highest and lowest incremental cost estimates for each of the added neurotoxicity tests. As expected, estimates of acute toxicity test costs are lower than those for repeated-dose studies, and estimates of costs for tests using the oral route of exposure are lower than those for tests using the inhalation route.

Median cost estimates for each of the base test protocols and each of the added neurotoxicity tests are presented in table 8-5. (Because this kind of survey is likely to yield outliers at both the high and low ends of distribution, the median is the preferable estimate.) The median estimates indicate that a complete set of core neurotoxicity tests, including a functional observational battery, motor activity, and neuropathology, may add from 40 to 240 percent to the cost of conventional toxicity testing of a single chemical. The major portion of the added cost is due to the requirements of the neuropathological examinations. Based on its survey, OTA found that acute neurotoxicity tests (including EPA's functional observational battery, motor activity test, and neuropathology evaluations) are likely to add a total of about $50,000 to standard toxicity test costs of a single chemical. Subchronic neurotoxicity tests may add up to $80,000, and chronic tests may add well over $100,000. The EPA subchronic schedule-controlled operant behavior test (which is only likely to be done after the other neurotoxicity tests) may add about $64,000. However, the functional observational battery alone would add only $2,500 to the cost of a conventional acute toxicity test. The added cost impact is highest for the acute test protocols. A conventional acute test involving oral exposure costs about $21,000.

EPA median cost estimates (50) are considerably lower than OTA survey estimates for identical protocols—from one-half to nearly one-fourth. Although the EPA estimates were developed approximately 6 months before the OTA study, the 1988 inflation rate of 4 to 5 percent during this period does not account for differences of this magnitude.

Table 8-3-Protocols for Which Cost Estimates Were Solicited

Protocol	Neurotoxicity Test			
	Functional Observational Battery	Motor Activity	Neuro-pathology	Schedule-Controlled Operant Behavior
Acute inhalation	x	x	x	
Acute oral	x	x	x	
Subchronic inhalation	x	x	x	
Subchronic oral			x	x
Subchronic oral	x	x	x	
Chronic oral	x	x	x	

SOURCE: Office of Technology Assessment, 1990.

Table8-4-Ranges in Cost Estimates for Animal Toxicity Tests Combined With Neurotoxicity Evaluations for 1988 (thousands of dollars)

Protocol	ToxicityTest Base Cost	Neurotoxicity Test (incremental costs)			
		Functional Observational Battery	Motor Activity	Neuro-pathology	Schedule-Controlled Operant Behavior
Acute inhalation	$8.8-47.2	$11-213	$1.2-12.3	$4.7-187.6	NA
Acute oral	6.9-39.7	1.1-21.3	1.2-11.3	4.7-179.6	NA
Subchronic inhalation	99.1-391.0	2.9-32.9	2.1-11,8	6.2-362.9	NA
Subchronic oral	69.5-183.0	2.7-32.9	2.1-11.8	6.2-271.5	NA
Subchronic oral (NP & SCOB)*	69.5-183.0	NA	NA	6.2-271.5	11.0-80.3
Chronic oral	234.0-783.9	3.8-85.8	4.8-38.2	11.3-602.0	NA

"Neuropathology (NP);schedule-controlled operant behavior (SCOB)

SOURCE: Office of Technology Assessment 1990.

Table 8-5-Median Cost Estimates for Animal Toxicity Tests Combined With Neurotoxicity Evaluations for 1988 (thoussnds of dollars)

Protocol	Toxicity Base Cost[a]	Neurotoxicity Test (incremental rests)				Median Total Increment[a]	Increment as a Percent of Base
		Functional Observational Battery	Motor Activity	Neuro-pathology	Schedule-Controlled Operant Behavior		
Acute inhalation	$ 26.6(7)[a]	$ 2.5(5)	$ 4.5(6)	$42.0(5)	NA	$ 49.9(5)[b]	188
Acute oral	21.2(7)	2.4(5)	4.4(6)	42.0(5)		49.9(5)	235
Subchronic inhalation	190.6(7)	4.8(5)	4.7(6)	42.0(5)	NA	79.1(5)	42
Subchronic oral	111.0(7)	4.8(5)	4.7(6)	29.7(5)		79.1(5)	42
Subchronic oral(NP & SCOB)*	109.8(5)	NA		41.7(4)	64.1(5) ,	87.0(4)	79
Chronic oral	308.0(6)	12.5(5)	19.8(6)	59.7(5)	NA	113.2(4)	37

[a]Number of observations shown in parentheses.
[b]Because of incomplete responses, columns do not add to total.
*Neuropathology (NPhschedule-controlled operantbehavior (SCOB).

SOURCE: Office of Technology Assessment, 1990.

NEUROTOXICITY TEST COSTS AND INNOVATION

In order to assess the impacts of testing for neurotoxicity on innovation in the drug, pesticide, and chemical industries, it is essential to describe the patterns of innovation for drug, pesticide, and chemical products. While there are certain similarities among the three, there are important economic differences between the development process for new chemicals and that for new drugs or pesticides.

Drug and Pesticide Development

There are many similarities in the process of developing new drugs and pesticides. The key factors governing the pattern of innovation in these industries are the high costs and long development times experienced from discovery of a new compound to commercialization of it. Hundreds of new

compounds may be screened for each new pesticide and drug that is eventually marketed. Approximately 10 years may elapse from discovery to first registration (31,33). The pharmaceutical industry estimates that it currently costs well over $100 mil1ion to develop, test, and bring to market **a new** drug product (52). The pesticide industry estimates development costs for anew pesticide of about $25 million, with another $25 to $50 million required for building and equipping production facilities (4).[15]

Agrichemical and pharmaceutical companies spend from 9 to 15 percent of sales revenue on R&D (31,33). Most R&D in pesticide and pharmaceutical companies is internally financed and conducted in order to protect the proprietary status of new innovations. The disadvantage of this practice is that uncertainties imposed by the regulatory process, either as delays in the introduction of new products or as unexpected limitations or bans on the sale of these products, may reduce the return on industry's investments in research.

The high costs and long time from discovery to commercialization force the development process for new pesticides and drugs toward those applications that are likely to have very high returns. Only a relatively small number of markets are large enough to make it economically worthwhile for firms to develop these products. Consequently, pesticides are developed and initially registered for major uses, for example, on crops such as corn or soybeans. Subsequently, they are tested for use on minor crops.

The actual discovery of a new drug entity-anew chemical with therapeutic potential-is just the first step in a lengthy process of R&D. The discovery phase of the process consists of chemical synthesis and animal testing to establish a compound's toxicology and pharmacology. The development phase encompasses clinical testing to assess potential toxic effects in healthy humans and, subsequently, to establish in patients the therapeutic efficacy of a new drug candidate.

The average effective period of patent protection for anew chemical entity declined between 1966 and 1979 (16). The estimate of 9.5 years of protection is about one-half the maximum period of patent protection of 17 years. This decline in patent life, which has been largely attributed to longer development and regulatory approval times, became a major policy issue in the early 1980s. Congress addressed the problem in 1984 with the Drug Price Competition and Patent Restoration Act (Public Law 98-417). This law allows restoration of part of the patent protection time that elapses during development and FDA approval.

The recent estimate of $125 million (1986 dollars) as the total research and development cost for an approved new drug is based on new drugs approved between 1970 and 1985 (52). The increasing costs of developing new drugs are due in part to an increasing focus on therapies for chronic conditions. The development of drugs of this kind requires more extensive testing (33).

Neurotoxicity Tests and Innovation in Dregs and Pesticides

The above discussion of the processes for developing drugs, pesticides, and chemicals provides a framework within which the innovation impacts of conducting animal tests for neurotoxicity may be assessed. The impacts of testing on innovation depend on overall test costs, duration of the tests, and the timing (scheduling) of the tests within the innovation period.

One possibility would be for the animal toxicity tests with combined neurological evaluations to take place during the preclinical and pre-field testing phases for drug and pesticide development, respectively. In this scenario, the additional costs of testing for neurotoxicity would occur during the second or third years of a 10-year developmental period.

If neurotoxicity test protocols are totally incompatible with other concurrent animal toxicity testing, then the additional costs of obtaining neurotoxicity data would be the capitalized value of the full test costs at the expected date of marketing approval. The expected date of marketing approval is 7 to 8 years in the future. At the assumed 10 percent rate of interest, the capitalized value of $190,000-the median cost estimate for subchronic oral toxicity testing with functional observation, motor activity, and neuropathology evaluations-is from $370,000 to $430,000. The capitalized value of $420,000-the median cost estimate for chronic oral toxicity testing with the same neurotoxicity evaluations-is from

[15]These amounts appear to be in line with earlier detailed estimates by Goring (14) of the costs of commercializing a new pesticide.

$820,000 to $900,000. These **amounts are small, compared to current estimates of total capitalized costs of developing a new drug or pesticide.**

A second possibility would be for neurotoxicity test data to be requested at the very end of the drug or pesticide development process. In this instance, timing of the tests is of much greater importance than their costs. Testing that, for example, extends the innovation period by 1 year at the end of the development period has an associated opportunity cost equal to the interest on the total cumulative R&D investment. For drugs and pesticides, the costs of delaying marketing approval at this point clearly overshadow any outlays required to conduct the tests.

Neurotoxicity Tests and Innovation in Chemicals

The pattern of new product innovation in chemicals is considerably different from that of drugs or pesticides (45). For one thing, there is greater diversity among chemical products, which include plastics, solvents, fibers, detergents, catalysts, and basic organic and inorganic chemical feedstocks. More important from an economic perspective, however, is the fact that new drugs and pesticides are developed for quick penetration into large markets. In contrast, the initial market for the vast majority of new chemical products is very small, and failure rates are high. Markets for large-volume chemicals develop slowly over a number of years.

Data on the number of new chemicals introduced annually into commerce before TSCA are uncertain. Estimates of the rate of new chemical innovation range from 700 to 1,400 compounds annually (3,12). Of these, as many as 70 percent were estimated to have annual production volumes of less than 1,000 pounds, which is regarded as a threshold level of output for a viable commercial product (3). Furthermore, many low-volume products were, in all likelihood, developed and marketed by very small firms in the business of "custom-manufacturing" chemicals. Since the implementation of the final PMN rule in 1983, the annual receipt of PMNs by EPA has increased steadily, to nearly 1,700 compounds in 1986 (6).



Photo credit: U.S. Environmental Protection Agency

Under section 5 of TSCA, EPA does not require that chemical manufacturers conduct toxicity testing prior to submission of a PMN; manufacturers are only required to supply any health or environmental test data that are available at the time of submission. Although EPA can request additional toxicity testing of new chemicals, it has used this authority sparingly.[16] In a recent analysis of 8,000 PMNs received by EPA from July 1979 through September 1986, fewer than one-half contained toxicity test data (6).

Although data are not readily available on the average costs of developing and introducing a PMN chemical, as noted above, many of them are produced and marketed as specialty products. Expected profits from the sale of small-volume chemicals

[16]If, in reviewing the PMN submission, EPA decides the chemical may present unreasonable risks to health or the environment, the agency can limit production and utilization of the substance while more test data are developed (15 U.S.C. 2604(e)). If EPA decides the chemical will present unreasonable risks, the agency can require the development of additional test data (1U.S.C. *2604(0).* Auer and Gould reported that EPA had ordered submission of more test data for about 200 PMN chemicals from 1979 to 1986. An additional 150 PMNs had been subject to voluntary actions, some of which involved testing. Finally, 164 chemicals were voluntarily withdrawn by the submitted when presented with the likely prospect of conducting more testing (6).

cannot, in most cases, cover the costs of extensive testing, especially if there are substitute products already on the market. Thus, a request for neurotoxicity testing, which could add substantially to costs of testing currently being done, could lead to a reduction in the rate of innovation in certain classes of low-volume products, particularly those that are vulnerable to even modest regulatory compliance costs.

ECONOMIC BENEFITS OF REGULATING NEUROTOXIC SUBSTANCES

It is important to distinguish between the adverse effects of neurotoxic substances and the benefits of reducing or "preventing these adverse effects. The adverse effects of neurotoxic substances are expressed as impacts on human health and the environment and are measured in terms of mortality, morbidity, disability, and environmental damage. They should include effects on mental status, such as memory loss and cognitive dysfunction, that may be associated with exposures to neurotoxic substances.

Reducing or preventing the risks of exposure to neurotoxic substances means reducing the magnitude of these adverse effects. The human and monetary values placed on risk reductions are a measure of the benefits of regulation. In the economics of health and safety, several approaches have been used to assign monetary values to reduced risk of mortality, morbidity, and disability. These approaches have been broadly categorized as valuation through adjudication (jury awards), political processes, individual preferences, and resource or opportunity costs.[17] Valuation through resource or opportunity costs will be discussed here.

Knowledge Requirements for Estimating Benefits

To estimate the benefits of policies to reduce or prevent neurotoxic risks requires knowledge and quantification of the following:

. the relationship between economic activities and the rates of use of neurotoxic substances;
. the relationship between the environmental fate and transport mechanisms that determine ambient environmental concentrations and, hence, human exposures to these substances;
- the relationship between the activities of individuals (e.g., eating, working, exercise) and the rates of human intake of these substances;
- the biological mechanism by which these substances cause disease in humans; and
- the relationship between changes in health status and the utilization of health care.

Only the first and the last of these relationships are basically-although not exclusively—in the realm of economics. The intervening ones represent the interface of science and economics-in particular, they are the substance of risk assessments of exposures to neurotoxic substances (35).

The fact that exposures to neurotoxic substances result in more effects and more varied effects on health than, say, exposures to carcinogens is an important distinction and one that poses analytical difficulties in risk assessment and benefits analysis. In contrast to carcinogenicity, which can usually be characterized as a single outcome with discrete measures of health status (i.e., the disease is present or it is not), neurotoxicity may be manifested as multiple effects, each of which may produce a continuum of health states ranging from mild to severe.

The Health Costs of Neurotoxicity

As noted above, the opportunity costs of morbidity and mortality that can be attributed to neurotoxic - ity provide a measure of the potential economic benefits of reducing neurotoxic risks to human health. These opportunity costs, frequently called the social costs of illness, include direct and indirect costs of illness and death. The direct costs of illness consist of the payments for health-care products and services utilized in providing patient care. The indirect costs of illness encompass the expected earnings an individual loses as a result of not working. Medical care costs and foregone earnings are estimated for each year from the onset of illness to expected year of death. This time stream of costs is then discounted to present values.

Estimating benefits in this manner is known as the productivity, or human capital, approach. Most economists regard this approach as providing lower-

[17] Valuation according to individual preferences, or willingness to pay, is frequently cited by economists as the most appropriate measure Of the value of redueing the risks of adverse health effects (13).

Table 8-6-Personal Health-Care Expenditures for the 10 Most Expensive Medical Conditions in the United States in 1980 (millions of dollars)

Medical condition	All ages	Under 65	65 or over
Diseases of the circulatory system	$33,184	$13,078	$20,015
Diseases of the digestive system	31,755	26,084	
Mental disorders	20,301	14,612	5,689
Injury and poisoning	19,248	15,042	4,206
Diseases of the nervous system and sense organs	17,499	13,028	4,471
Diseases of the respiratory system	17,305	13,164	4,141
Diseases of the musculoskeletal system and connective tissue	13,645	9,821	3,824
Neoplasms	13,623	8,302	6,322
Diseases of the genitourinary system	13,162	10,721	2,441
Endocrine, nutrition metabolic system, and immunity disorders	7,656	4,689	2,968

SOURCE: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, *Health United States,* 1983, DDHS Pub. No. (PHS)84-1232 (Washington, DC: U.S. Government Printing Office, 1983)

bound estimates of the benefits of improving health because it does not attempt to measure and include the disutility experienced by persons having these diseases or by their families and friends. This kind of disutility is particularly relevant for dementia, retardation, and other mental disorders in which neurotoxicity may be a causative or contributing factor.

The Costs of Mental Disorders and Diseases of the Nervous System

Mental disorders and diseases of the nervous system contribute substantially to health costs in the United States. In 1980 (the most recent year for which costs of illness were estimated for specific disease categories) they ranked as the third and fifth most expensive medical conditions, respectively, in terms of personal health-care expenditures (table 8-6). The estimate of nearly $40 billion (1980 dollars) for these two categories of morbidity does not include values for lost productivity, restricted activity, and other social costs (e.g., rehabilitation for drug and alcohol abuse) that may accompany mental illness or other forms of cognitive and behavioral impairment.

The Costs of Neurotoxicity As an Element of Dementia

Dementia is defined as the loss of intellectual function. It is manifested as a complex of symptoms that can be caused by as many as 70 underlying conditions. The causes of disorders that produce the vast majority of dementia cases are still not understood (44); however, some dementias maybe caused or exacerbated by neurotoxic substances in prescription drugs, metals, solvents, and other chemicals (21). Other dementia diagnoses include necrosis of brain tissue due to vascular obstruction, various infectious diseases, tumors, and toxicity from alcohol (21).

Although the costs of dementia to the Nation can be only crudely approximated, they are high and are bound to increase as the population ages. Estimates of the costs of dementia are presented here as a basis for estimating the health costs of neurotoxicity. One study has estimated that at least 2 to 3 percent of dementia patients were diagnosed as having disorders involving drug toxicity (21). If this can be regarded as a lower-bound estimate, then from 2 to 3 percent of the costs of dementia may be taken as a lower-bound estimate of the social costs of neurotoxicity. Applying 2 to 3 percent to each of the above estimates for the overall costs of dementia yields estimates of $0.5 billion to $1.5 billion annually for neurotoxicity alone.

The Costs of Exposure to Lead

Epidemiologists have demonstrated associations between excessive lead exposure, particularly during childhood, and several kinds of adverse neurological and behavioral effects.[18] In the past, public health agencies focused principally on severe lead exposure and the resultant symptoms of overt lead poisoning.

More recently, medical scientists have shown that important neurochemical changes are induced by lead in much smaller amounts than those generally associated with clinical symptoms of lead poisoning. Finally, there is considerable epidemiological evidence that low-level exposure can result in altered behavior, including attentional disorders,

[18]For a recent comprehensive review of the adverse health effects of lead, see ref. 47.

learning disabilities, or emotional disorders that impair classroom performance.

For these reasons, an analysis of the health costs attributable to excessive lead exposure during childhood must recognize at least three categories of costs:

- direct medical care expenditures, including hospitalization, doctors' fees, drugs, and convalescent care for preschool children who have been diagnosed as being at risk with respect to lead absorption;
- special education or institutionalization costs, or both, for school-age children who suffer permanent neuropsychological effects from exposure to lead; and
- costs to society in terms of reduced production and tax contibutions from adult members of the labor force who have permanent impairments stemming from excessive exposure to lead during childhood.

Calculating health costs of lead exposure involves multiplying estimates of the number of preschool, school-age, and adult individuals with lead-induced health and intelligence deficits by cost factors that represent the opportunity costs to avoid or correct those deficits (34). Two recent analyses of regulatory proposals to reduce human exposures to lead used this approach.

In a cost-benefit analysis of options for removing lead additives from gasoline, one study (39) estimated the reduction in the number of children who would have elevated levels of lead in their blood (defined in this study as more than 25 grams per deciliter) as a consequence of removing lead from gasoline.[19] The study assumed that 20 percent of all children with elevated levels would be affected severely enough to warrant compensatory education for up to 3 years. Other studies suggest that the cognitive effects and lead-induced behavioral problems may persist for at least 3 years (9,10). In the valuation step, the number of person-years in compensatory education was multiplied by an estimate of the additional costs of providing part-time special education to a child for 1 year. These estimates are presented in table 8-7. The benefits of reducing lead in gasoline continue to increase for a number of years, as the use of leaded gasoline is gradually phased out. As the table indicates, the total health benefits of reducing the neurotoxic effects of lead on U.S. children was estimated to total more than $500 million annually between 1986 and 1988. If adult exposure to lead, including workers' exposure, were included, the benefits would be considerably greater.

Another study developed similar estimates of the savings in medical care and compensatory education costs that would occur in a single year as a consequence of reducing the maximum contaminant level for lead in drinking water from 50 to 20 grams per liter (23). The health benefits estimate for this one-time reduction were $81.2 and $27.6 million (in 1985 dollars) for compensatory education and medical care costs, respectively.

SUMMARY AND CONCLUSIONS

Regulating neurotoxic substances involves consideration of both the economic benefits of using these substances and their actual or potential risks to human health and the environment. The problem of balancing benefits, risks, and the costs of regulation is not unique to the control of neurotoxic substances; it arises in all forms of health, safety, and environmental regulation. Regulations that are designed to reduce or prevent neurotoxic risks can benefit society through improvements in public health and environmental amenities. In most cases, however, society incurs costs to achieve these regulatory ends. The costs of complying with health and safety regulations may also result in increases in market prices, reductions in industry profits, and declines in new product innovation.

Many of the key Federal laws under which neurotoxic substances are regulated require agencies to ascertain the positive and negative economic consequences of regulation. In implementing these laws, Congress has generally intended that agencies prepare regulatory analyses and document the balancing of benefits, costs, and risks of proposed alternatives.

[19] In order to estimate the health benefits of controlling neurotoxic substances, it is important to have good data on the extent to which human populations are exposed, as well as epidemiological data that link exposures to adverse health effects. Estimates of the benefits of reducing human exposures to lead were greatly facilitated by the availability of national estimates of the prevalence of lead exposure obtained through the National Health and Nutrition Examination Survey (NHANES-II) (2).

Table 8-7-Estimates of the Health Benefits of Reducing the Neurotoxic Effects of Lead in Children
(millions of 1983 dollars)

	Savings					
Service	1985	1986	1987	1988	1989	1990
Compensatory education	$187	$447	$408	$374	$338	$309
Medical care	65	155	141	130	117	107
Total	252	602	549	504	455	416

SOURCE: J. Schwartz et al., Costs *and Benefits of Reducing Lead in Gasoline: Final Regulatory Impact Analysis, EPA-230-05-85-O06* [Washington, DC: U.S. Environmental Protection Agency, 1985).

In addition to these legislative provisions, the executive branch,. through the Office of Management and Budget, has also mandated that agencies conduct regulatory impact analyses for regulations that may have major effects on the economy. The current OMB requirement, which has evolved through a series of executive orders, specifies that agencies must conduct benefit-cost evaluations for any regulatory proposal that is likely to have an annual effect on the economy of $100 million or more.

To date, only a small number of regulatory actions, and hence a small number of regulatory analyses, have been directed at reducing the risks of neurotoxicity. Most of these actions have been taken to control environmental and occupational exposures to lead. Regulatory impact analyses of regulations to reduce the amounts of lead in gasoline and in drinking water provide some of the best examples to date of assessments of the economic consequence of controlling neurotoxic risks.

Analyzing the economic consequences of controlling neurotoxic risks is a two-step process. The first step, risk assessment, involves using data from epidemiological, toxicological, and other studies to estimate the health and environmental risks associated with various levels of exposure to the substance in question. The second step involves making estimates of the costs, benefits, and other economic impacts associated with achieving a specific level of risk reduction.

One economic issue that has emerged in regulating neurotoxic substances concerns the costs of screening and testing these substances for their neurotoxic hazard potential. Experience with neurotoxicity testing is still relatively limited, creating uncertainty regarding the available cost estimates for this type of testing. Because of the uncertainty regarding these costs, OTA obtained estimates of the costs of several types of neurotoxicity tests from a number of individuals in government, industry, and academia.

Cost estimates were obtained for standard acute, subchronic, and chronic toxicity test protocols augmented with four neurological evaluations: functional observational battery, motor activity, neuropathology, and schedule-controlled operant behavior. The median estimates derived from OTA's survey indicate that a complete set of core neurotoxicity tests, including a functional observational battery, motor activity, and neuropathology, may add from 40 to 240 percent to the costs of conventional toxicity tests currently required by EPA. By far the largest portion of the added cost comes from the addition of neuropathology evaluations, which are needed to determine whether structural change in the nervous system has occurred and the nature and significance of the change. Based on its survey, OTA found that acute neurotoxicity tests (including EPA's functional observational battery, motor activity test, and neuropathology evaluations) may add about $50,000 to the cost of standard acute toxicity tests. Subchronic neurotoxicity tests may add $80,000, and chronic tests may add about $113,000. The EPA subchronic schedule-controlled operant behavior test may add about $64,000. However, the functional observational battery alone would add only $2,500 to the cost of conventional acute toxicity test. A conventional acute test involving oral exposure costs about $21,000.

Testing costs should be viewed in the context of the total cost to industry of marketing anew product, potential profits resulting from the sale of the product, the impact of initially high test costs on the innovation process, and the health benefits of minimizing public exposure to neurotoxic substances.

For the development of new drugs and pesticides, which have development times of 8 to 10 years and development costs of $50 million to $100 million or

more, the costs of additional neurotoxicity testing are very small. For industrial chemicals with specialty uses, on the other hand, additional neurotoxicity testing could add substantially to costs of tests that are currently done and could lead to a reduction in the innovation of certain classes of low-volume products.

The benefits of regulating neurotoxic substances can be measured in terms of the human and monetary values placed on reduction of risk. A number of approaches have been used to assign monetary values to reducing the risks of mortality, morbidity, and disability. Lead has been the subject of an in-depth economic analysis. A 1985 study estimated that the total health benefits of reducing the neurotoxic effects of lead on U.S. children would be more than $500 million annually between 1986 and 1988. If adult exposure to lead, including workers' exposure, were included, the benefits would be considerably larger.

Although the health and economic benefits of limiting public exposure to neurotoxic substances are more difficult to estimate than the costs of regulation, the example of lead illustrates the importance of considering the potentially large monetary benefits of regulatory actions. Like other toxicity testing, neurotoxicity testing is conducted to prevent adverse health effects; hence, the benefits of such testing may not be readily apparent and may accrue well into the future. Often, the immediate costs of testing receive considerable attention, but the sizable potential benefits of preventing public exposure to a hazardous substance receive comparatively little attention.

As indicated earlier, neurotoxic substances, in particular abused drugs, play a significant, causal role in the development of neurological and psychiatric disorders; however, the precise extent of the contribution remains unclear. Mental disorders and diseases of the nervous system contribute substantially to health costs in the United States. In 1980, they ranked as the third and fifth most expensive medical conditions in terms of personal health-care expenditures (see table 1-3 in ch. 1). The estimate of nearly $40 billion (1980 dollars) does not include values for the lost productivity, restricted activity, and other social costs that frequently accompany mental illness or other forms of mental impairment.

CHAPTER 8 REFERENCES

1. Aidala, J., *Proposed Senate Amendments to FIFRA* (Washington, DC: Congressional Research Service, 1988).
2. Annest, J. L., and Mahaffey, K., *Blood Lead Levels for Persons Ages 6 Months and 74 Years in the United States, 1976-1980,* DHHS Pub. No. PHS 84-1683 (Hyattsville, MD: U.S. Department of Health and Human Services, National Center for Health Statistics, 1984).
3. Arthur D. Little, Inc., *Impact of TSCA Proposed Premanufacturing Notification Requirements,* EPA 230/2-12/78-005 (Washington, DC: U.S. Environmental Protection Agency, 1978).
4. Aspelin, A. L., *Economic Aspects of Current Pesticide Regulatory Programs and Outlook for the Future* (Washington, DC: U.S. Environmental Protection Agency, Mar. 14, 1983).
5. Aspelin, A. L., Economic Analysis Branch, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, DC, personal communication, Apr. 5, 1989.
6. Auer, C. M., and Gould, D. H., ''Carcinogenicity Assessment and the Role of Structure Activity Relationship (SAR) Analysis Under TSCA section 5," *Journal of Environmental Science and Health C5(1):29-71, 1987.*
7. Clymer, H. A., "The Changing Costs of Pharmaceutical Innovation, ' *The Economics of Drug Innovation,* J.D. Cooper (cd.) (Washington, DC: The American University, 1970).
8. Council on Agricultural Science and Technology, *Impact of Government Regulation on the Development of Chemical Pesticides for Agriculture and Forestry,* Rep. No. 87 (Ames, IA: 1981).
9. de la Burde, B., and Choate, M. S., Jr., "Does Asymptomatic Lead Exposure in Children Have Latent Sequelae?" *Pediatrics 8:1088-1091, 1972.*
10. de la Burde, B., and Choate, M. S., Jr., "Early Asymptomatic Lead Exposure Development at School Age," *Pediatrics 8:638-642, 1975.*
11. *Dreyfus,* M., Economics and Technology Division, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, personal communication, Jan. 19, 1989.
12. Foster D. Snell, Inc., "Study of the Potential Economic Impacts of the Proposed Toxic Substances Control Act as Illustrated by Senate Bill S.776," prepared for the Manufacturing Chemists Association, Washington, DC, 1975.
13. Freeman, A. M., III, *The Benefits of Environmental Improvement, Theory and Practice* (Baltimore, MD: Johns Hopkins University Press, 1979).
14. Goring, C. A., "The Costs of Commercializing Pesticides, *Pesticide Management and Insecticide Resis-*

tance, D.L. Watson and A.W. Brown (eds.) (New York, NY: Academic Press, 1977), pp. 1-33.
15. Grabowski, H. G., *Drug Regulation and Innovation: Empirical Evidence and Policy Options* (Washington, DC: American Enterprise Institute, 1976).
16. Grabowski, H. G., and Vernon, J. M., *The Regulation of Pharmaceuticals: Balancing Benefits and Risks* (Washington, DC: American Enterprise Institute, 1983).
17. Grabowski, H.G., Vernon, J.M., and Thomas, L. G., ''Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry, ' *Journal of Law and Economics 21(1):133-163, 1978.*
18. Hattan, D.G., "Role of the Food and Drug Administration in Regulation of Neuroeffective Food Additives," *Nutrition and the Brain,* vol. *6,* R.J. Wurtman and J.J. Wurtman (eds.) (New York, NY: Raven Press, 1983).
19. ICF, Inc., *Regulatory Impact Analysis for New Chemical Reporting Alternatives Under Section 5 of TSCA* (Washington, DC: U.S. Environmental Protection Agency, May 10, 1983).
20. Jadlow, J., "Competition and Quality Within the Drug Industry: The 1962 Kefauver-Harris Drug Amendments as Barriers to Entry," *Antitrust Law and Economic Review 5(2), 1971-72.*
21. Katzman, R., Lasker, B., and Bernstein, N., "Accuracy of Diagnosis and Consequences of Misdiagnosis of Disorders Causing Dementia, " prepared for the Office of Technology Assessment, Washington, DC, 1986.
22. Lave, L., *The Strategy of Social Regulation: Decision Frameworks for Policy* (Washington, DC: Brookings Institution, 1981).
23. Levin, R., *Reducing Lead in Drinking Water: A Benefit Analysis, EPA-230-09-86-019* (Washington, DC: U.S. Environmental Protection Agency, 1986).
24. Mathtech, Inc., *Economic Impact Analysis of Final Test Rule for 33 Solid Waste Chemicals* (Washington, DC: U.S. Environmental Protection Agency, Mar. 10, 1988).
25. Merrill, R. A., "Regulating Carcinogens in Food: A Legislator's Guide to the Food Safety Provisions of the Federal Food, Drug and Cosmetic Act," *Michigan Law Review 77(2):171-250, 1978.*
26. Mund, V. A., "The Return on Investment of the Innovative Pharmaceutical Firm,' *The Economics of Drug Innovation,* J.D. Cooper (cd.) (Washington, DC: The American University, 1970).
27. National Academy of Sciences, National Research Council, *Decisionmaking for Regulating Chemicals in the Environment* (Washington, DC: National Academy of Sciences, 1975).
28. National Academy of Sciences, National Research Council, Lead *in the Human Environment* (Washington, DC: National Academy Press, 1980).
29. National Academy of Sciences, National Research Council, *Regulating Pesticides* (Washington, DC: National Academy Press, 1980).
30. National Academy of Sciences, National Research Council, *Toxicity Testing: Strategy To Determine Needs and Priorities* (Washington, DC: National Academy Press, 1984).
31. National Academy of Sciences, National Research Council, *Regulating Pesticides in Food: The Delaney Paradox* (Washington, DC: National Academy Press, 1987).
32. Peltzman, S., *Regulation of Pharmaceutical Innovations: The 1962 Amendments* (Washington, DC: American Enterprise Institute, 1974).
33. Pharmaceutical Manufacturers Association, *Facts at a Glance* (Washington, DC: 1988).
34. Provenzano, G., "The Social Costs of Excessive Lead Exposure During Childhood,' Low Level *Lead Exposure: The Clinical Implications of Current Research,* H. Needleman (cd.) (New York, NY: Raven Press, 1980).
35. Provenzano, G., ''Economic Consideration in Regulating Neurotoxic Substances," prepared for the Office of Technology Assessment, Washington, DC, April 1989.
36. Regulatory Research Service, *TSCA Section 5 Submission: A Critique of the EPA Economic Impact Analysis of Proposed Section 5 Notice Requirements,* prepared for Chemical Manufacturers Association, EPA Doc. Control No. OPTS-50018-C8 (Washington, DC: 1981).
37. Regulatory Research Service, *Impact of the Toxic Substances Control Act on Innovation in the Chemical Specialties Manufacturing Industry,* prepared for the Chemical Specialties Manufacturers Association (Washington, DC: 1982).
38. Sarett, L. H., ''FDA Regulations and Their Influence on Future R&D," *Research Management 16(2):18-*20, 1974.
39. Schwartz, J., *Costs and Benefits of Reducing Lead* in *Gasoline: Final Regulatory ImpactAnalysis, EPA-230-05-85-006* (Washington, DC: U.S. Environmental Protection Agency, 1985).
40. Shapiro, M., "Issues for the Economic Analysis for Section 4 Testing Rules Raised by the OSW Testing Rule and Future Category Rules," memorandum, Economics and Technology Division, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, Dec. 31, 1988.
41. U.S. Congress, General Accounting Office, *Cost-Benefit Analysis Can Be Useful in Assessing Environmental Regulations Despite Limitations, GAO/ RECD-84-62* (Washington, DC: 1984).
42. U.S. Congress, House Committee on Interstate and Foreign Commerce, *Toxic Substances Control Act,*

94th Cong., 2d sess. (Washington, DC: U.S. Government Printing Office, 1976).

43. U.S. Congress, House Committee on Science and Technology, *Neurotoxins: At Home and the Workplace, 99th* Cong., 2d sess. (Washington, DC: U.S. Government Printing Office, 1986).
44. U.S. Congress, Office of Technology Assessment, *Losing a Million Minds: Confronting the Tragedy of Alzheimer's Disease and Other Dementias* (Philadelphia, PA: J.B. Lippincott Co., 1987).
45. U.S. Congress, Office of Technology Assessment, "Technological Innovation and Health, Safety and Environmental Regulation, unpublished report, 1981.
46. U.S. Council on Wage and Price Stability, *Pre-Manufacture Notification Under the Toxic Substances Control Act* (Washington, DC: Executive Office of the President, 1981).
47. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, *Air Quality Criteria for Lead, EPA-600/8 -/028F* (Research Triangle Park, NC: 1986).
48. U.S. Environmental Protection Agency, Office of Policy, Planning and Evaluation, *EPA's Use of Benefit-Cost Analysis: 1981-1986, EPA-230-05-87-028* (Washington, DC: 1987).
49. U.S. Environmental Protection Agency, Office of Toxic Substances, "preliminary Assessment of the Health Risks From Exposure to Acrylamide," draft report, Washington, DC, March 1988.
50. U.S. Environmental Protection Agency, Office of Toxic Substances, Economic and Technology Division, *TSCA Chemical Fate Affects Guidelines and Cost Estimates* (Washington, DC: Aug. 8, 1988).
51. Warden, W. M., "Introduction of New Therapeutic Drugs in the United States and Britain: An International Comparison," *Clinical Pharmacology and Therapeutics,* May *1973.*
52. Wiggins, S. N., *The Cost of Developing a New Drug* (Washington, DC: The Pharmaceutical Manufacturers Association, 1987).

Chapter 9

International Regulatory and Research Activities

‘‘The need for generally accepted scientific principles and requirements in all areas of toxicology particularly applies to the newly developed field of neurotoxicology. Methods continue to be developed in isolation, and the comparability of results is often in doubt. Furthermore, until scientific principles have been agreed on, internationally accepted strategies to test the effects of chemicals on the many functions of the mammalian nervous system will not be developed. ”

Principles and Methods for the Assessment of Neurotoxicity Associated With Exposure to Chemicals
World Health Organization, 1986

“The NACA supports additional neurotoxicological and behavioral effects testing as a legitimate component of the requirements for re-registration and registration.

John F. McCarthy
Vice President for Scientific and Regulatory Affairs
National Agricultural Chemicals Association, 1989

“Exporting banned pesticides demonstrates that from the cradle to the grave---or from production to use and disposal--dangerous chemicals are discharged into our environment, and threaten the public health both here and abroad. ”

Sandra Marquardt
Exporting Banned Pesticides: Fueling the Circle of Poison
Greenpeace USA, 1989

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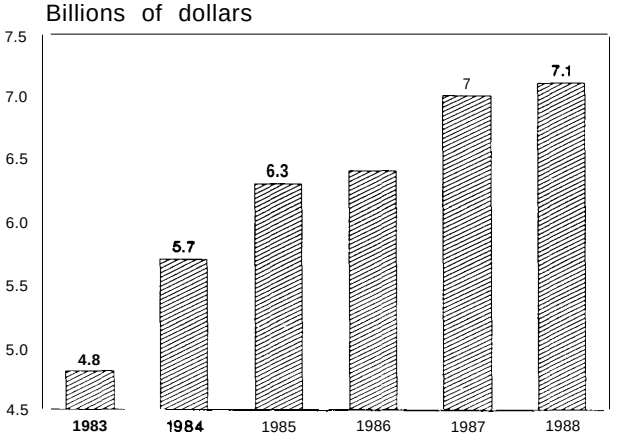
Chapter 9
International Regulatory and Research Activities

This chapter examines the international regulatory and research programs devoted to neurotoxic substances in general and neurotoxic pesticides in particular. The first part of the chapter addresses the export of neurotoxic pesticides that have been banned or severely restricted (a limited ban) in the United States. Regulatory programs in foreign countries, both industrialized nations and developing nations, are discussed. The second part of the chapter focuses on international research activities. This chapter does not address the export of food additives, drugs, and other chemicals.

INTERNATIONAL REGULATORY ACTIVITIES

According to the U.S. General Accounting Office (GAO), from 1977 to 1987, the worldwide agricultural chemical market doubled in size, to more than $17 billion. U.S. pesticide export sales currently represent approximately one-quarter of the world pesticide market. Although U.S. export statistics vary, the best estimates conclude that about 400 to 600 million pounds of U.S.-manufactured pesticides are exported each year to foreign countries. According to GAO, unregistered pesticides, including banned or restricted pesticides as well as pesticides that may never have sought U.S. registration, now account for about 25 percent of all U.S. pesticide exports (61).

Figure 9-l—Total U.S. Pesticide Exports, 1983-88

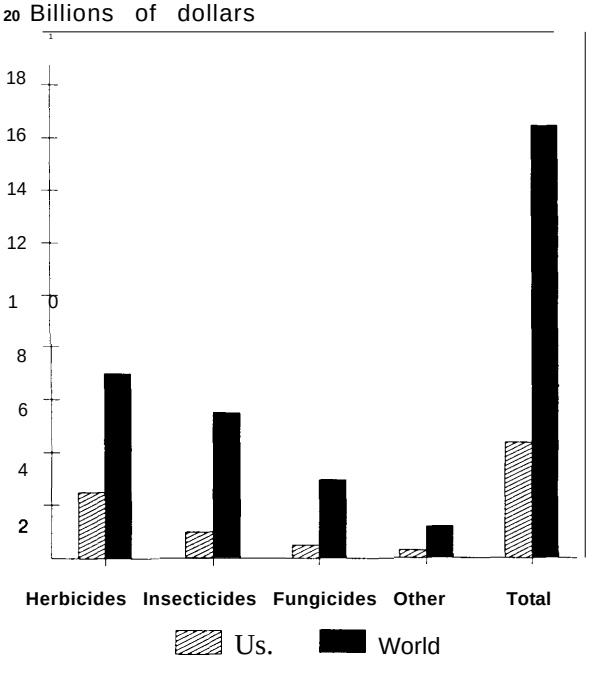


SOURCE: Office of Technology Assessment, 1990, based on U.S. Department of Commerce, Bureau of the Census, Statistical *Abstract of the United States 1989,* 109th ed. (Washington, DC: 1989).

According to other estimates, the United States supplies approximately one-half of the pesticides imported in most Latin American countries, where a substantial amount of the fresh fruits and vegetables eaten in the United States in the winter months are grown (42). Figure 9-1 illustrates U.S. pesticide exports for 1983 to 1988. In recent years, approximately 50,000 different pesticide products have been registered for use by the Environmental Protection Agency (EPA) (61). This figure does not include pesticides that have never been registered but are manufactured and exported for use outside the United States. Figure 9-2 compares U.S. pesticide sales with world pesticide sales for 1987.

Some developing nations have few or no regulations to protect workers and consumers from the harmful effects of neurotoxic substances. Developing nations that do have regulations often do not have adequate resources to implement and enforce them. This lack of effective regulation and enforce-

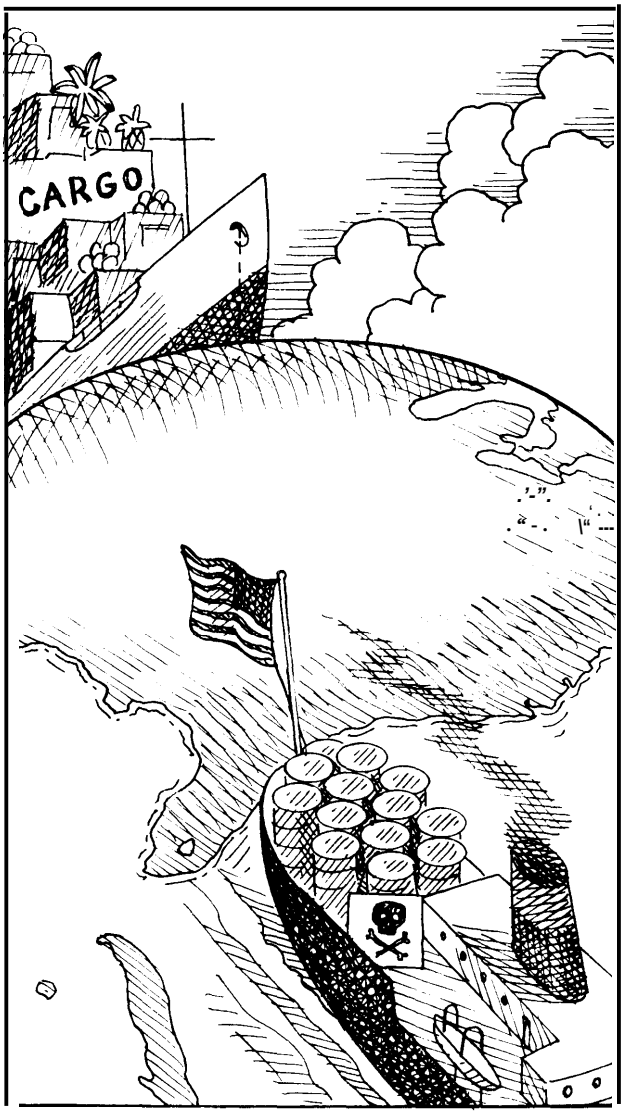
Figure 9-2—U.S. and World Pesticide Sales
(Basic Producer Level, 1987)



SOURCE: Pesticide Industry Sales and Usage: 1987 Market Estimates, Economic Analysis Branch, Biological and Economic Analysis Division, Office of Pesticide Programs, Environmental Protection Agency, Washington, DC, September 1988.

ment in developing nations has a negative impact not only on the public health and environment in user countries, but also in industrialized nations, including the United States, where people process and consume imported crops that may contain pesticide residues.

Despite many regulations promulgated in this country for the protection of consumers and workers, U.S. citizens are exposed to banned and severely restricted pesticides through what has come to be referred to by critics as the ''boomerang effect' or the "circle of poison" (41,70). At times, food in U.S. supermarkets has been imported from developing countries where farmers use pesticides manufactured in the U.S. that have been banned, severely restricted, or never registered for use here. Figure 9-3 indicates the dollar value of total U.S. food imports from 1983 to 1988. One organization has estimated that 70 percent of the pesticides exported to developing countries are used on crops grown for export to industrialized countries (70). This effectively circumvents the protection that the regulatory action was intended to provide.

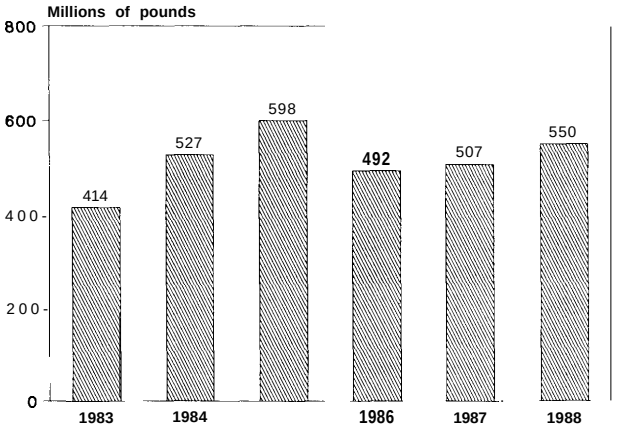


Illustrated by: Ray Driver

Federal law currently permits U.S. companies to manufacture and distribute banned, severely restricted, and never registered pesticides for use in developing nations, despite the possibility that food products containing residues of these pesticides may be imported to the United States and made available to U.S. consumers. Little definitive information exists on the identity and quantity of residues of banned, severely restricted, and never registered pesticides that return to the United States on imported crops and meats. This is due in part to the relatively small number of Food and Drug Administration (FDA) and U.S. Department of Agriculture (USDA) personnel available to screen sufficient quantities of imported crops and to limitations in the technology for detecting residues (62). However, data are available on the dollar value of crops that are produced domestically versus the value of crops that are imported. Figure 9-4 compares domestic production with imports of selected major crops. Some crops, such as coffee, are not produced domestically, so the United States must depend entirely on imports to supply consumer demand.

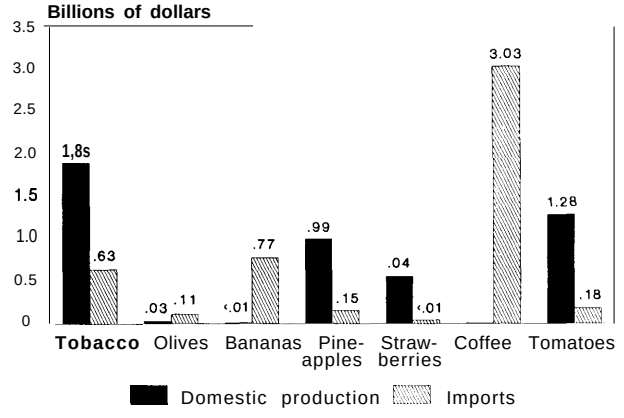
One example of the effect of current policies is the export of the insecticide chlordane. This product was taken off the U.S. agrichemical market in 1978 due to concerns about its carcinogenicity (it is also neurotoxic) and its persistence in animal fatty tissue and in the environment. Yet Federal law allows it to be manufactured and exported, without prior notification, to developing countries which do not have to adhere to U.S. use controls. Chlordane and heptachlor export formulations were both registered under section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and as such are exempt from the export notification requirements imposed by language in section 17 of FIFRA. At least twice in 1988, adulterated beef from Honduras, contaminated with chlordane, was imported into the United States and consumed by people in Florida, Kentucky, and Minnesota before the contamination was discovered (33,54). In one such instance, the

Figure 9-3-Total U.S. Food Imports, 1983-88



SOURCE: Office of Technology Assessment, 1990, based on U.S. Department of Commerial, Bureau of the Census, Statistical Abstract *of the United States 1989,* 109th ed. (Washington, DC: 1989).

Figure 9-4-Domestic Production v. Imports of Selected Major Crops



SOURCE: Office of Technology Assessment,1990, based on U.S. Department of Commerce, Bureau of the Census, Statistic/Abstract *of the United States 1989,* 109th ed. (Washington, DC: 1989).

chlordane residue was reported to be eight times the approved tolerance (33). Chlordane has been banned for all agricultural use in the United States yet is widely used in agricultural settings in countries such as Argentina, Australia, Colombia, and the Dominican Republic (33). In some cases, residues are not the result of direct application to crops or livestock. The Honduran problem was attributed to the use of chlordane on nearby sugarcane.

The misuse of registered chemicals, many of them neurotoxic, is an equally important issue *(38).* Registered chemicals used by untrained farmworkers without proper protective clothing and equipment, in inappropriate amounts on inappropriate crops, and without attention to other safety regulations, have been known to cause significant public health and environmental problems. Moreover, a substantial proportion of all pesticides are used to destroy pests that primarily affect the appearance of agricultural crops. Consumers often demand that their fruits and vegetables look "picture perfect"; however, cosmetic imperfections usually do not affect either the taste or the nutritional value of most foods (22). Although limited use of less hazardous pesticides is generally considered to be economically beneficial and to pose a minimal health risk, overuse of the more hazardous pesticides is an increasing concern among public health officials worldwide.

U.S. Regulation of Neurotoxic Substances

Export Laws

The United States has several laws governing export of toxic substances. The Toxic Substances Control Act (TSCA) was enacted in 1976 to address the risks presented by hazardous chemicals and is the primary statute regulating the export of industrial chemicals. Section 12 of TSCA addresses exportation of hazardous chemicals. Section 3017 of the Resource Conservation and Recovery Act (RCRA) discusses the export of hazardous waste, and section 17 of FIFRA governs importation and exportation of pesticides and devices.

Under TSCA, chemicals for domestic use that present an unreasonable risk of injury to humans and are imminent hazards to the environment can be regulated. The Act requires that regulation be done in such a way as not to impede unduly or create unnecessary economic barriers to technological innovation. Section 12 provides that, in most instances, the requirements of TSCA do not apply to substances manufactured, processed, or distributed for export. The requirements will apply, however, if it is determined that the substance, mixture, or article will present an unreasonable risk of injury to the health of persons within the United States or to the environment of the United States. The Act also provides that any person who exports or intends to export a substance for which submission of data is required under this Act must notify the Administra-

tor of the Environmental Protection Agency of the exportation or intent to export. Moreover, the Administrator shall then furnish to the government of the importing country notice of the availability of the data submitted for each substance.

RCRA provides for the management and disposal of solid wastes to avoid contamination of the environment. Section 3017 prohibits any exporting of hazardous waste unless the importing country has been given notice of and has consented to the shipment of the waste. However, exporters are not required to describe the contents or toxicity of the waste they are shipping. In addition, incinerator ash and municipal waste, both of which contain neurotoxic metals and chemicals, are not covered by the consent scheme.

Section 17 of FIFRA states that pesticides and devices intended solely for export are exempt from the testing and review requirements of the Act. Accordingly, pesticide manufacturers and distributors can legally export pesticides that have been banned or never registered for use in this country. Little is known about pesticides that have never been registered because they are exempt from public health and environmental testing requirements if domestic use is not intended (32).

U.S. pesticide manufacturers are required to notify the importing purchaser, and EPA notifies the country, if the pesticide to be exported has been banned or never registered for use in the United States. EPA requires these statements annually for the first shipment of each banned or unregistered product to a particular purchaser for each importing country. Although EPA has streamlined the transmittal process for export notices to U.S. embassies, no formal procedures govern the processing and transmittal of FIFRA notices once they arrive at an embassy (61). Most embassies destroy files as recent as 1985, and staff at every embassy surveyed by GAO indicated that they sometimes do not retain copies when transmitting files to the foreign governments (61). According to GAO, **as** recently as 1988, EPA had no program to determine whether pesticide manufacturers were complying with the export notification requirements and had no assurance that importing countries were adequately notified of unregistered U.S. pesticides entering their borders (61). Moreover, shipment of the unregistered pesticide may proceed before the foreign government has received the notice, since its purpose is only informational.

Although the language in section 17(a) of FIFRA governing notification requirements for unregistered pesticides provides for no exceptions, EPA, in 1980, established a policy that effectively waives notification requirements for unregistered pesticides that are "minor variations" on formulations and active ingredients registered in the United States and that are ''similar in composition and use" to registered pesticides. These exempted pesticides are commonly referred to as "me-toos." Thus, never-registered pesticides must bear the statement "Not Registered for Use in the United States of America' when they are exported to foreign markets, but me-toos are exempt from the labeling requirement, despite the fact that the active ingredient and inert ingredient formulation may be different from that registered in the United States and thus pose a different risk (32). Accordingly, it would be difficult for an importing foreign purchaser or nation to know the degree of hazard of such a product. Moreover, GAO determined that EPA did not send required notices for three of four pesticides, despite the fact that they were voluntarily canceled because of concern about toxic effects (42). Although EPA finalized cancellations of these four pesticides between 1975 and 1987, a notice was issued on only one of them (42). Consequently, foreign governments may not be alerted to unreasonable hazards associated with using particular pesticides.

Section 17(b) of FIFRA requires that EPA notify foreign governments and appropriate international agencies "[whenever a registration, or a cancellation or suspension of the registration of a pesticide becomes effective, or ceases to be effective. . . ." EPA has no regulation or formal policy statement on when to issue such a notice. Instead, the Agency issues notices for cancellations and suspensions it deems to be of "national or international significance" (42). EPA periodically publishes a booklet summarizing and clarifying its actions on canceled, suspended, and restricted pesticides (67); however, this booklet was last published in 1985. If updated annually, this booklet could be used by foreign governments and others as a reference guide to U.S. regulatory actions on pesticides (42).

On January 15, 1981, several days before the end of his term, President Jimmy Carter issued Executive Order No. 12264, "On Federal Policy Regard-

ing the Export of Banned or Significantly Restricted Substances,' including pesticides. This order put controls on exports of substances that were banned or severely restricted in the United States. Several days after becoming President, Ronald Reagan revoked the order.

Regulation of Pesticide Residues in Domestic and Imported Food

Federal jurisdiction over pesticide residues in food is divided among three agencies—EPA, FDA, and USDA. Their authority derives primarily from five laws: FIFRA; Federal Food, Drug, and Cosmetic Act (FFDCA); Federal Meat Inspection Act (FMIA); Poultry Products Inspection Act (PPIA); and Egg Products Inspection Act (EPIA) (62).

Under FIFRA, a pesticide must be registered (even conditionally) or have its registration pending before it can be used in the United States. In registering a pesticide, EPA considers the results of numerous public health and environmental fate studies (submitted by the manufacturer) to determine the risks and benefits associated with the use of that pesticide. Registration includes identification of the specific commodities on which the pesticide can be used. During the registration process, EPA attempts to determine if the pesticide's use will cause an *unreasonable* risk to humans or the environment (see ch. 7). The registration requirements for pesticides are set forth in section 3 of FIFRA and are defined more fully in EPA regulations (40 CFR 1987 ed. 158, 162).

If use of a pesticide will leave a residue on food or feed commodities, EPA, under FFDCA, establishes a legal maximum level, or "tolerance," for the pesticide residue. A tolerance, or an exemption from a tolerance, must be granted before a pesticide is registered. Tolerances cannot be legally exceeded, and residues of pesticides for which no tolerance has been established or exempted are prohibited on foods. Commodities that violate these prohibitions are subject to seizure by FDA, USDA, or a State enforcement agency (62).

If a pesticide has never been registered for use in the United States and the manufacturer does not expect residues to occur on imported foods, a tolerance will not necessarily have been set. Also, tolerances may not have been established if a registration application is pending. Any imported food contaminated with a pesticide that does not have a tolerance is considered adulterated and is subject to seizure at the U.S. border. However, if USDA and FDA border inspectors are not told that these pesticides have been used or they are unable to test for them, illegal residues in imported food will not necessarily be detected.



Photo credit: Michael Hansen

One pesticide industry spokesman has indicated that increased monitoring for pesticide residues would strengthen and bolster U.S. consumer confidence in the quality of the food supply *(35)*. Additional testing of agricultural chemicals, called ''reregistration, '' is under way, and over the next 9 years, the agricultural chemical industry expects to pay $170 million in fees to help EPA finance the effort (35).

FDA, under FFDCA, is responsible for enforcing tolerances established by EPA for food and animal feed in interstate commerce. It is also responsible for enforcing the prohibition in food or animal feed of residues of pesticides for which no tolerance has been set or exemption given. In the past, when FDA considered low levels of a residue to pose little risk to human health, it would set informal residue levels, called action levels. At these levels, FDA would take regulatory action; below them the food was considered safe. A recent court opinion struck down

this practice, and EPA and FDA are currently determining how to address this issue.[1]

The USDA is responsible for enforcing tolerances in meat and poultry under authority of the Federal Meat Inspection Act and the Poultry Products Inspection Act. It is also responsible for monitoring pesticide residues in raw egg products (dried, frozen, or liquid eggs) and for enforcing tolerances at establishments having official USDA egg products inspection services, under authority of the Egg Products Inspection Act (62). While most of the focus has been on food crops, more insecticide is used on cotton on a worldwide basis than any other crop (23).

International Effects of U.S. Export Practices

Regulations governing the export and import of neurotoxic substances are far from uniform. Many nations, including the United States, have policies and procedures in place, but too often they work only on paper. In practice, they may allow neurotoxic substances to slip through the regulatory cracks. Regulatory requirements designed to protect workers and consumers from the harmful effects of toxic substances may be ineffective in some countries. The United Nations Food and Agriculture Organization (FAO) has implemented an International Code of Conduct on the Distribution and Use of Pesticides to outline responsible behavior on the part of persons who deal with pesticides. Pesticides are known as the group of chemical products that includes insecticides, acaricides, molluscicides, rodenticides, nematicides, anthelmintics, fungicides, and herbicides (26). Although many consider the code a step in the right direction in terms of providing notification, use, and transport protections (among others), it is only a voluntary code, and FAO has no enforcement authority. The objectives of the code are to set forth standards of conduct for all entities engaged in distributing and using pesticides. Pesticides are biologically active, and their uncontrolled release will always present a potential threat to the environment (27). The code describes the shared responsibility of many segments of society, government, industry, trade, and international institutions to use pesticides when necessary without adversely affecting people or the environment (40).

The Pesticide Development and Safe Use Unit of the International Program on Chemical Safety has toxicologically evaluated 83 pesticides widely used in agriculture and public health and established average daily intake and maximum residue limits for 23 of them (43). The Codex Alimentarius Commission (Codex) has established maximum residue tolerances for numerous chemical residues, contaminants, and food additives (43). Sampling and analysis principles to determine pesticide residues in food and animal feed have also been developed (43).

Despite numerous regulations governing the export and import of pesticides and other neurotoxic products in the United States and abroad, some countries do not have the regulatory framework and resources to adequately protect human health and the environment from these substances. Nearly all major U.S. corporations producing pesticides that have been banned, severely restricted, or never registered for use in the United States are multinational and have subsidiaries or other distributors in developing countries. In some cases it is through these subsidiaries and distributors that such pesticides are imported and distributed in developing countries. This also allows corporations with stocks of toxic substances that can no longer be sold in the United States to sell existing products.

In addition to concern about food products that are imported into the United States with residues of banned, severely restricted, or unregistered pesticides, critics are concerned that exported pesticides may not be properly packaged or labeled. At times, the package labeling and instructions may be written in English instead of the native language of the importing country. In some cases, farmworkers using the pesticides are illiterate and thus could not read the labels even if they were written in their native language.

Improper labeling may prevent implementation of appropriate safety measures or precautions by farmworkers and consumers. In July 1986, phosdrin, a potent neurotoxic insecticide classified by the World Health Organization (WHO) as "extremely hazardous," was purchased in Benguet Province, Philippines. The product label had seven labeling infringements, all of them in direct violation of the FAO code (20). Similar violations of the FAO code have

[1]See 21 CFR secs. 109 and 509, 1987; FDA Compliance Policy Guides, 1986. The informal process by which these action levels were set was vacated by the Federal Appeals Court in the *District of Columbia Consumer Nutrition institute v. Young, 818* F.2d 943 (D.C. Cir. 1987).

been discovered recently in Ecuador, Papua New Guinea, Thailand, Senegal, Colombia, South Korea, Sudan, and Mexico (18). In Iraq in 1973, an epidemic of methyl mercury poisoning resulted from improper labeling. Farmers and their families ate bread made from seed treated with mercury. The bags in which the grain was imported were clearly labeled in English and Spanish (neither of which is a native language of Iraq). More than 1,000 people died from mercury poisoning, and 10 times more were hospitalized (see box 2-A, in ch. 2) (2).

In some instances, even if the pesticide is properly packaged and labeled when it leaves the exporting country, it is repackaged in the importing country without the necessary labeling. Accordingly, the pesticide product that actually reaches the user may lack very important health and safety information. Repackaging is frequent, because pesticides are often shipped in 35- to 100-gallon drums and are then transferred into smaller, more manageable sizes for the consumer. On an international scale, pesticides are widely available to the general public, and few warnings are given (18). In some countries, pesticides are sold in markets alongside vegetables and grains. People can scoop up pesticides in cartons, bottles, cans, plastic or paper bags—whatever they bring to the market. Often they do not know the name of the chemical they are purchasing because the container is not labeled. In some countries, pesticides are marketed as ‘‘plant medicines, " and farmers are encouraged to use them to keep their crops healthy in much the same way that medicines are used to keep people healthy (24).

The pesticide industry is aware of the illiteracy problem and is taking steps to circumvent it. One approach is to use illustrations, or ‘‘pictograms, ’ that convey to an illiterate worker the appropriate way to mix, use, store, or clean up pesticides. These pictograms were designed by the International Group of National Associations of Manufacturers of Agrochemical Products, an international consortium of pesticide manufacturers, formulators, and distributors, in cooperation with the FAO. Figure 9-5 shows examples of pictograms currently used by some pesticide companies in developing countries. It is not yet known how extensively the pictograms are used or with what degree of success.

It is not only in export and use that pesticides pose problems, however. Pesticides are frequently manufactured in developing countries, where there are less stringent regulations. U.S. manufacturers claim that it is safer to produce pesticides in the United States, with its many regulations, than in developing countries. The combination of lethal ingredients and deficient safety precautions was dramatically demonstrated by the 1984 leak at the Union Carbide pesticide plant in Bhopal, India, which killed more than 2,000 people and injured tens of thousands (69).

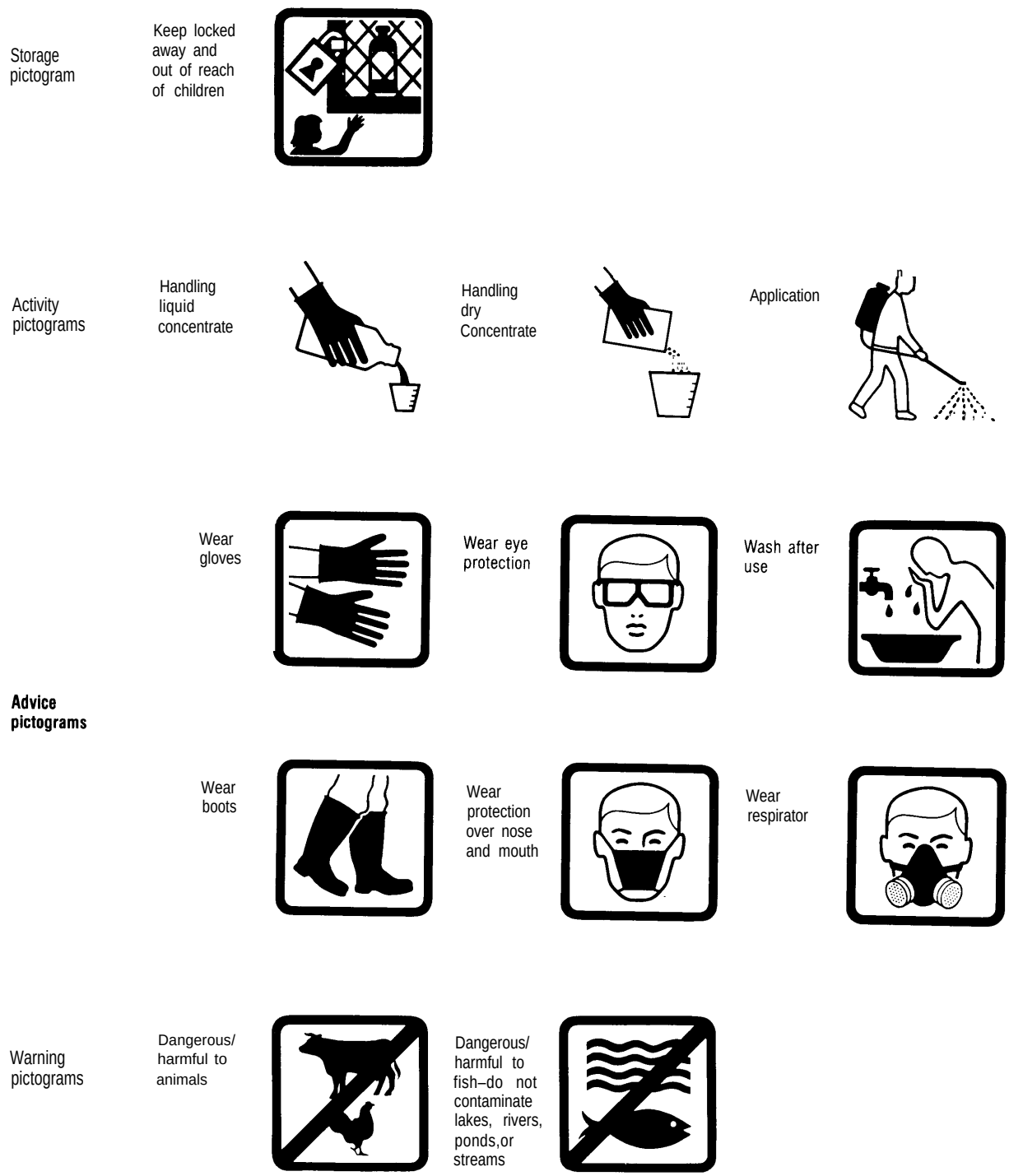
Pesticide manufacturers justify U.S. export practices and advocate increased use of pesticides by maintaining that developing nations need pesticides to combat famine. The world population is growing rapidly: in 1975 it was 4.1 billion; in 1987 it had grown to 5,1 billion; and the projected figure for 2005 is 6.7 billion (64). Feeding this ever-increasing population is a problem because land available for farming is not increasing significantly. Moreover, the population increase is greatest in developing nations.

Critics of U.S. export practices argue that pesticides in the developing world are more often applied to luxury export crops than to staples eaten by local inhabitants and that, in any case, nonchemical methods of pest control could and should be implemented (70). According to the World Bank, the world produces enough grain alone to provide every human being on the planet with 3,600 calories a day (72). In a major 1986 study of world hunger, it found that a rapid increase in food production does not necessarily result in less hunger. Hunger can only be alleviated by redistributing purchasing power and resources to those who are undernourished (72). In India, for example, despite a 24-million-ton grain surplus (25), per-capita consumption of grain has not increased in 20 years and nearly half the population lacks the income necessary to buy a nutritious diet (63). Availability of grain in India has actually declined in recent years, despite a rise in pesticide use (57). Furthermore, numerous plantations and other agricultural areas have been forced to turn away from pesticide use due to resistance problems developed by insects, weeds, and fungi overdosed with pesticides (23).

The USDA has addressed the issue of world hunger, particularly in developing nations, as follows:

> First, the food problem of the developing countries is not a global lack of food. More than enough food is produced and stored in the world to provide

Figure 9-5-Pictograms for Agrochemical Pesticides



SOURCE: International Group of National **Associations of Manufacturers of Agricultural Products, 1988** ***Pictograms for Agrochemical Labels: An Aid to the Safe Handling of Pesticides.***

people everywhere with adequate diets. In times of crises, countries have the capacity to respond quickly with food and other needed supplies to alleviate hunger and suffering. Unfortunately, political differences within and between countries and logistics sometimes impede the efforts to save lives, as in the current food crisis in sub-Saharan Africa (59).

Regulatory Policies in Other Industrialized Nations

For the most part, regulations in industrialized countries are enforced, and public health and environmental problems from pesticide importation, distribution, and use are not as severe as in developing nations. However, this does not mean that pesticide problems are nonexistent in industrialized nations. The following discussion summarizes the activities of some industrialized nations with major regulatory programs.

Canada

Within Canada primary responsibility for environmental issues with international and interprovincial components lies with the federal government, while the provinces are generally responsible for enforcing regulations governing industries within their borders (12). Environment Canada, established in 1971, is the federal department that administers legislation relating to environmental protection. A major reorganization of Environment Canada in 1986 and 1987 consolidated the department's activities into three main branches: Conservation and Protection, Atmospheric Environment (responsible for meteorology), and Parks (responsible for maintenance of national parks). Conservation and Protection includes the Canadian Wildlife Service, Environmental Protection, and the Inland Waters and Lands Directorate.

The primary federal legislation controlling the availability, sale, and use of pesticides is the Pest Control Products Act, administered by Agriculture Canada (12). The Act requires annual registration of pesticides and prohibits import or sale of unregistered pesticides. It is intended to ensure that no person shall use a pesticide under conditions that are unsafe to human or animal health or that will adversely affect the environment. The Act also requires that such products be effective for their intended purposes (46). There are currently plans to upgrade the legislation to require more stringent testing of pesticide products.

Agriculture Canada calls on various federal departments to provide expert advice on hazards that may be associated with the use of a product. Health and Welfare Canada requires and reviews a range of toxicological studies to assess potential health hazards that may be associated with exposure to a chemical, including acute, subacute, chronic, reproduction, teratology, and metabolism studies. In addition, studies to estimate anticipated human exposure during typical field use of the chemical are required.

The federal departments primarily involved in the pesticide review process are Agriculture Canada, Fisheries and Oceans Canada, Environment Canada, and Health and Welfare Canada (12). The Pesticides Directorate of Agriculture Canada receives the manufacturer's application for registration of the pesticide and is responsible for the evaluation process and the coordination of reviews from the other agencies (46).

Federal Republic of Germany

The Federal Republic of Germany, one of the world's largest exporters of pesticides, divides and sometimes shares lawmaking and enforcement powers between the federal government (Bund) and the 11 states (Lander). The Federal Ministry for Environment, Nature Protection, and Nuclear Safety was created in 1986, in the aftermath of the accident at the nuclear power plant in Chernobyl in the Soviet Union. It was created out of the Environment and Nuclear Safety divisions of the Ministry of Interior and the Nature Protection Division of the Ministry of Nutrition, Agriculture, and Forest (MNAF) (14).

Pesticides are regulated under the Pfalnzenschutgesetz (Plant Protection Law), which outlines the terms of licensing, prohibition, or restriction of use, application, and export (43). Licensing, which is issued only if the pesticide is safe, efficacious, and in compliance with requirements for human and animal health and safety, provides for classification, testing, labeling, and packaging (43).

The Federal Environmental Agency (FEA), under the authority of the MNAF, is responsible for general environmental policy-related research, including maintenance of an environmental information planning system, collection of information necessary to develop and implement federal laws, and preparation of legislation and administrative regulations. The FEA has done considerable work

on the development of environmental impact assessment procedures (14). A separate organization, the Conference of State Ministers for the Environment, which includes the Federal Environment Ministry, is the major forum for coordination of state and federal environmental policy. Federal-state working committees have been established to coordinate programs in all major areas of environmental protection (14).

The Federal Ministry for Foreign Affairs is responsible for international relations and environmental policy. The Federal Ministry of Food, Agriculture, and Forestry houses the Agricultural Research Center, which monitors soil biology, agrichemicals, agricultural waste recycling, plant ecophysiology, and water pollution, and the Federal Center for Biological Research in Agriculture and Forestry, which is responsible for pesticide measurement and control, biological pest control, and inspection of commercial chemical preparations for plant protection and pest control (14).

A number of environmental laws are in effect. The Act on Protection Against Dangerous Substances, which was adopted in 1980 and amended in 1986, establishes a testing and notification system for new chemical substances placed on the market after September 1981. The Act seeks to protect public health and the environment from harmful effects of dangerous substances by: 1) compulsory testing of and notification regarding substances; 2) compulsory classification, labeling, and packaging of dangerous substances and preparations; 3) prohibitions and restrictions on use; and 4) specific legal provisions concerning toxicity and occupational safety. The Act covers foodstuffs, tobacco products, cosmetic agents, animal feedstuffs and additives, pharmaceuticals, wastes, radioactive wastes, waste water, and waste oils (14).

The Act requires notification at least 45 days prior to placing a substance into initial circulation in a country that is a member of the European Community (EC), whether on a commercial basis or within the framework of any other business undertaking. There is no requirement for notification if the substance was manufactured and notified by an equivalent procedure in any other EC member country (14). Six administrative regulations have been adopted concerning information required in notifications, designation of the Federal Office for occupational and Safety Policy to receive notifications, inventory of existing chemical substances, labeling of hazardous substances, and general administrative procedures.

Criminal violations of environmental legislation are generally codified in division 28 of the criminal code, adopted in 1975 and last amended in 1987. Penalties range from fines to jail sentences and are usually defined in the particular environmental law (14).

Belgium

Environmental programs in Belgium are less well developed than those in other European countries. Because implementing legislation must, in most instances, be enacted by the regional administrations, norms and enforcement vary throughout the country (11).

A 1969 act regulates the manufacture, composition, storage, transport, and marketing of pesticides. Such activities may be carried out only by licensed persons. The maximum concentrations of residue after decomposition may also be controlled under the act, as well as the conditions of use of pesticides. Pesticides themselves are subject to an approval procedure, and the license usually lasts for 10 years. The approval is made subject to conditions, and it is an offense to use pesticides other than in accordance with these conditions (1 1).

A royal order of 1975 regulates the storage, trade, and use of pesticides and plant protection products. Pesticides are subject to premarket registration, and certain labeling and packaging requirements are set out (11). A royal decree of 1977 implements EC Directive 76/1 16, which prohibits the marketing of manure and fertilize, as well as all products with a specific action to stimulate crop production. This decree also regulates the information and indications to be put on the package, the documents required for transport, the packaging requirements, and the method of taking and analyzing samples (11).

A royal decree of 1982 requires that before placing a dangerous substance on the market, any manufacturer or importer must submit to the Minister of Public Health a dossier that includes a declaration of the unfavorable effects of the substance for the various uses envisaged. The decree establishes a Committee on Dangerous Substances, composed of officials of different ministerial departments and attached to the Ministry of Public Health. The committee is responsible for examining the

notification procedure and advises on the completeness of the application. A dangerous substance cannot be placed on the market during the 45 days it takes to complete the notification procedure (1 1).

France

Pesticides for agricultural use are governed by a 1972 law that controls manufacture, sale, and use as well as packaging and labeling (43). Prior to approval for production, toxicity and efficacy must be assessed, and the pesticide must be classified in terms of toxicity (43). Tolerance limits in foods are prescribed by presidential decree (43).

The Chemicals Control Law, adopted in 1977, governs hazardous substances. It is intended to protect public health and the environment against risks that may arise from natural or industrially produced chemicals, but it does not apply to chemicals used in research or to food additives, cosmetics, or drugs (13). The law provides for premanufacture notification for all chemicals that have not yet been marketed. Producers or importers must declare any new risk that may result from a change of manufacturing process or from emission of the said chemical into the environment (37).

Producers or importers of new chemicals must also submit a technical dossier providing the information needed for assessment of potential hazards. The competent authority may classify a substance as a "dangerous product' request from the manufacturer or importer any relevant information with respect to potential health or environmental effects; and prohibit or restrict the production, composition, storage, transportation, conditioning, labeling, marketing, use, or disposal of any chemical where deemed necessary to protect the public (37).

Producers of already marketed substances maybe required to provide public authorities with appropriate technical or toxicological data to evaluate potential health or environmental risks. Violation of the law may result in imprisonment or fines or both.

Japan

Agricultural chemicals are regulated by a 1948 law that has been amended several times, most recently in 1983 (43). It requires that pesticides be registered with appropriate government agencies, which classify pesticides according to persistence in crops and soil and water pollution potential (43). Limits are placed on the amount of active ingredients and the maximum allowable harmful ingredients for each pesticide (43). The applicant must provide test results on pesticide effectiveness, toxicity, phytotoxicity, and persistence (43). Labeling and packaging must represent truthfully all statements and facts on which the pesticide was registered and must include, among other things, the dangers posed and precautions to be taken for storage and use (43).

Other toxic substances are regulated by the Chemical Substances Control Law of 1973. The need for comprehensive measures to prevent environmental pollution has been recognized following environmental crises such as the mercury poisoning incident at Minamata Bay in the 1950s (see ch. 2).

The law requires notification and testing of all new chemical substances produced in quantities exceeding 100 kilograms. The law does not apply to chemicals in use before the law came into effect, but an agreement reached in the Diet makes some 800 existing chemicals subject to the same review standards as the new substances. The law also provides that, prior to production or importation, all new chemicals must be submitted to official examination regarding persistence, accumulative tendency, and toxicity to human beings.

A substance may be classified as a "specified chemical substance" if it accumulates easily in biological organisms, if it resists chemical changes caused by natural effects, and if it may harm human health when ingested over a period of time. The law was passed in response to polychlorinated biphenyl (PCB) poisoning (9). Chemicals tested and designated ''specific substances' are subject to prohibition or restriction. Although only PCBs have been formally listed as specific substances under the law, government officials say that two or three chemicals are withdrawn from testing every month when manufacturers learn that the chemicals probably would be specified and the manufacturer's name revealed. Another two or three applications for approval are suspended each month for lack of data (9).

The Pollution-Related Health Damage Compensation Law of 1974 was further modified, in the case of Minamata victims, by the Minamata Relief Law in 1978. The beneficiaries of this law are the victims of certain pollution-related diseases who have 'lived, worked, or otherwise been present" in designated areas. Testing for functional developmental disor-

ders, including behavior disorders, has become one of the most important aspects of the evaluation of developmental toxicity of chemicals, especially pharmaceutical drugs. There are two guidelines for developmental toxicity testing of chemicals-one a three-segment study for drugs, the other a multigeneration study plus embryotoxicity for environmental chemicals (56). In the case of specific diseases, where the source of pollution is known, the company responsible must pay compensation. In nonspecific cases, there is a levy on polluting industries to cover claims. Certified victims, that is, persons who have been examined by government medical panels, are entitled to medical care expenses and a monthly physical handicap payment, the amount being determined by the victim's age, sex, and ability to work. There are also child compensation allowances and survivors' benefits. Payment is made by local governments through the Pollution-Related Health Damage Compensation Association. The government covers the association's overhead costs, but payments to victims are financed by polluters.

United Kingdom

Pesticides are regulated under the Dangerous Substances Regulations and the Food and Environment Protection Act (43). The regulations specify which toxicity tests are necessary to categorize each pesticide, based on EC Directive 78/631 of 1978 (43). Packaging and labeling requirements are also set out in the regulations (43). Pesticide manufacturers must notify the government prior to marketing a new pesticide or suggesting new uses of an old one (43). Manufacturers must also provide sufficient data to enable government assessment of pesticide dangers, and warnings, precautions, and names of active ingredients must be included on all labels (43). The government has authority to request withdrawal of unsafe products and to specify maximum pesticide residues on crops, foods, and livestock feed (43).

Responsibility for protection of the environment lies primarily with the Department of the Environment. It has responsibility for introducing and implementing acts of Parliament and statutory instruments. Other ministries also have some responsibility for environmental protection. These include the Ministry of Agriculture, Fisheries, and Food, which controls the ocean disposal of wastes and has joint responsibility with the Department of the Environment and the Welsh Office for control of radioactive discharges from nuclear sites; the Department of Employment, which is responsible for health and safety; the Department of Health and Social Security; and the Department of Transport. Within the Department of the Environment is the Central Directorate on Environmental Pollution, staffed by a pool of scientists and administrators coordinating national regulatory policy in the environmental protection field, including participation in international activities (10).

Numerous divisions within the department are concerned with land use, conservation of wildlife and habitats, control of toxic substances, air and water pollution, and wastes. The Toxic Substances Division, for example, is responsible for developing policy aimed at protecting human health and the environment. Its responsibilities also extend to participation in international initiatives. However, the International Division has prime responsibility for coordinating United Kingdom policies on environmental affairs and presenting those policies before the United Nations, the Organization for Economic Cooperation and Development, the EC, and other bodies (10).

In 1987, a new, centralized agency was formed to enforce environmental laws and regulations in England and Wales. Her Majesty's Inspectorate of Pollution brought together several existing pollution control agencies: HM Industrial Air Pollution Inspectorate, for controlling major emissions to the atmosphere; HM Radiochemical Inspectorate, for controlling all radioactive discharges and disposals; the Hazardous Wastes Inspectorate, for monitoring the activities of local Waste Disposal Authorities; and the divisions of the Department of the Environment and the Welsh Office responsible for issuing consents for discharges by the Water Authorities.

Regulatory Issues in Developing Nations

Developing nations, especially those with a large agricultural economy, depend on pesticides to produce maximum yields. In many of these nations, agriculture is the primary industry and provides the country's primary income. In Ghana, for example, cocoa exports provide a majority of foreign exchange earnings (8). Misuse and excessive use of pesticides and chemicals are a significant and widespread problem in developing countries (15). The WHO has estimated that someone in a developing country is poisoned by pesticides

every **minute (65).** This is due in part to lack of a pesticide policy in many developing nations. The FAO estimated in 1988 that some 50 countries still did not have pesticide regulations (20). Those nations with a policy often do not have the infrastructure or economic resources to implement the policy. Moreover, in some developing nations, government officials charged with enforcing pesticide policies have a vested financial interest in maintaining a strong pesticide economy (20). In fact, the governments of many countries are pesticide importers, manufacturers, and exporters, as well as regulators of pesticides (20). Consequently, regulations designed to protect public health and the environment may receive little attention. In other cases, pesticides are heavily subsidized, making it cheaper to use pesticides than not (45).

Because of the lack of governmental controls, many developing nations must depend on the pesticide industry to regulate the importation, distribution, and use of pesticides, as well as to safeguard public health and the environment. In light of this, discussions of regulatory policy often focus on how much responsibility pesticide manufacturers and the governments of pesticide exporting countries should assume. Nations around the world agree that responsibility for safety and efficiency in distribution and use of pesticides must be shared by foreign manufacturers, exporters, and importers, as well as local formulators, distributors, repackers, advisers, and users (58). To facilitate the implementation of this duty, FAO adopted in 1985, and amended in 1987, a code covering such issues as proper pesticide transport, marketing and advertising, recalls, and notification on the part of regulators and manufacturers.

The code calls on industry to adhere voluntarily to its provisions and places an even higher responsibility on industry in countries that lack appropriate pesticide legislation and advisory services (58). The code maintains that manufacturers have a duty to retain an active interest in following their products to the ultimate consumer. Some assert that the ultimate consumer is the local farmer who buys a small amount of repackaged pesticide product for use. Following this line of reasoning, the manufacturer's duty would end with this purchase. On the other hand, there is the argument that a farmer who produces cash crops, as distinguished from a subsistence farmer, is not a consumer but a producer (6). These producer-farmers use factors of production—land, seed, labor, water, fertilizer, pesticides-to produce a cash crop. The consumerism the person who buys the produce with the intent of eating it. Accordingly, the pesticide manufacturers have a duty to retain an active interest in following their products—pesticides-to the dinner tables of the families and individuals of the world community(6). One could further argue that U.S. manufacturers have a special duty to protect and ensure the safety of food treated with U.S.-manufactured pesticides and eaten by U.S. consumers, regardless of where that food is grown.

One controversial provision of the code intended to address the issues of regulation and education is that of prior informed consent (PIC). Under PIC, a pesticide that has been banned or severely restricted in one country cannot be exported to another country unless the importing country's government has been fully informed of the reasons for the regulatory action and has consented to the importation of the pesticide (58). Pesticide exporting countries generally do not favor PIC and assert that it is too time-consuming, expensive, and burdensome for industry (20). Representatives of importing countries, on the other hand, claim that, in the absence of regulatory controls, PIC is the only avenue for allowing governments to determine if pesticides banned in other countries should be permitted within their borders. Although PIC is still a voluntary practice, the Netherlands became the first country to incorporate it into legislation and seek to make it legally binding (20).

The WHO has classified pesticides on the basis of the hazards they pose. Hazard is defined as the likelihood that a pesticide will cause immediate or short-term adverse effects or injury under circumstances of ordinary use. These classifications are based on the oral and dermal toxicity of the pesticide's active ingredient. Countries adopting the FAO code are also supposed to adhere to the following WHO toxicity classification in labeling their pesticides:

. IA Extremely Hazardous,
. IB Highly Hazardous,
. 11 Moderately Hazardous, and
. III Slightly Hazardous.

In addition, the Pesticide Action Network (PAN) has initiated a Dirty Dozen Campaign on an international scale to publicize the 12 most hazardous pesticides used worldwide, most of which are

neurotoxic. Since the campaign began, some countries have banned certain pesticides on the Dirty Dozen list, and others have restricted the availability of them (20). The pesticides are:

- camphechlor (toxaphene),
- chlordane/heptachlor,
- chlordimeform (Galecron),
- dibromochloropropane (DBCP),
- DDT,
- aldrin/dieldrin/endrin,
- ethlene dibromide (EDB),
- lindane/hexachlorocyclohexane (HCH),
- paraquat,
- ethyl parathion,
- pentachlorophenol (PCP), and
- 2,4,5-T.

Pesticide workers in developing countries are frequently not provided with appropriate protective clothing and equipment to guard against oral and dermal exposure when applying pesticide products (30). In tropical or semitropical climates, the temperature is often too hot to permit workers to comfortably wear protective clothing designed for use in more temperate climates (protective clothing is often made of plastic, rubber, or other nonporous material). Despite workers' lack of protective clothing, pesticides are sometimes sprayed from aircraft while workers are in the fields. Pesticides may also be sprayed from canisters strapped to the backs of unprotected workers.

Besides allowing the export of pesticides that have been banned or severely restricted for use in this country, present EPA regulations allow the export of pesticides that have never been reviewed by the Agency. Some critics argue that if a pesticide is not safe enough for use in the United States, it should not be exported. The FAO code holds that the fact that a product is not used or registered in the exporting country is not necessarily a valid reason for prohibiting export of that pesticide (58). Most developing countries are located in tropical and semitropical regions. Their climatic, ecological, agronomic, and environmental conditions, as well as their social and economic needs, may be different from those of industrialized nations. Accordingly, their pest problems may be quite different. The government of the exporting country, therefore, may not be in the best position to judge the suitability, efficacy, safety, or fate of the pesticide under conditions in the country where it may ultimately be used.

Critics of this export policy argue, however, that foreign relations problems could arise if products considered too unsafe and hazardous for use by people in the United States are deemed safe for use by people abroad. Although people in developing countries use only 10 to 25 percent of the world% pesticides (7,21), it is estimated that they account for as much as 50 percent of the acute poisonings of pesticide applicators and between 73 and 99 percent of their deaths (15). Furthermore, residents of the exporting nation are exposed to potentially dangerous chemicals during domestic production and eventual consumption of imported foods treated with the pesticides.

Following is a summary of regulatory activities in certain developing countries where pesticides are used. Boxes 9-A and 9-B illustrate problems that have occurred in developing nations. Although each of the profiled countries has some regulatory structure in place, each also has many problems with the import, distribution, and use of pesticides, resulting in health problems of varying degrees for farmworkers and consumers. In selecting the countries for this section, an attempt was made to obtain a geographic spread.

Malaysia

The Pesticides Board under the Malaysian Department of Agriculture has regulatory authority for pesticides in Malaysia. The Pesticides Act, the Pesticide Registration Rules of 1976, the Pesticide Rules on Importation for Educational or Research Purposes of 1981, and the Food Act of 1983 set out the language governing pesticide use (39).

Malaysia follows FAO guidelines with respect to data requirements for pesticide registration. However, all data, including efficacy data, may be from foreign sources. Data are evaluated and a recommendation is submitted to the Pesticides Board, which has authority to grant registration (39). Accordingly, a pesticide may be reviewed and approved for use in Malaysia with the approving authority depending entirely on data from the country of export.

The Department of Customs controls the import of all pesticides except those imported for research purposes, which are controlled by the Malaysian Department of Agriculture. The Department of Agriculture also controls the production, sale, and

Box 9-A—Problems With Neurotoxic Pesticides in Developing Countries

Irregularities concerning labeling, packaging, storage, sale, import, and advertising of pesticides have caused illness, injury, and death in many developing countries, as the following examples illustrate:



Photo credit: Widjanarka

Pesticides are commonly repackaged without labels in Senegal, but labels are of little use anyway, because most pesticide users are illiterate. Instructions such as "in case of intoxication, call a doctor" are meaningless in rural areas where there are no doctors for miles, no telephones, and only sporadic transport.

. In Indonesia, an outbreak of mosquito-spread dengue fever caused several deaths. The Ministry of Health sent an officer to spray the area with malathion, a class HI, slightly hazardous pesticide. The officer was photographed spraying malathion while children were running behind him to play in the pesticide mist (see photograph above).

- In Papua, New Guinea, very few companies provide labels in Tok-Pisin, the widely spoken local language. Some pesticide products had labels in French. One pesticide, selecron, was found in stores with no label at all.
- Many of the pesticides in Thailand, Indonesia, and the Philippines do not have child-proof packaging. Some liquid pesticides have easily opened screw caps, and powdered pesticides can be bought in plastic bags that an older child can open.

. In Indonesia, some pesticides were repackaged into clear plastic bags without labels. Workers wore no masks or gloves. Unlabeled bags of temik, which is 10 percent aldicarb, a class IA, extremely hazardous neurotoxic pesticide, were available in stores. Aldicarb is more acutely toxic to mammals than any other pesticide presently in use.

. In the Sudan, a family of eight died in 1985 from eating pesticide-poisoned bread made from pretreated wheat meant for seed. The pretreated wheat had been in badly labeled sacks stacked next to consumable wheat in an agricultural store.

In Brazil, a 1987 advertisement described deltamethrin as "the safest insecticide in the world." Deltamethrin is classified as class II—moderately hazardous by the International Code of Conduct on the Distribution and Use of Pesticides of the Food and Agriculture Organization of the United Nations.

- In Senegal, used pesticide containers are often recycle-d to carry food, milk, or cooking oil. In one village, 19 people from two families died as a result. The cook used oil sold in a bottle that had previously contained ethyl parathion, a class Ia, extremely hazardous pesticide.

. In Brazil, when a number of states passed laws banning imports of pesticides banned in their countries of origin, translational pesticide corporations and importers filed legal action and succeeded in getting the laws declared unconstitutional.

SOURCE: G. Goldenman and S. Rengam, *Problem Pesticides, Pesticide Problems* (Penang, Malaysia: International Organization of Consumers Unions and Pesticide Action Network, 1988).

use of pesticides and checks for compliance with regulatory policies. The Pesticides Board regulates advertisements of pesticides (39).

Residues on vegetables are monitored under the Food Act of 1983. To date, there is no system for monitoring pesticide poisoning except for occasional reports from hospitals. Following the deaths of two teenage girls from field exposure to paraquat in 1985, it was revealed that 1,200 workers had been killed by exposure to just that one pesticide (48). Both government and the private sector have implemented training programs on the safe handling of pesticides. These programs are geared toward farmers, applicators, dealers, distributors, manufacturers, and medical personnel (39).

Residues on vegetables are monitored under the Food Act of 1983, which prescribes maximum residue limits (5). In reality, monitoring and testing

Box 9-B—Incident at Lake Volta, Ghana

In Achedemade Bator, a fishing village on Lake Volta, a serious poisoning incident resulted from improper use of Gammalin 20, the trade name for lindane, a potent neurotoxic substance. The villagers, almost all of them illiterate, derived their income through fishing on the lake. The village fishermen discovered that by pouring lindane into the lake, fish would float to the surface and could be easily caught. This proved to be a very quick and efficient way of hauling in a catch. Any fish not consumed were salted, smoked, or sold.

Exposure to lindane may cause dizziness, headaches, convulsions, muscle spasms, brain disturbances, and unconsciousness. Some villagers experienced symptoms of lindane poisoning from consuming poisoned fish and using the lake as a source of drinking water but never associated their health problems with use of the chemical. Fishermen knew something was wrong when the fish population in the lake rapidly declined, and housewives could easily identify Lake Volta fish by their smell, but villagers continued to eat the deadly fish. When a connection was made between the illnesses and fish consumption, villagers cut off the heads of the fish and continued to eat the bodies, believing that decapitation would rid the fish of all poison.

Other plants and animals in the lake were killed as well. It was not until the intervention of the Association of People for Practical Life Education, a Ghanian organization, and the blessing of the village witch doctor that the villagers stopped using lindane for fishing and returned to nets and traps. In villages throughout Africa, fishing with pesticides continues where people have not been educated about the safe and effective use of these toxic substances.

SOURCE: R. Norris (cd.), *Pills, Pesticides & Profits* (Croton-on-Hudson, NY: North River Press, 1982).

are minimal (5). Concern about pesticide residues in food has resulted in the formation of the Consumers Association of Penang (CAP), the largest and most vocal citizens' organization in the developing world focusing specifically on consumer rights (70). CAP has discovered organochlorine pesticides (DDT, aldrin, BHC, dieldrin, chlordane), many of which are banned in the United States, in Malaysia's rainwater, soil, drinking water, and food crops. CAP monitors pesticide poisoning of workers and residues in food and has pressured the Malaysian government to tighten its regulations on pesticides (70). In a recent study conducted by the Malaysian Department of Agriculture, it was discovered that 54 percent of the 1,214 agricultural workers studied had experienced some form of pesticide poisoning (22,44).

Philippines

In the Philippines the private sector controls the pesticide industry, which is dominated by local organizations representing the major multinational companies (5). Virtually all of the pesticide business is transacted by some 20 companies in the trade association-the Agricultural Pesticide Institute of the Philippines (5).

There are several laws affecting the pesticide industry. A presidential decree enacted in 1977 regulates pesticides. Quality control of pesticides is done by the Fertilizer and Pesticide Authority (FPA) through the Bureau of Plant Industry (BPI) and the Philippine Institute for Pure and Applied Chemistry, on the basis of complaints from users (39). Quality control during production and for imports is done by private companies. Pesticide dealers and ports of entry in the 72 provinces and 12 regions are inspected, but critics argue that this system needs improvement and strengthening (39). An FPA permit is required for all imports of pesticides, regardless of quantity. The FPA controls production, sale, and use of pesticides through a licensing scheme, and in collaboration with the Philippine Board of Advertisers controls advertisements of pesticides (39).

There is no system in operation to monitor pesticide poisoning cases in humans except for occasional reports from hospitals and doctors trained under the FPA Agro-Medical Program. Pesticide dealers must be trained in the safe handling of pesticides before they can obtain a retail license. Commercial pest control companies must obtain certification for all of their operators (39). Market-basket samples of vegetables are routinely analyzed for residues, particularly for organochlorines and organophosphates, by the BPI (5). Other agencies monitor residues in lakes, rivers, and streams, while exporters of agricultural products analyze shipments prior to export (5).

The Philippines is the home of the International Rice Research Institute, which helped create the green revolution of the 1970s. This revolution saw

the production of new hybrid seeds, developed to produce higher yields with the correct amount of fertilizer and water (70). These laboratory-bred seeds were more susceptible to pests and required increased use of pesticides. Although the new seeds have increased production, the Philippines remains one of the hungriest nations in Asia, according to the Asian Development Bank and WHO (70).

Some. years ago, the Farmer's Assistance Board was formed by peasants and students to study pesticides. The board blames the large volume of pesticide use in the Philippines on the big exporters, as well as on the International Rice Research Institute. The board points to the demand for highest yield and blemish-free products as the reasons for the country's continued dependence on large quantities of pesticides.

India

The Insecticides Act (1968) and the Insecticides Rules (1971) govern pesticides in India. The Act regulates manufacture, formulation, distribution, and sale of pesticides through a licensing system. Five agencies have been created to implement these laws. Locally generated toxicity and residue data for formulations are required in most instances; however, complete efficacy data are required only for registration of a new pesticide. The Pesticide Registration Committee and the Central Insecticides Board review data for registration, referring to publications and decisions by FAO, WHO, and EPA, among other organizations. India does not adhere to FAO guidelines with respect to labeling. It does follow the FAO color coding of labels based on toxicity, but the warning symbols differ from those suggested by FAO. Pesticides are classified into various categories of toxicity, but the limits set differ from those recommended by WHO (39). To date, 119 active ingredients and their formulations have been registered.

The improper use of pesticides is a major problem in India (5). Few farmers are aware of the potential hazards associated with the use of pesticides (5). Crops are often sprayed with insecticide immediately before and after harvest because of a belief that pre- and postharvest spraying will increase freshness and preservation (5).

India "phase registers" new pesticides. First there is a trials clearance, then a provisional registration, which is valid for 2 years and subject to certain conditions, and finally a full registration. There is also "me-too" registration, which allows a second registrant to obtain registration for a pesticide subject to proof that the product is identical to the one already registered. There is usually a letter of agreement between parties on use of data (39).

The Insecticides Act mandates that pesticide quality be checked by the Central Insecticide Laboratory. Rigid controls are set for preregistration purposes, but once a product is on the market, quality control is not pursued (39). Quality control of products during production is monitored not by the government, but by private companies. Compliance with regulatory policies is enforced by state governments, and imports are allowed only through certain ports of entry (39). No pesticide may be imported without a registration certificate. It is interesting to note that many pesticides which have been banned or severely restricted in the United States are produced in India (70). Several foreign manufacturers have plants in India (70).

Increased agricultural output does not necessarily mean increased food consumption for local residents if the residents are too poor to afford food. Despite the fact that there were vast increases in wheat yields in the Punjab district in the 1960s, the portion of the rural population living below the poverty line increased from 18 to 23 percent (28). While true that pesticide use may increase crop yield and bolster the economy of a developing country, in this particular instance the economic prosperity of the local inhabitants declined.

The Central Food Laboratories monitor pesticide residues and adulterants in food, but this system needs strengthening. State governments are required to obtain reports from their officers on pesticide poisonings, but this is not a thorough monitoring system. Both state and central governments and the pesticide industry have implemented training programs for safe use and application of pesticides (39).

Costa Rica

The Law for the Control of Pesticides (1979) and the Law Governing Occupational Health (1981) regulate pesticides in Costa Rica. Along with other Central American countries, Costa Rica has adopted the provisions of the Basic Document on Regulation of Registration, Marketing and Control of Agricultural Chemicals for Countries of Central America, prepared under the auspices of the Inter-American

Institute for Cooperation on Agriculture in 1985. A Pesticide Commission has also been formed to carry out the pesticide registration program (39).

Registration requirements are generally in accordance with FAO guidelines. Local efficacy data for new products are to be generated either directly by government research organizations or by private companies under government supervision. Efficacy data from other Latin American countries are acceptable for products already registered. EPA tolerances must also be submitted, along with a certificate of registration and a certificate of analysis from the country of origin and evidence of registration from other countries. Labeling is evaluated according to guidelines agreed on under the Basic Document. Full registration is valid for 3 to 5 years, experimental permits are issued, and me-too registration is allowed. As with Mexico and Ecuador, all chlorinated compounds that accumulate in the food chain are banned, but the government reserves the right to use them in cases of emergency when economical substitutes are not available (39).

Costa Rica has one of the strongest enforcement systems in Central America. Import permits are necessary, and there is a licensing scheme for formulation, distribution, and sale of pesticides. The Ministry of Health has done some monitoring of food residues and keeps a record of poisoning cases. The government and private sector carry out training programs for pesticide workers, and the government has published a training manual for physicians.

Mexico

In Mexico, the principal pesticide legislation is the Law on Plant and Animal Protection, which was adopted in 1940. The law was amended in 1974, and rules were added in 1980 to implement it. FAO guidelines are generally followed, with local efficacy data generated either directly by government research organizations or by private companies under government supervision (39). All test protocols must be approved by the government. Emphasis is on evaluation of efficacy data, while toxicological and residue data are reviewed by experts. Label evaluation follows the Basic Document guidelines agreed on by Latin American countries, and the WHO classification system for pesticides has been adopted, with certain modifications (39). Full registration is valid for 3 to 5 years, with permits issued



Photo credit: Kay Treakle, Greenpeace

Unprotected workers spray paraquat on coffee plants, Chiapas, Mexico

for experimental purposes. Me-too registration is allowed with the same data and information requirements as for all registered products.

All chlorinated compounds that accumulate in the food chain are banned, but the government reserves the right to use them in cases of emergency when economical substitutes are not available (39). As recently as 1987, some 28 pesticides that were banned or severely restricted in the United States were being used in Mexico (18). Endrin, which was severely restricted in the United States in 1979, was given a renewal registration for 2 years in 1984 (18). Mexico imports a large percentage of pesticides, but there are also some 300 formulation plants in the country (18). In 1987, domestic production of pesticides was estimated at 32,000 tons per year (18).

The government and private industry share responsibility for quality control, but compliance with regulatory policies is usually enforced only after complaints from the field. Training programs for farmers, distributors, and physicians are sponsored by government and private industry, but monitoring of pesticide poisonings is sporadic. Imports are controlled through the issuance of import permits, and formulation, distribution, and sale of pesticides is controlled through a licensing scheme (39). Residues in export crops are monitored regularly, following regulations imposed by the importing country (39).

Ecuador

In addition to enacting its own legislation in 1984, Ecuador has consented to implement guidelines dealing with registration data and labeling agreed on by Latin American countries in the Andean region. FAO guidelines form the basis for data requirements. Either government research organizations or private companies under government supervision must generate local efficacy data. Further, proof of registration in the country of origin and registration in other countries is required (39).

There is little evaluation of data except for efficacy. Labeling is strictly evaluated, based on the guidelines agreed on by the Latin American countries. Other organizations are looked to for guidance, among them FAO, WHO, EPA, the National Agricultural Chemicals Association, and the International Group of National Associations of Manufacturers of Agrochemical Products.



Photo credit: Amerkan Cyanamid

Worker spraying banana plants in Ecuador

All chlorinated compounds that accumulate in the food chain are officially banned, but the government reserves the right to use them in cases of emergency when economical substitutes are not available (39). Parathion and toxaphene are two pesticides banned in Ecuador, while DDT and methyl bromide are among those restricted to specified uses. U.S. EPA regulations regarding banning and restrictions are supposed to be closely followed (39), yet DDT, which has been banned by EPA for use in the United States, can be used in certain circumstances in Ecuador.

Both government and private industry have quality control programs. The Fundacion Natura (Nature Foundation), an environmental group, monitors compliance with regulatory policies and reports violations to the government. Government inspectors are also assigned to monitor compliance. The Department of Commerce and the Ministry of Agriculture issue import permits, and there is a licensing scheme for formulation, distribution, and sale of pesticides.

Prior government approval is needed for any pesticide advertising, but there has been minimal

monitoring of residue on food and crops. A record of any poisoning cases reported by hospitals is maintained by the Ministry of Health. Government and the private sector, as well as industry, have training programs for extension workers, farmers, distributors, doctors, and technical and sales representatives.

Kenya

In Kenya, the Pesticide Control Board Act was implemented in 1982, with regulatory authority vested in the Pesticide Control Product Board. The Specialist Approval Committee for Agricultural Pesticides evaluates data generally, in accordance with FAO guidelines. At present, there is no information available concerning labeling requirements, no national residue tolerances, and no system of pesticide classification, although WHO classification is being reviewed for possible adoption. Only registered products can be imported and used, but there are no restrictions regarding the availability of these products (39).

For the most part, quality control is left to industry. Residue monitoring is not usually done, and there is no system in operation for monitoring pesticide poisoning cases (39).

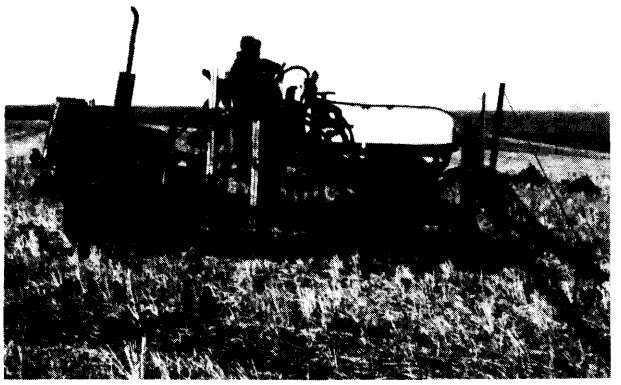


Photo credit: Monsanto Agricultural Co.

Surveying the harvest, Kenya

INTERNATIONAL NEUROTOXICOLOGICAL RESEARCH

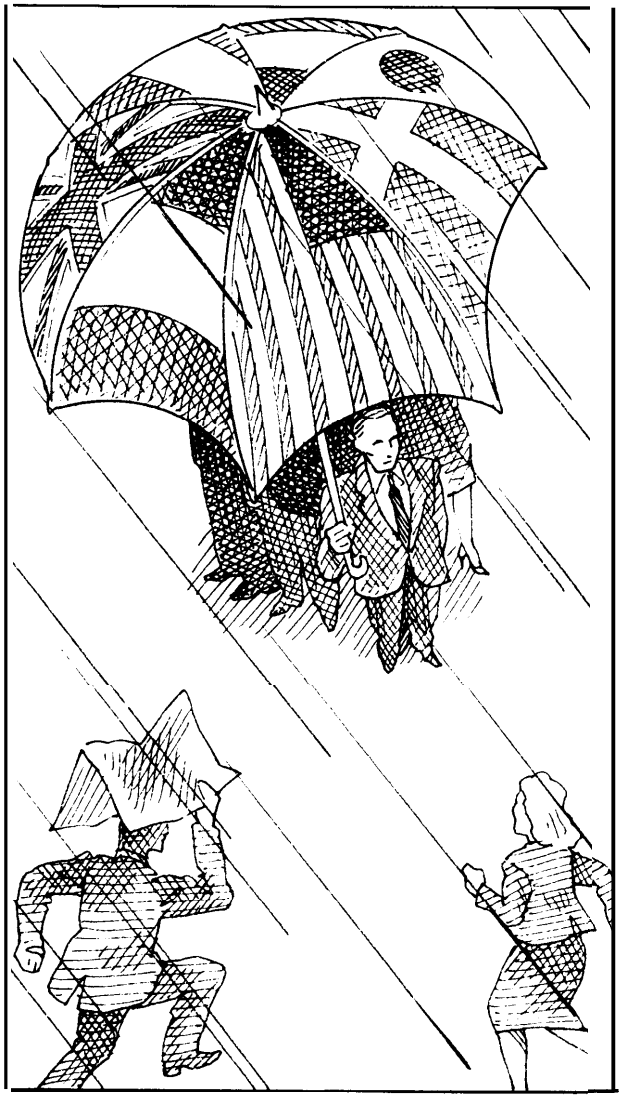
Active interest in neurotoxicity began in the United Kingdom during and after World War II. Since that time, research efforts in the United States have gradually increased. The United States is now the world leader in environmental legislation and in government funding of neurotoxicology research. Research in other countries has been narrower and more specific. The Scandinavian countries have been active in research on the neurotoxicity of organic solvents (73), and other European countries have supported research on compounds of particular concern in occupational settings, such as pesticides and heavy metals (16,36). In most cases, however, no systematic national effort has been undertaken similar to that in the United States (2).

Several international conferences have taken place during the past 10 years on the subject of neurotoxicology, some of which were sponsored by EPA and the National Institutes of Health. Two international journals published in the United States, *Neurotoxicology and Teratology* and *Neurotoxicology,* were established in 1979, and the Society of Toxicology in the United States has a sizable subsection devoted to neurotoxicology. Outside the United States, sufficient interest has been generated in neurotoxicological issues that a new society, the International Neurotoxicology Association, has been formed. This society held its first meeting in 1987, with attendance by approximately 200 scientists from Europe and the United States. The first comprehensive text on neurotoxicology was published in 1980 (52).

Major Directions of Academic, Industrial, and Government Research

In the past, research efforts were often initiated following industrial exposures that caused severe human intoxications. For example, with the advent of the vulcanization of rubber, carbon disulfide poisoning in workers in the rubber industry became common in many European countries (71). With the introduction of rayon, the manufacture of which also required the use of carbon disulfide, poisonings due to use of this solvent became a worldwide problem (68). Improvements in occupational hygiene have largely eliminated cases of severe poisoning; nevertheless, what has emerged instead is the problem of chronic low-level exposures to this and other compounds. The development of human testing procedures to measure more subtle symptoms has been largely accomplished in Finland (49).

The toxicity of lead has been known since antiquity (51). Nonetheless, large-scale lead poisoning continues to be an international public health problem because of lead water pipes, the use of



Illustrated by: Ray Driver

lead-based paints, and the addition of lead to gasoline. Much of the basic research involving animal models of lead toxicity was done in the United States (67). Using the diagnostic procedures developed for the detection of exposure to organic solvents, Finnish researchers have demonstrated nervous system damage in low-level occupational exposures of adults to lead (49). Research into lead toxicity is still supported enthusiastically in many countries because of accumulating evidence that even exposure levels previously considered harmless (particularly in children) have been shown to have adverse effects on health (ch. 9). This has led the WHO European Office to sponsor a multinational study of the effects of childhood lead intoxication. As of 1989, lead additives have been restricted in the United States and in some parts of Europe. Thus, worldwide interest in lead toxicity continues, although outside the United States research is not supported in a programmatic way by individual governments. It appears that this role has been taken over by international bodies such as WHO.

Another major environmental contaminant is mercury. Exposures to mercury in industrial settings have been well described since the 19th century (34). Mercury became a public health problem because of the widespread use of organic mercury compounds in agriculture as fungicides. The first major outbreak of methyl mercury poisoning occurred in Japan in 1953 and was followed by outbreaks in many other parts of the world, notably Iraq (see ch. 2). Japanese scientists have actively pursued research on the mechanism of neurotoxicity of organic mercury compounds (55). This was followed by a large Scandinavian (mostly Swedish) research effort because of contamination of lakes by mercury runoff (19). U.S. investigators have been involved in mercury research since the Iraq episode, in 1971 to 1972, and have examined such problems as the teratogenic effects of methyl mercury on the behavior of animals (17). Other metals that have been studied internationally include manganese, cadmium, and the organotins.

Interest in the neurotoxicity of organic solvents has increased in recent years. Pioneering work in Scandinavia was followed by mechanistic studies in the United States (47) that revealed the relationship between human symptoms and underlying biological alterations. Scandinavian workers have been the focus of a number of occupational hazard studies. A recent monograph entitled *Organic Solvents and the Central Nervous System* was published jointly by WHO and the Nordic Council of Ministers (73). This document addresses the problems of occupational exposures, the illness caused by these exposures, and the diagnostic procedures for identifying the illness. In 1988, the WHO-Nordic Council of Ministers met to design the "definitive" study of chronic effects of exposure to solvents on the nervous system of workers (75).

The widespread use of highly toxic pesticides has led to intense worldwide research on the neurotoxicity of these compounds. In fact, the beginning of the environmental movement has been attributed to the publication of Rachel Carson's book *Silent Spring,*

which dealt with the ecological effects of indiscriminate pesticide application. The continuing development of new pesticides has caused the research effort to be sustained, not only to protect human populations, but also to safeguard nontarget populations from inadvertent exposure to these compounds.

One way to document international research trends is to summarize the distribution of research papers published by non-U.S. authors in the two international journals devoted to neurotoxicology. Table 9-1 indicates the various neurotoxic substances investigated in papers published in two journals between 1979 and 1987.

Heavy metals as a group clearly represent the major area of interest. They are followed by organic solvents, pharmaceutical agents, and pesticides. Since the two neurotoxicology journals are relatively new, one can assume that a large proportion of neurotoxicological research has also been published in other journals. In addition, each of the non-English-speaking countries listed has journals in its own language, and researchers also publish in those journals. This is particularly true of scientists in the Soviet Union, who publish only infrequently in English-language journals. Thus, while this survey of published research outside the United States may not be truly representative of international neurotoxicological research, it is probably a reasonable indicator of general trends in international research.

To gain another view of current research trends, it is useful to examine projects presented at the first meeting of the International Neurotoxicology Association in the Netherlands, May 10-16, 1987. The meeting was attended by 135 scientists from 21 countries. The largest contingent came from the United States (23), followed by the Netherlands (20), West Germany (15), England (1 1), Italy (1 1), and all other countries (fewer than 10 each). An examination of their places of employment indicates that 37 percent of the attendees were from government laboratories, 37 percent from academia, 23 percent from industry, and the remainder from a variety of institutions. Of the U.S. participants, 22 percent were from government laboratories, 65 percent from academia, and 9 percent from industry. An examination of the topics presented indicates that the trends outlined above have not changed markedly (table 9-2). Following tradition, 50 percent of the papers dealing with solvent toxicities came from Scandinavian countries.

Table 9-1-Neurotoxic Substances Investigated in Papers Published in Two International Journals, by Country, 1979-87

Country	Substances investigated (No. of papers)
Canada	Ethanol (3); manganese (2); cadmium (2); lead (2); pharmaceutical agents (2); acrylamide (1); zinc (1); aluminum (1); herbicides (1); hydrogen peroxide (1); chlorinated hydrocarbons (1)
England	Pyrethrins (7); pharmaceutical agents (7); organophosphates (2); solvents (l); acrylamide (l); mercury (1); herbicides (1)
Italy	Pharmaceutical agents (8); organophosphates (2); mercury (1); solvents (1); bismuth (1); caffeine (1)
India	Manganese (4); organophosphates (l); lead (l); cadmium (1); solvents (l); sulfur dioxide (1); zinc (1); styrene (l); herbicides(1)
Japan	Mercury (5); solvents (3); cadmium (l); pyrethron (1); pharmaceutical agents (1)
France	Mercury (3); solvents (1); tellurium (l); lead (1)
Mexico	Solvents (6)
Finland	Lead (4): solvents *(4):* ethanol (1)

SOURCE: Office of Technology Assessment, 1990.

Table 9-2-Subjects of Neurotoxicological Research Presented at a Major International Conference

Chemical	Papers (No.)
Insecticides	*25*
Solvents	23
Lead	8
PCBs	2
Acrylamine	2
Methyl mercury	1
Styrene	1
Carbon monoxide	1
Nitrous oxide	1
Pharmaceutical agents	4
Experimental compounds	6

SOURCE: **Office of Technology Assessment, 1990.**

One meeting may not represent a typical sample of international research in neurotoxicology, but it provides a useful example of current neurotoxicological research in the Western industrialized world. No researchers from the Soviet Union attended this meeting; however, two individuals from Eastern Europe, one each from Hungary and Czechoslovakia, attended. The number of neurotoxicologists in both of these countries is very small, as determined by publications in the literature. For much of the rest of the world, neurotoxicology as a discipline does not exist. There are some exceptions, however. For example, there are active researchers in Japan, India, China, and Argentina, with well-identified centers for such research. Indian researchers have traditionally published in English, and this practice is becoming increasingly common among Chinese researchers as well. In addition, experimental re-

search on the neurotoxicity of the grass pea is now under way in Ethiopia.

Neuroepidemiology

International activities in neuroepidemiology have taken place on all six inhabited continents. Neuroepidemiologists in England are currently studying risk factors for stroke and are investigating the epidemiology of multiple sclerosis. In Japan, epidemiological inquires into the etiology of neurodegenerative disorders (including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease) have been undertaken. One country with a major effort in neuroepidemiology is Italy. Italian efforts in this area may be traced back to a series of courses on neuroepidemiology taught in 1979 by a group of U.S. and Italian epidemiologists. The fruits of these efforts have included major work in the epidemiology of dementia. More recently, WHO has begun an international initiative in the epidemiology of dementia. It is not clear, however, whether this work will be extended to other neurodegenerative conditions. It is possible that some of these efforts will be focused on geographic isolates of neurological conditions, for example, the Faroe Islands and multiple sclerosis, Guam and dementia, and Guam and amyotrophic lateral sclerosis. An international collaboration to investigate the latter two phenomena is now forming and will likely begin its activities within the next year (31).

International Cooperation

Neurotoxicological research has been primarily an intranational effort. In recent years, some international cooperation has been initiated by WHO and the U.S. National Toxicology Program, but thus far this has occurred only in specific areas, such as lead toxicity, solvent toxicity, and the development of testing methodologies (74). The limited scope of international cooperation is large] y due to the lack of funds available for such efforts.

Comparison of U.S. and Foreign Research Programs

The neurotoxicity research effort in the United States is larger in depth and scope than that in other nations. Both leading books in this area were written by American authors and editors (4,52). Both international journals in the field are published in the United States, and a review of the published literature in neurotoxicology reveals that about 90 percent originates in the United States. The quality of the work is generally considered to be excellent. As mentioned previously, other countries have excelled in some areas of research; this is particularly true with respect to the solvents research conducted in Scandinavia. American research on the mechanisms of toxicity of solvents is generally considered to be outstanding.

Resources

The United States has a limited number of doctoral-level training programs in neurotoxicology. Because of its unique educational system, more scientific manpower is available in the United States than in other countries. In most European countries, the standard educational program in the life sciences is the medical degree, or the equivalent of the M.D. Consequently, almost all researchers in Italy, Scandinavia, and Germany are trained first as physicians and then as researchers. These individuals may eventually obtain a doctorate if they choose a research career. In countries such as Italy, where research positions are very difficult to obtain, most physicians choose nonresearch careers rather than risk being unemployed. Although employment opportunities are somewhat better in Scandinavia than in Italy, it is still difficult to establish a research career because of the scarcity of positions.

The success of the American research enterprise is due not only to the relative availability of funding, but also to the manner in which the funds are administered. Despite some inherent flaws, the peer review system in the United States generally ensures that the best scientists in a given field obtain funding. In many other parts of the world, research is often supported by a system in which funding decisions are made solely by the director of an institute or the chairman of a department, without peer review of the proposed research.

Future Directions

A recent review (1) listed 850 chemicals in the workplace that may be neurotoxic. Apart from the substances listed in tables 9-1 and 9-2, most of these chemicals have not been studied. The international chemical industry produces several thousand new chemicals every year, most of which are not tested for neurotoxicity. Japan and France now require neurotoxicity testing for new chemicals (53), but these tests are elementary in nature and are likely to miss more subtle and insidious toxic effects.



Photo credit: Jerry Deli

At present, the major classes of neurotoxic substances-heavy metals, solvents, and pesticides—have been identified. However, despite major research efforts, there is still no clear understanding of the mechanisms of toxicity of most of these chemicals. In order to protect human populations from chronic low-level intoxication, it is essential to understand the properties and potential health effects of new and existing chemicals. Because of the enormity of the testing task, a coordinated international approach would be highly beneficial.

Foreign Governments Likely To Take Leadership Roles

In some European countries, notably West Germany and Sweden, environmental movements are becoming increasingly influential. It is likely that these nations will play leading roles in supporting research and in developing regulations to control toxic substances. The Federal Republic of Germany has already acted to remove lead from gasoline and to fund studies of lead toxicity in children. As outlined above, all of the Scandinavian countries (Sweden, Denmark, Norway, and Finland) have traditionally supported research on solvents. These patterns are likely to continue and may broaden to the investigation of other agents as environmental movements grow. Political events in the Soviet Union have led to the emergence of an environmental movement, and it appears that the Soviet government will also take a more active role in these issues. In the Far East, both the People's Republic of China and Japan are faced with major pollution problems and are becoming increasingly involved in toxicological issues.

SUMMARY AND CONCLUSIONS

Like most environmental concerns, neurotoxicity is a problem not limited by national boundaries. Pollutants can readily cross national borders, hazardous chemicals are frequently imported and exported among both industrialized and developing nations, and adulterated food and commercial products enter the United States despite current regulatory efforts. Strategies to limit human exposure to neurotoxic substances should be devised in the context of both national and international regulatory and research initiatives.

Despite numerous regulations governing the export and import of neurotoxic chemicals and products containing them, most countries do not adequately protect human health and the environment from these substances. Most industrialized nations have policies and procedures in place to regulate the import, distribution, and use of toxic chemicals, implicitly including neurotoxic substances. Some developing nations have limited regulations to protect workers and consumers from the adverse effects of neurotoxic substances. Developing nations that do have regulations often do not have the resources to enforce them. Developing countries use only 10 to 25 percent of the world's pesticides, but they account for as much as 50 percent of the acute poisonings of pesticide applicators and between 73 and 99 percent of their deaths. This lack of effective regulation and enforcement in developing nations has a negative impact not only on public health and environment in the user country, but also in industrialized nations, including the United States, where people process and consume pesticide-treated crops imported from developing nations.

Both TSCA and FIFRA contain provisions exempting certain products produced for export from the requirements that apply to products sold for use in the United States. In most instances, TSCA requirements do not apply to substances manufactured, processed, or distributed for export. The requirements do, however, apply if it is determined that the substance will present an unreasonable risk of injury to public health or the environment within the United States. In addition, because pesticides intended solely for export are exempt from the public health protection provisions of FIFRA, pesticide manufacturers can legally export banned, severely restricted, or never registered substances that have been deemed too hazardous for use in this country. Companies that do so are required to notify the importing country that the exported pesticides have been banned, severely restricted, or never registered for use in the United States. Some such pesticides are used on food crops that are imported back into the United States for consumption. Critics of this practice have termed it the 'circle of poison.

On January 15, 1981, several days before the end of his term, President Jimmy Carter issued an Executive Order which put controls on exports of substances that were banned or severely restricted in the United States. Several days after Ronald Reagan became President, he revoked the order.

While pesticides may be needed to obtain sufficient food to feed the ever-increasing world population, many observers argue that ample food supplies are currently available and that better distribution of existing food stores is necessary. Responsible conduct on the part of persons who manufacture, distribute, and use pesticides is mandatory if irreversible harm to world public health and the world environment is to be minimized. Education and literacy levels of persons handling pesticides must be considered and appropriate information tailored to their needs. Regulations currently in place must be adhered to and new legislation enacted when the need arises. Alternative methods of pest control should be investigated and developed. Cooperative efforts on the part of governments in industrialized and developing countries, industry, environmental groups, and other international organizations are necessary to ensure the safety of the world community.

Active interest in neurotoxicity began in England during and following World War H. Since that time, efforts in the United States have gradually increased. Today, the United States is the world leader in environmental legislation and government funding of neurotoxicological research. The Scandinavian countries have been active in research on the neurotoxicity of organic solvents. Other European countries have supported research on compounds of particular concern in occupational settings, such as pesticides and heavy metals.

International research activities tend to focus on the heavy metals (lead and mercury), organic solvents, and pharmaceutical agents. Foreign neurotoxicology-related scientific papers published in international journals most often originate from authors in Canada, England, Italy, Australia, and Japan. A number of papers originate from authors in France, India, Sweden, Finland, and Mexico, as well.

International cooperation in the neurotoxicology field is very limited. Neurotoxicological research has been primarily an intranational effort. In recent years, some international cooperation has been initiated by WHO and the U.S. National Toxicology Program, but thus far this has only occurred in specific areas, such as lead toxicity, solvent toxicity, and the development of testing methodologies. The limited scope of international cooperation is largely due to the lack of funds available for such efforts.

In some European countries, notably the Federal Republic of Germany and Sweden, environmental movements are becoming increasingly influential. It is likely that in the future these governments will play leading roles in supporting research and in developing regulations to control toxic substances. The Federal Republic of Germany has already acted to remove lead from gasoline and to fund studies of lead toxicity in children. All of the Scandinavian countries have traditionally supported solvent research. This will likely continue and may broaden to include the investigation of other agents as environmental movements grow.

CHAPTER 9 REFERENCES

1. Anger, K., "Workplace Exposures," *Neurobehavioral Toxicology*, Z. Annau (cd.) (Baltimore, MD: Johns Hopkins University Press, 1986).
2. Annau, Z., ''International Neurotoxicity Research—Current Activities and Future Directions," prepared for the Office of Technology Assessment, Washington, DC, 1989.

3. Annau, Z., Professor of Environmental Health Sciences, Department of Environmental Health Sciences, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, personal communication, July 7, 1989.
4. Annau, Z. (cd.), *Neurobehavioral Toxicology* (Baltimore, MD: Johns Hopkins University Press, 1986).
5. Asian Development Bank, *Handbook on the Use of Pesticides in the Asia-Pacific Region* (Manila: 1987).
6. Baker, I., Professor of Law, Washington College of Law, The American University, Washington, DC, personal communication, July 25, 1989.
7. Bottrell, D., "Social Problems in Pest Management in the Tropics, "*Insect Science Applications4(1-2): 179-184, 1983.*
8. Bull, D. A., *Growing Problem: Pesticides and the Third World Poor* (Birmingham, England: Oxfam Third World Publications, 1982), p. 37, notes 4,5.
9. Bureau of National Affairs, Inc., *International Environment Reporter: Japan* (Washington, DC: 1979).
10. Bureau of National Affairs, Inc., *International Environment Reporter: United Kingdom* (Washington, DC: 1983).
11. Bureau of National Affairs, Inc., *International Environment Reporter: Belgium* (Washington, DC: 1988).
12. Bureau of National Affairs, Inc., *International Environment Reporter: Canada* (Washington, DC: 1988).
13. Bureau of National Affairs, Inc., *International Environment Reporter: France* (Washington, DC: 1988).
14. Bureau of National Affairs, Inc., *International Environment Reporter: West Germany* (Washington, DC: 1988).
15. Conservation Foundation, *Opportunities To Assist Developing Countries in the Proper Use of Agricultural and Industrial Chemicals,* vol. 1 (Washington, DC: 1988).
16. Desi, I., ''Neurotoxicological Investigations of Pesticides in Animal Experiments, ' *Neurobehaviora/ Toxicology and Teratology 5:503-516, 1983,*
17. Eccles, C. U., and Annau, Z., "Prenatal Exposure to Methyl Mercury," *The Toxicity of Methyl Mercury,* C.U. Eccles and Z. Annau (eds.) (Baltimore, MD: Johns Hopkins University Press, 1987).
18. Environment Liaison Center for Pesticide Action Network, *Monitoring and Reporting the Iimplementation of the International Code of Conduct on the Use and Distribution of Pesticides: Final Report October 1987* (Nairobi: Pesticide Action Network, 1987).
19. Friberg, L., and Vestal, J. (eds.), *Mercury in the Environment* (Cleveland, OH: CRC Press, 1972).
20. Goldenman, G., and Rengam, S., *Problem Pesticides, Pesticide Problems* (Penang, Malaysia: International Organization of Consumers Unions and Pesticide Action Network, 1988).
21. Goodman, L.W., and Portilla, B., "Foreign Toxins: Multinational Corporations and Pesticides in Mexican Agriculture, " paper presented at the World Resources Institute Conference, 1985.
22. Greenpeace, *Toxics* (Washington, DC: Greenpeace USA, 1989).
23. Hansen, M., *Escape From the Pesticide Treadmill: Alternatives to Pesticides in Developing Countries* (Mount Vernon, NY: Consumers Union of United States, 1988).
24. Hansen, M., Institute for Consumer Policy Research, Consumers Union, Mount Vernon, NY, personal communication, May 3, 1989.
25. "Huge Grains Surplus Poses Problems," *Economic Times* (of India), Dec. 25, 1985.
26. International Group of National Associations of Manufacturers of Agrochemical Products, *Guidelines for the Safe and Effective Use of Pesticides* (Brussels: 1983).
27. International Group of National Associations of Manufacturers of Agrochemica1 Products, *Guidelines for Safe Warehousing of Pesticides* (Brussels: 1988).
28. International Labor Office, "Third World Seen Losing War on Rural Poverty," *Information,* February 1980, p. 8.
29. Lansdown, R., "Lead, Intelligence, Attainment and Behavior, *Mercury in the Environment,* R. Lansdown and W. Yule (eds.) (Cleveland, OH: CRC Press, 1972).
30. Lappe, F. M., and Collins, J., *World Hunger: Twelve Myths (New* York, NY: Grove Press, 1986).
31. Lilienfeld, D., Mount Sinai School of Medicine, New York, NY, personal communication, Sept. 14, 1989.
32. Marquardt, S., Pesticide Information Coordinator, Greenpeace USA, Washington, DC, personal communication, June 14, 1989.
33. Marquardt, S., *Exporting Banned Pesticides: Fueling the Circle of Poison, A Case Study of Velsicol Chemical Corporation's Export of Chlordane and Heptachlor* (Washington, DC: Greenpeace USA, 1989).
34. Marsh, D. O., "Dose-Response Relationships in Humans: Methyl Mercury Epidemics in Japan and Iraq, " *The Toxicity of Methyl Mercury,* C.U, Eccles and Z. Annau (eds.) (Baltimore, MD: Johns Hopkins University Press, 1987).
35. McCarthy, J., Vice President for Scientific and Regulatory Affairs, National Agricultural Chemicals Association, testimony before Subcommittee on Toxic Substances, Environmental Oversight, Research, and Development, Committee on Environment and Public Works, U.S. Senate, May 15, 1989.
36. Moore, M.R., "Lead in Humans," Lead *Toxicity,* R. Lansdown and W. Yule (eds.) (Baltimore, MD: Johns Hopkins University Press, 1986).
37. Morton, D. M., "Requirements for the Toxicological Testing of Drugs in the USA, Canada, and Japan,"

Testing for Toxicity, J.W. Gorrod (cd.) (London, England: Taylor & Francis Ltd., 1981).
38. Murray, D. L., Texas Center for Policy Studies, Houston, personal communication, May 15, 1989.
39. National Academy of Sciences, Board on Agriculture, *Pesticide Registration and Regulatory Policies in Developing Countries: Directory and Implementa - tion Status* (Washington, DC: National Academy Press, 1987).
40. Norris, R. (cd.), *Pills, Pesticides& Profits* (Croton-on-Hudson, NY: North River Press, 1982).
41. North Atlantic Treaty Organization, *Toxicology of Pesticides: Experimental Clinical and Regulatory Aspects,* ASI series, vol. H13, L. Costa (cd.) (Berlin: Springer-Verlag, 1987).
42. Peach, J. D., Assistant Comptroller General, Resources, Community, and Economic Development Division, U.S. General Accounting Office, "Export of Unregistered Pesticides Is Not Adequately Monitored by EPA, " testimony before the Subcommittee on Environment, Energy, and Natural Resources, Committee on Government Operations, U.S. House of Representatives, May 3, 1989.
43. Prabhu, M. A., "International Pesticide Regulatory Programs," *Environment 30(9), 1988.*
44. Ramasamy, S., and Nursiah, M.T.A., "A Survey of Pesticide Use and Associated Incidence of Poisoning in Peninsular Malaysia, ' *Journal of Plant Protection in the Tropics 5(1):1-9, 1988.*
45. Repetto, R., *Paying the Price: Pesticide Subsidies in Developing Countries* (Washington, DC: World Resources Institute, 1985).
46. Ritter, L., and Curry, P. A., "Regulation of Pesticides in Canada," *Toxicology and Industrial Health 4(3), 1988.*
47. Sabri, M.I., and Spencer, P. S., ''Toxic Distal Axonopathy: Biochemical Studies," *Experimental and Clinical Neurotoxicology,* P.S. Spencer and H.H. Schaumberg (eds.) (Baltimore, MD: Williams & Wilkins, 1980).
48. Sahabat Alam Malaysia, *Pesticide Dilemma in the Third World-A Case Study of Malaysia* (Penang, Malaysia: 1984).
49. Seppalainen, A. M., and Hernberg, S., "Sensitive Techniques for Detecting Sub-Clinical Lead Neuropathy, " *British Journal of Industrial Medicine 29:443, 1972.*
50. Seppalainen, A.M., et al., "Neurophysiological and Psychological Picture of Solvent Poisoning,' *American Journal of Industrial Medicine 1:31-42, 1980.*
51. Smith, M., "Lead in History, " Lead *Toxicity,* R. Lansdown and W. Yule (eds.) (Baltimore, MD: Johns Hopkins University Press, 1986).
52. Spencer, P. S., and Schaumburg, H.H. (eds.), *Clinical and Experimental Toxicology* (Baltimore, MD: Williams & Wilkins, 1980).
53. Steinberg, M., "The Use of Traditional Toxicologic Data in Assessing Neurobehavioral Dysfunction," *Neurotoxicology 9:403-409, 1987.*
54. Stolfa, P., Deputy Administrator, International Programs, Food Safety and Inspection Service, U.S. Department of Agriculture, letter to Sandra Marquardt, Pesticide Information Coordinator, Greenpeace USA, Washington, DC, June 26, 1989.
55. Takeuchi, T., "Human Effects of Methyl Mercury as an Environmental Neurotoxicant *Neurotoxicology,* K. Blum and L. Manzo (eds.) (New York, NY: Marcel Dekker, 1985).
56. Tanimura, T., "Guidelines for Developmental Toxicity Testing of Chemicals in Japan, *Neurobehavioral Toxicology and Teratology 7%47-652, 1985.*
57. United Nations Food and Agriculture Organization, *Food Balance Sheets 1979-1981 and 1981-1983* (Rome: 1984).
58. United Nations Food and Agriculture Organization, *International Code of Conduct on the Distribution and Use of Pesticides* (Rome: 1986).
59. *U.S. Agriculture in a Global Economy, 1985 Yearbook of Agriculture* (Washington, DC: U.S. Government Printing Office, 1985).
60. U.S. Congress, General Accounting 0ffice, *Better Sampling and Enforcement Needed on Imported Food,* Rep. No. RCED-86-219 (Washington, DC: September 1986).
61. U.S. Congress, General Accounting Office, *Export of Unregistered Pesticides Is Not Adequately Monitored by EPA,* Rep. No. RCED-89-128 (Washington, DC: April 1989).
62. U.S. Congress, Office of Technology Assessment, *Pesticide Residues in Food: Technologies for Detection, OTA-F-398* (Washington, DC: U.S. Government Printing Office, October 1988).
63. U.S. Department of Agriculture, *Agricultural Outlook December 1985* (Washington, DC: 1985).
64. U.S. Department of Commerce, Bureau of the Census, *National Data Book and Guide to Sources: Statistical Abstract of the United States, 1988* (Washington, DC: U.S. Government Printing Office, 1988).
65. U.S. Department of State, *Proceedings of the U.S. Strategy Conference on Pesticide Management* (Washington, DC: U.S. Government Printing Office, June 1979).
66. U.S. Environmental Protection Agency, *Air Quality Criteria for Lead, EPA-600/8-77-017* (Washington, DC: U.S. Government Printing Office, 1977).
67. U.S. Environmental Protection Agency, *Suspended, Cancelled and Restricted Pesticides* (Washington, DC: 1985).
68. Vigliani, E. C., "Carbon Disulfide Poisoning in Viscose Rayon Factories,' *British Journal of Industrial Medicine 11:235-244, 1954.*

69. Weir, D., *The Bhopal Syndrome: Pesticide Manufacturing and the Third World* (Penang, Malaysia: International Organization of Consumers Unions, 1986).
70. Weir, D., and Schapiro, M., *Circle of Poison: Pesticides and People in a Hungry World* (San Francisco, CA: Institute for Food and Development Policy, 1981).
71. Wood, R. W., "Neurobehavioral Toxicity of Carbon Disulfide," *Neurobehavioral Toxicology and Teratology 3:397-405, 1981.*
72, World Bank, *Poverty and Hunger: Issues and Options for Food Security in Developing Countries* (Washington, DC: 1986).
73. World Health Organization, *Organic Solvents and the Central Nervous System, Report on a Joint WHO/Nordic Ministers Working Group* (Copenhagen: 1985).
74. World Health Organization, *Principles and Methods for the Assessment of Neurotoxicity Associated With Exposure to Chemicals* (Geneva: 1986).
75. World Health Organization, "Chronic Effects of Organic Solvents on the Central Nervous System—Development of Core Protocol for International Collaborative Study," meeting in Copenhagen, Denmark, Nov. 15-18, 1988.

Chapter 10

Case Studies: Exposure to Lead, Pesticides in Agriculture, and Organic Solvents in the Workplace

"If we were to judge the interest excited by any medical subject by the number of writings to which it has given birth, we could not but regard the poisoning by lead as the most important to be known of all those that have been treated up to the present time. "

M.P. Orfila
A General System of Toxicology
1817

"*mere* is . . . no systematic monitoring of the health or exposure to pesticides of the more than 2 million farmworkers, applicators, harvesters, irrigators, and field hands who work around pesticides. Industrial workers who produce these pesticides receive the benefits of such monitoring. "

National Academy of Sciences
Alternative Agriculture
1989

"When I was in the Navy, I remember my commanding officer called me in and he was very upset because an air control operator had abandoned the tower, his position of duty, with seven aircraft stacked up calling for landing instructions. I was supposed to examine him. As I look back, I completely missed what was happening until years later. He was working in his off hours loading pesticides into spray planes, which caused a tremendous change in his personality and his behavior and his ability to cope. "

Gordon Baker, M.D.
Testimony before the Committee on Environment and Public Works
U.S. Senate
March 6, 1989

"..+ doctors tell me my nervous system has been heavily damaged, my brain has been damaged, and I suffer chemically induced asthma. I also have kidney, liver, and vision difficulties. I had a tumor removed from my eyes less than 1 year ago, and have been told that I have more, not to mention the chronic muscle pains throughout my body . . . . Throughout my entire 8 years at this truck manufacturing company, I was never informed of the hazards of the solvents I used, None of these products were adequately, clearly, or should I say, truthfully labeled. Yet the hazards for most of the products had been known for years by the chemical manufacturers and other people.

Frank Carsner
Testimony before the Committee on Science and Technology
U.S. House of Representatives
October 8, 1985

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Chapter 10

Case Studies: Exposure to Lead, Pesticides in Agriculture, and Organic Solvents in the Workplace

INTRODUCTION

The best way of illustrating the adverse effects of toxic substances on the nervous system is by looking at substances or classes of substances that are known to be neurotoxic. These case studies discuss attempts to control human exposure to lead, pesticides, and organic solvents. They illustrate the prevalence of neurotoxic substances, the susceptibilities of certain subpopulations, special hazards in occupational settings, and how Federal agencies address these concerns.

As it exists in the earth, lead is bound in chemical compounds and presents little risk to humans. As it is mined and utilized, however, it is distributed throughout the environment, presenting a risk to the entire population, but especially children, who are most vulnerable to its effects. Research shows that children are directly exposed to multiple sources of lead, are more sensitive to exposure, and suffer worse effects than adults. A great deal of progress has been made by Federal agencies in reducing public exposure by regulating the lead contents of paint, gasoline, plumbing systems, and food containers, but lead poisoning continues to be a major national health problem.

Chemical pesticides also present a significant risk to the population as a whole, but especially to agricultural workers and others who apply them or work close to them. Several Federal agencies have regulations that are intended to protect these workers from pesticide poisoning, but critics argue that more could be done. Many States have their own regulations, some of which are more stringent than Federal regulations, especially in protecting farmworkers. This chapter reviews the different types of pesticides in use and summarizes what is known about their neurotoxic effects.

Many solvents are neurotoxic and threaten the health of the industrial workers who come in contact with them. Solvents may cause a variety of functional changes, ranging from temporary memory loss to unconsciousness, depending on the duration and extent of exposure; major structural changes in the nervous system may also result. Engineering controls to avoid contamination, isolation of workers, and issuance of protective equipment to workers are some of the preventive measures currently in use. This chapter gives examples of how various solvents have been regulated under the Occupational Health and Safety Act, including the new standards for worker protection proposed by the Occupational Health and Safety Administration in 1988. It discusses criticisms of the existing regulations and offers suggestions as to how they might be improved.

EXPOSURE TO LEAD

As discussed in previous chapters, regulation of neurotoxic substances is a two-part process, one being identification of new hazardous chemicals and prevention of human exposure to them, the other being reduction of exposure to existing toxic substances. Lead is a prominent example of a substance long known to be toxic to the human nervous system (see box 1O-A). Unlike some elements, such as sodium or zinc, lead serves no useful biological purpose; since the body can neither use nor metabolize it, lead accumulates in body tissues, especially bones and teeth. Debate continues as to what maximum level is tolerable, although the only way to prevent any toxic accumulation is to limit exposure to zero. This chapter highlights some of the difficulties of removing or preventing exposure to a neurotoxic substance that has been extensively used in industry and therefore is especially prevalent in the environment.

Efforts to reduce public exposure to lead by removing current sources and preventing new ones have been undertaken by several Federal agencies. The Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) have taken steps to reduce the amount of lead in gasoline and food, and EPA is currently considering more stringent methods for controlling exposure to lead from drinking water. Other sources of lead, however, are more difficult to control. Lead has been used consistently in industrial and commercial activities and, despite awareness of its inherent dangers, continues to be used in product manufacturing. The use of lead in manufacturing ultimately results in its distribution in the environment in the form of waste.

Box 10-A—Lead: A Historical Perspective

Lead is the oldest, most extensively studied, and probably most ubiquitous neurotoxic substance. It is mentioned in ancient Egyptian manuscripts and was used by the Egyptians as a cosmetic; both the Egyptians and the Remans used lead in cooking tools and vessels. The Remans used it as a sweetener and preservative in wines and eiders; lead acetate is often called "sugar of lead" because of its sweet taste. The Remans also used lead in building houses and transporting water. In fact, the words plumber and plumbing originate from the Latin word for lead, plumbum. Lead was mined in Great Britain as far back as the reign of Julius Caesar. Remnants of these mines contaminate local farms and gardens today.

At least some of the toxic effects of lead were known early on. The Greek thinker Dioscorides stated in the 2nd century B.C. that "Lead makes the mind give way.' Pliny the Elder cautioned that inhaling the fumes of molten lead was dangerous (although he continued to recommend that it be used in making wine). Indeed, the continued use of lead, despite recognition of its dangers, has caused many outbreaks of lead poisoning over time. Benjamin Franklin may have been the first person to recognize lead as an occupational hazard: in a letter about lead poisoning he wrote, "How long a useful truth may be known and exist, before it is generally receiv'd and practis'd on."

SOURCES: A. Fischbein, "Environmental and Occupational Lead Exposure, " *Environmental and Occupational Medicine,* W.N. Rom (cd.) (Boston, MA: Little, Brown, 1983); J.S. Lin-Fu, "Lead Poisoning and Undue Lead Exposure in Children: History and current Status,' *Low Level* Lead *Exposure: The Clinical Implications of Current* Research, H.L. Needleman (cd.) (New York, NY: Raven Press, 1980); R.H. Major, ''Some Landmarks in the History of Lead Poisoning, " *Annals of Medical History* 3:218-227, *1931;* H.L. Needleman and D. Bellinger, "The Developmental Consequences of Childhood Exposure to Lead: Recent Studies and Methodological Issues,' *Advances in Clinical Child Psychology, vol. 7,* B.B. Lahey and A.E. Kazdin (eds.) (New York, NY: Plenum Press, 1984); H. Waldron, ''Lead Poisoning in the Ancient World," *Medical History* 17:391-398, *1973.*

For example, lead is found in commodities such as solders, batteries, and paint, but it is also present in dust and soil as waste material. There is no agreement as to who bears responsibility for removing the various forms of lead from the environment. Although the Consumer Product Safety Commission has reduced the amount of lead permitted in paint to prevent future exposure, the danger of lead poisoning from leaded paint in old housing remains.

In addition to the remedial measures being taken, preventive measures must be considered for some currently minor sources that may become larger problems in the future, Incinerators, for example, may significantly increase exposure to lead in the environment as we attempt to reduce our reliance on landfills.

Sources of Exposure

Lead exists in both organic and inorganic forms. Although organic lead is more toxic than inorganic lead because it degrades quickly in the atmosphere and the body, it constitutes only a small proportion of the total lead to which the population is exposed (16). Organic lead is most commonly found as a fuel additive and can reach significant levels in heavy traffic areas and underground garages (16), but it is rapidly converted to the inorganic form. This chapter will therefore focus on inorganic lead. Significant sources of exposure to inorganic lead include water, food, soil, lead-based paint, leaded gasoline, and industrial emissions (see table 10-1).

Levels and sources of exposure vary according to surroundings. In remote areas, proximity to stationary sources of lead such as smelters maybe the main source of exposure, whereas in older cities leaded paint may be the most common source (165). Individuals living near industrial sources of lead, people who drink contaminated water, adults with occupational exposure, and children who ingest lead-contaminated paint, soil, or dust have the greatest exposure to lead (109,172).

When discussing exposure to lead, a distinction is often made between children and adults, since children both ingest and inhale more lead per unit of body weight than adults and are more vulnerable to its effects (165). Children, given their normal tendency to put things in their mouths, are likely to ingest paint, soil, or dust, all of which are potential sources of lead. Lead gives paint a sweet taste, increasing its appeal for children. Children also have a higher absorption rate of ingested lead than adults: whereas adults absorb between 5 and 15 percent of ingested lead and usually retain less than 5 percent of what is absorbed, one study found that infants on regular diets absorb an average of over 40 percent of ingested lead and retain over 30 percent

Table 10-l Significant Sources of Exposure to Lead

Leaded paint
. lead released into the air through destruction and weathering of structures painted with leaded paint
• lead ingested by children from household dust, less commonly by eating leaded paint chips

Leaded gasoline
. lead released into the air in exhaust fumes
. lead released into the air during fueling

Stationary sources
. lead released into the air by industrial activity, e.g., smelting, refining, and battery recycling
. occupational exposure of factory workers, exposure of children to lead on the clothing of parents

Dust, soil
. paint
. industrial activity
. gasoline

Water, plumbing
. **lead in water** source
. leaching from lead pipes
. leaching from lead solder
. leaching from brass or bronze

Food
. lead contained in food items from contaminated water or soil
. lead-soldered food cans
• lead deposited on crops from automobile exhaust
. lead deposited on crops from industrial activity
• lead contamination during food processing
. lead glazes in dishes and pottery

SOURCE: Office of Technology Assessment, 1990.

of that amount (57). Children also retain more of the lead they absorb than do adults, since lead in blood is stored in growing bones (165). The effects of lead on children are more severe than the effects of lead on adults: children have less bone tissue in which lead can be stored, and thus lead remains in the bloodstream, free to exert toxic effects on various organs of the body. Nutritional deficiencies, more likely to occur in the growing child, can also contribute to higher absorption levels of lead (165,169). Children's nervous systems, especially their blood-brain barriers, are not yet fully developed, and the same cellular lead exposure may produce disproportionate results in children compared to adults (84,145). Also, cognitive effects occur at lower levels in children. For similar reasons, fetuses may be even more vulnerable to lead's toxicity than children (84). There is some evidence that lead stored in women's bones from previous exposure may be mobilized during pregnancy and lactation, and thus expose the fetus and infant through the placenta and breast milk (148).

Estimates of the number of children exposed to lead, listed by source, are found in table 10-2. The

Table 10-2-Estimated Number of Children Exposed to Sources of Lead

Source	Number of children[a] (millions)
Leaded paint	12.00
Leaded gasoline	5.60
Stationary sources	0.23
Dust, soil	5.90-11.00
Water, plumbing	10.40
Food 0	1.00

[a]Numbers in the table are not additive since children are usually exposed to multiple sources of lead in the environment.

SOURCE: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry and Center for Environmental Health and Injury Control, "Childhood Lead Poisoning—United States: Report to the Congress by the Agency for Toxic Substances and Disease Registry," *Morbidity and Mortality Weekly Report* 37:481-485, 1988.

type and availability of data for each of these sources vary considerably, therefore the estimates are not comparable and cannot be used to rank the severity of the problem by source of exposure (165).

For adults, the workplace is a major source of exposure. The National Institute for Occupational Safety and Health has listed 113 occupations that potentially increase workers' exposure to inorganic lead (74). In adults not exposed to occupational sources of lead and in children older than 6 to 8 years, food and water are most likely to be the major sources (74). For most adults, lead in the air is no longer as significant a source of exposure as lead in the diet, but as one study found, levels of lead in the blood of adults remain correlated with levels of lead in air (74), as do levels of lead in children's blood (15). Before the phase-out of lead from gasoline, however, airborne lead was the predominant source of exposure to lead for adults and children (6,173, 175).

Routes of Exposure

Lead can enter the human body through three routes: inhalation, ingestion, or absorption through the skin, although the latter is significant only for organic compounds of lead (51). Intake through inhalation depends on particle size and volubility in body fluids (51). Gastrointestinal absorption is influenced by a number of factors, primarily age and nutritional status (72). The proportion of lead absorbed through ingestion and inhalation differs by age and principal source of exposure, as discussed earlier.

Levels of Exposure

Lead is stored in the circulating blood, soft tissue, and bone. Because it has a long biological half-life and is only slowly excreted from bone, lead can accumulate in the body. Thus, the concentration of lead in the blood (the blood lead level) is not an accurate indicator of total exposure to lead, only of recent exposure. The amount of lead found in teeth and bones is a more useful indicator of cumulative exposure, but it yields no information about the time or duration of exposure, nor of current exposure. Furthermore, teeth are easily obtained only from young children, who lose their baby teeth. A technique using X-ray fluoroscope was developed in 1984 to measure lead in bone (28,77); its feasibility as a testing method is being evaluated (186).

For the most part, neurological deficits in adults have not been noted below a blood lead level of 40 micrograms of lead per deciliter of blood (ug/dl) (192), although elevations in blood pressure have been noted at 5 ug/dl (125, 126, 144). In children, however, adverse neurological effects are seen at much lower levels (33,87,165), and since 1943 the blood lead level found to be associated with neurobehavioral dysfunction has steadily decreased. Before that year, the cumulative effects of



Photo credit: U.S. Environmental Protection Agency

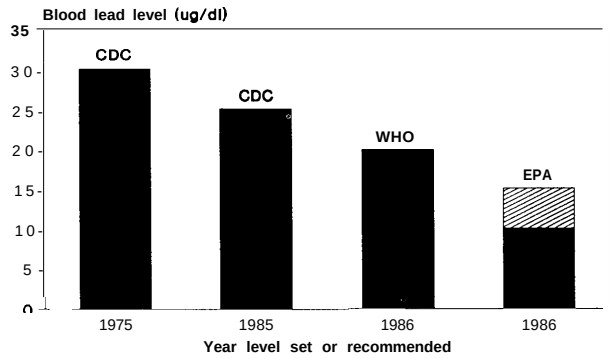
EPA has estimated that exposure to lead in drinking water is keeping more than 240,000 children from realizing their full intellectual potential.

lead poisoning went unrecognized, and physicians generally believed that if a child did not die of lead poisoning there would be no lasting effects (1 18). In 1943, however, researchers found that a group of children with mild lead poisoning in infancy did not progress satisfactorily in school, and they suggested that lead poisoning early in life might be widespread (22). Since then, the aggregate effects of lead poisoning have been recognized and its long-term effects have been studied. Researchers have correlated blood lead levels with neurobehavioral dysfunction.

Before the 1960s a blood lead level below 60 ug/dl was not considered dangerous (169). In 1975, the Centers for Disease Control (CDC) lowered the acceptable level for children to 30 ug/dl, and in 1985 it lowered the level again, to 25 ug/dl (169). The World Health Organization (WHO), in a 1986 report, stated that 20 ug/dl was the upper acceptable level (193). EPA% Clean Air Scientific Advisory Committee associated lead levels of 10 to 15 ug/dl and possibly lower with adverse effects (see figure 10-1) (172) and recommended 10 to 15 ug/dl as the maximum acceptable level. Recently, subtle deficits in neurobehavioral performance have been reported in fetuses and newborn babies exposed to low levels of lead (12,33,87,121,165).

In 1986, Congress requested that the Agency for Toxic Substances and Disease Registry (ATSDR) prepare a report on lead poisoning in children. One of the report's mandates was to estimate the total number of children exposed to potentially hazardous concentrations of lead. Approximately 2.4 million U.S. children age 6 months to 5 years living in Standard Metropolitan Statistical Areas (SMSAs) (or 17.2 percent) have blood lead levels greater than 15 ug/dl; 200,000 (1.5 percent) have blood lead levels greater than 25 ug/dl. No economic stratum of children was found to be free from the potential health risk of lead poisoning. However, since the data covered only black and white children, no reliable prevalence rates could be calculated for Hispanic children and children of all other races; further, since SMSAs include only about 80 percent of the children in the United States, the actual number of children with blood lead levels above 15 ug/dl may be higher than the ATSDR report indicates: more likely estimates are between 3 and 4 million affected children (21.4 to 28.6 percent) (165). The CDC is considering lowering its target level for medical intervention again.

Figure 10-l- Children's Blood Lead Levels Considered Acceptable by Various Agencies



= 10 to 15 ug\dl is the recommended maximum acceptable level.

SOURCE: Office of Technology Assessment, 1990.

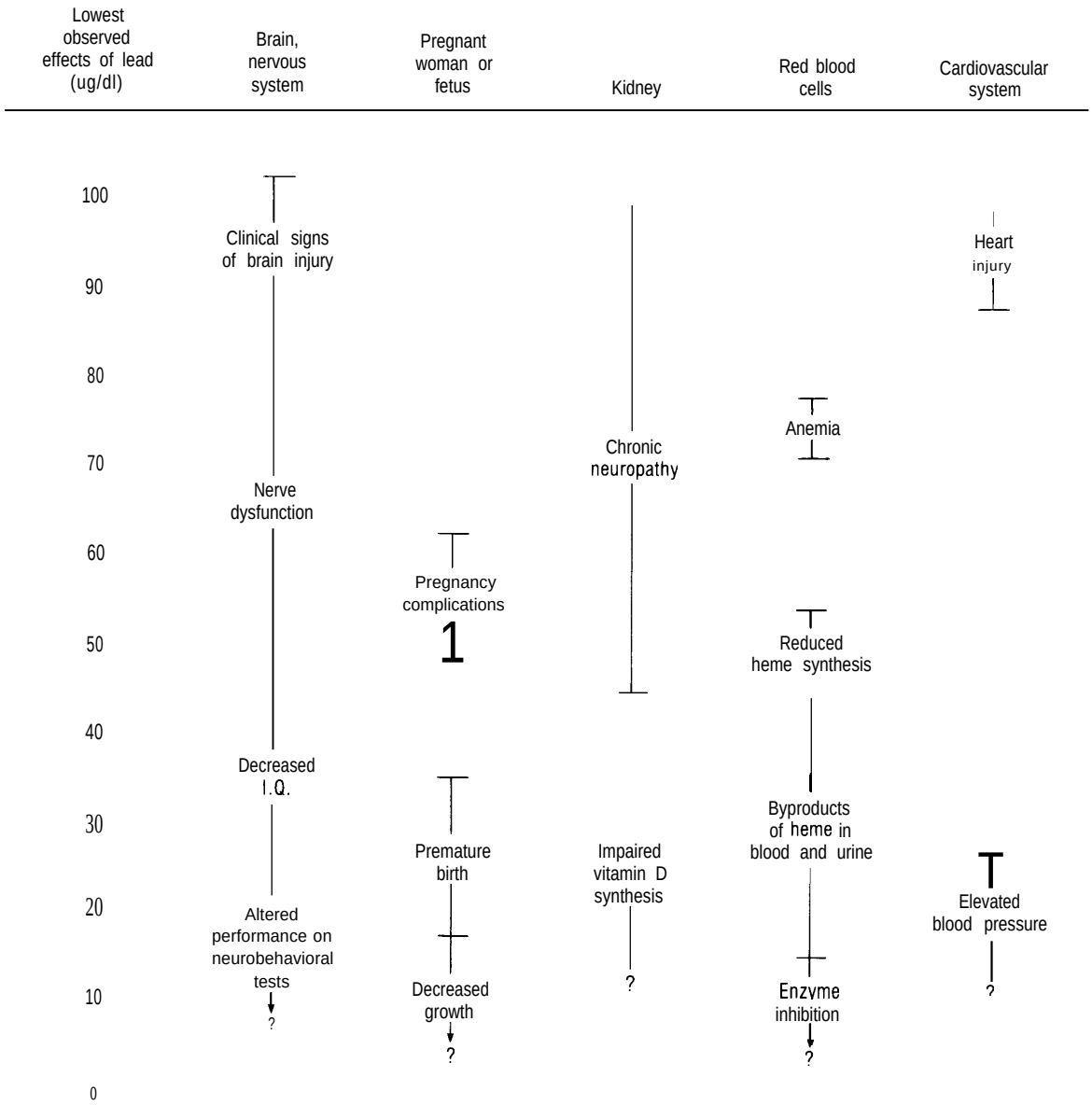
It is significant that some of the studies on children have not detected a threshold for adverse effects of lead (87,117,123), indicating that as tests for various impairments become more sensitive, the level at which adverse effects are observed may decrease further. Accurate, current information as to the lowest blood lead levels associated with neurotoxic effects is crucial for policymaking, since the regulations that set safety levels at 25 ug/dl do not adequately protect the many children whose blood lead levels fall below that; these children may be endangered at levels of 10 **to 15** ug/dl, or possibly lower.

Effects of Lead on the Human Body

Lead causes numerous adverse health effects. A summary of some observable effects and the blood lead levels with which they have been correlated is given in figure 10-2. In children, brain damage resulting from exposure to lead can range in severity from inhibited muscular coordination to stupor, coma, and convulsions at high levels (72). Acute brain damage is rare in adults; when it appears it is usually a result of high exposures to lead and is often accompanied by other factors, such as alcoholism. High exposures to lead can also damage the peripheral nervous system.

Since the discovery of chelation treatment, which removes lead from the blood, mortality from acute lead poisoning has declined. Yet as our ability to

Figure 10-2-Adverse Health Effects of Lead



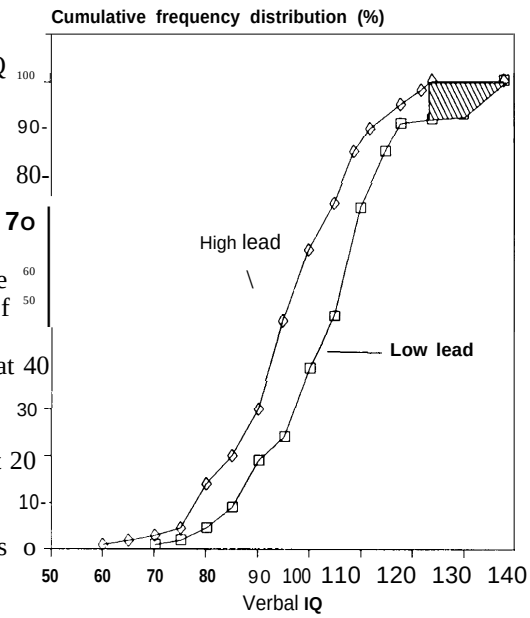
SOURCE: U.S. Environmental Protection Agency, "Drinking Water Regulations; Maximum Contaminant Level Goals and National Primary Drinking Water Regulations for Lead and Copper; Proposed Rules" (53 FR 31565), 1966.

detect subtle neurological deficits has improved, estimates of morbidity have increased. Effects of permanent damage to the central nervous system—for example, mental retardation, hyperactivity, seizures, optic atrophy, sensory-motor deficits, and behavioral dysfunctions-have been observed (see box 10-B). There is also some recent evidence that lead may cause minor hearing impairments (146). Chronic low-level exposure may ultimately be more damaging than acute exposure that is treated immediately (21).

Factors such as genetic variation in susceptibility, nutritional status, behavior, and age may alter an individual's vulnerability to lead poisoning (1 18). Most of these factors affect toxicity by altering the absorption of lead.

Box IO-B—Lead Poisoning and IQ

A study in 1979 found that children exposed to lead had intellectual, attentional, and behavioral deficits, It also found a difference of about 5 points in the mean IQ (intelligence quotient) of children with elevated lead levels and those with low lead levels. While this number is statistically significant, some question was raised as to whether it was biologically significant.



As the figure shows, the significance of this difference in **IQs** shows up most clearly at the ends of the IQ spectrum. Children with elevated lead levels were three times more likely to have a verbal IQ below 80; furthermore, none of them had superior IQ scores (greater than 125), while 5 percent of the children with low lead levels had scores in that range.

A follow-up study published in January of 1990 concluded that the effects of lead exposure upon cognitive development in early years persist into early adulthood. In this study, children who were originally examined in the first grade were reexamined as high school students. The subjects underwent extensive neurobehavioral analysis using a variety of tests for hand-eye coordination, grammatical reasoning, and reaction times. Deficits in central nervous system functioning resulted in poorer classroom performance, reduced vocabulary and reasoning scores, and higher absentee rates in school.

SOURCES: H.L. Needleman, C. Gunnoe, A. Leviton, et al., "Deficits in Psychologic and Classroom Performance of Children With Elevated Dentine Lead Levels," *New England Journal of Medicine* 300:689-695, *1979;* H.L. Needleman, A. Leviton, and D. Bellinger, "Lead-Associated Intellectual Deficit," New *EnglandJournal of Medicine* 306:367, *1982;* B. Weiss and T.W. ClarkSon, "Toxic Chemical Disasters and the Implications of Bhopal for Technology Transfer," *The Milbank Quarterly* 64:216, *1986.* H.L. Needleman, A. Schell, D. Bellinger, et al., "The Long Term Effects of Exposure to Low Doses of Lead in Childhood,' New *England Journal of Medicine* 322(2):83-88, *1990.*

Regulatory Activity Regarding Exposures to Lead

Action by Congress and various executive agencies has led to a reduction in exposure to lead in the United States. Their response marks the first time that specific neurobehavioral effects of a toxic substance were considered in determining regulatory policy. Although progress has been made, there is evidence that lead poisoning in the United States still occurs in epidemic proportions.

Lead in the Air

Removing lead from the air is the responsibility of EPA, whose statutory authority comes from the Clean Air Act, passed in 1970 and amended in 1977. The two major sources of lead in the air are leaded gasoline and stationary sources, such as lead smelt-*ers.*

In 1978, EPA promulgated regulations stating that the level of lead in the air must not exceed 1.5 micrograms per cubic meter (ug/m^3). Under the Clean Air Act, the States had to take steps to meet that standard by 1982. The standard includes contributions from both automobiles and industrial sources and was designed to prevent children from being exposed to concentrations of lead in the air that could lead to blood lead levels of more than 30 ug/dl (96).[1]

In 1973, EPA promulgated regulations requiring that major gasoline dealers sell at least one grade of "unleaded" gasoline (defined as containing no more than 0.05 gram of lead per gallon of gasoline).

[1]The recommended maximum for children's blood lead levels has been repeatedly revised: EPA Science Advisory Board established 10 to 15 ug/dl and possibly lower as the blood lead level of concern in 1986 (173).

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Lead in Food

Regulation of lead in food is the responsibility of FDA. Although the agency has set acceptable levels of lead for pesticides and food utensils in domestically produced food, much of its activity has focused on eliciting voluntary cooperation from domestic food manufacturers and processors (165). The success of this effort is illustrated in figure 10-4.

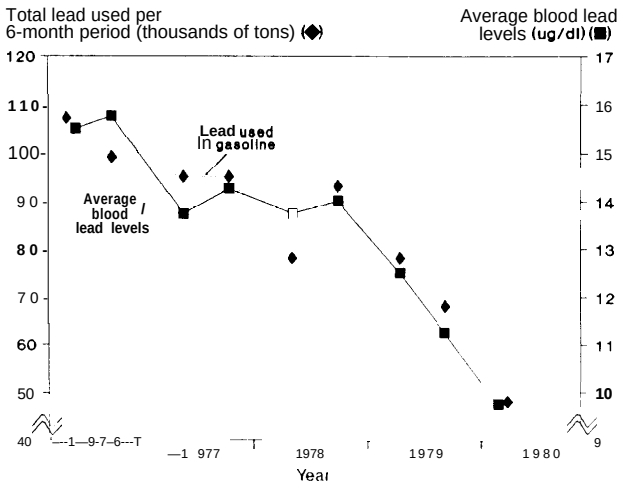
Regulation of lead by FDA began in the 1930s, when the agency established guidelines for limits on the use of lead in pesticides.[2] The next item of concern was lead in canned evaporated milk. In 1974, the agency proposed a tolerance level of 0.30 part of lead per million parts of milk (ppm) (39 FR



Photo credit: National Archives

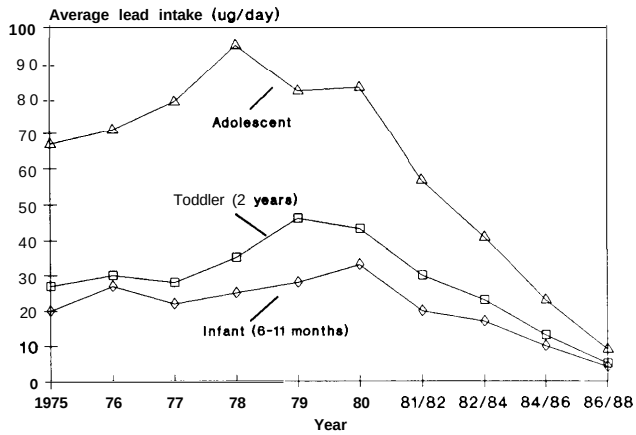
[2]Current permissible levels of lead in pesticides are 1 microgram per gram (ug/g) on citrus fruits and 7 ug/g on other fruits and vegetables.

Figure 10-3-Lead Used in Gasoline Production and Average Blood Lead Levels



SOURCE: J. Schwartz, H. Pitcher, R. Levin, et al., Costs *and Benefits of Reducing Lead in Gasoline: Final Regulatory Impact Analysis, EPA-230-05-85-O06* (Washington, DC: U.S. Government Printing Office, 1985).

Figure 10-4-Dietary Lead Intake



SOURCE: U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Food Safety and Applied Nutrition, *FDA Total Diet Study* (Washington, DC: 1989).

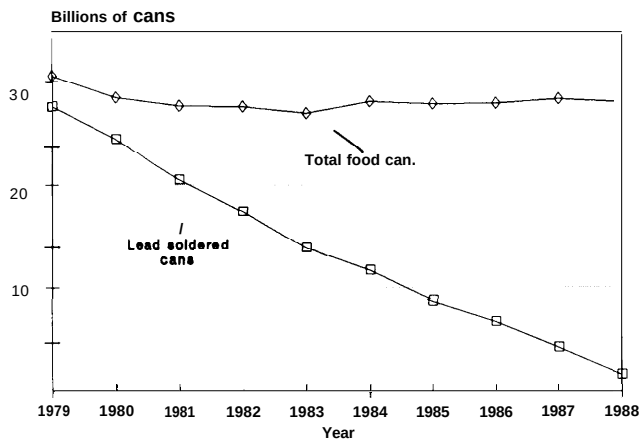
42745). As a result of its own studies and FDA's recommendations, the milk industry reduced the levels of lead in evaporated milk from 0.52 ppm in 1972 to 0.08 ppm in 1982 (30,109). Manufacturers of infant juices also took steps to lower lead levels in their products, eventually switching voluntarily from tin cans to glass jars (109), as did manufacturers of canned infant formula, who switched from lead-soldered cans to other types of cans (96).

There has been a significant decrease in the use of lead solder for food cans manufactured in the United States. In 1979, more than 90 percent of such cans contained lead solder; by 1989, less than 4 percent did. Figure 10-5 demonstrates the trend in reducing lead solder in cans and reflects the can manufacturing industry's plans to eliminate lead solder in all domestically produced food cans in the next 2 to 3 years (24). The number of imported cans containing lead solder is not known but maybe large (165).

Materials used for packing food have also been a source of concern. These materials are considered indirect food additives, because contaminants may migrate from packaging materials into the food. As of 1980, three indirect food additives were subject to limitations on the amount of lead they can contain (109).

Regulations concerning lead used in food utensils, specifically ceramic and hollowware products, have been promulgated by FDA (54 FR 23485). Large containers (in which food is likely to be stored) and cups used by children have lower limits on permissible lead content than do small utensils (100,109). FDA is currently considering lowering the acceptable limit for large containers. Although these limits apply to both imported and domestic utensils, few imported utensils are tested for lead content. In response to public concern, some retailers are testing imported dishes on their own (100, 182).

Figure 10-5-Food Can Shipments



SOURCE: Can Manufacturers Institute, Washington, DC, personal communication, 1989.

Occupational Exposure to Lead

In contrast to the reduction of lead in food, where strict regulations have not had to be imposed by government, the reduction of occupational exposure to lead has required more intervention. In response to the Occupational Safety and Health Act of 1970, the Occupational Safety and Health Administration (OSHA) promulgated regulations in 1978 (29 CFR 1910.1025) that set a maximum permissible level for lead in the air inhaled by workers.[3]

The lead industries immediately sued OSHA, challenging the validity of the standard. In 1980, the U.S. Court of Appeals for the District of Columbia Circuit upheld the limit and most other provisions of the regulation but ordered that the feasibility of engineering controls be reconsidered for many affected industries (180). OSHA states explicitly that industries must use engineering controls to reduce the overall level of lead in the air at the workplace, as opposed to simply giving workers respirators to remove lead from the air they inhale. The court instructed OSHA to reassess the feasibility of such engineering and work controls for approximately 40 industries. Only one of these studies has not been completed; however, because the courts will reexamine all the studies at once, these 40 industries are currently exempt from the requirement to achieve 50 ug/cm^3 through engineering and work practice controls.

The regulatory framework for ensuring minimal occupational exposure to lead is in place. Occupational exposure has been reduced considerably in most large industries, as indicated by decreases in cases of high-dose lead poisoning, mean blood lead levels in workers, and mean air lead levels in most workplaces (75). It remains a problem in small shops, however, which are covered by OSHA regulations but may not be routinely inspected. Some critics assert that enforcement of OSHA regulations is inadequate. Others state that, as revealed by several State screening programs, many employers are unaware of their responsibilities, and others ignore them. Many employees are not aware of their rights or are reluctant to report employers for fear of losing their jobs.

Lead in Paint

Although lead-based paint is now only rarely used, the paint that remains on the walls of older housing is the most significant source of lead poisoning today. Many children are exposed to lead-based paint, and efforts to remove paint from the walls as a preventive measure vary greatly from State to State. The U.S. Department of Health and Human Services reported in 1988 that 52 percent of all residential buildings have paint **containing lead in concentrations greater than or equal to that considered dangerous by the CDC (165, 169).**

In 1971, Congress attempted to address the issue of lead poisoning from lead-based paint. The Lead-Based Paint Poisoning Prevention Act and its 1973 and 1976 amendments directed the Consumer Product Safety Commission (CPSC) to establish a level of safety for lead in paint.[4] Most paints are regulated under this standard, but lead is still used in some paints (most often as a weather-resistant coating for metals) (51), and the yellow paint used for lining highways and roads contains lead as well (42). The CPSC has no control over lead-based paints already in houses and other dwellings or lead-based paint manufactured before 1977, when the regulation went into effect (165).

A second aspect of the lead-based paint legislation involves removing lead paint from housing under Federal jurisdiction, an activity that falls to the Department of Housing and Urban Development (HUD). HUD can only regulate paint in public housing or federally assisted dwellings (165). The Department's regulations currently ensure notification of residents in and purchasers of HUD-associated housing constructed before 1950 of the hazards of lead poisoning from lead-based paint. The regulations also prohibit the use of lead-based paint in HUD housing and federally owned and assisted construction or rehabilitation of residential structures, and ensure removal of lead-based paint in HUD-associated housing and federally owned prop-

[3]Before 1978, the permissible exposure limit was 200 ug/m^3 (over an average time period of 8 hours). The regulations lowered the limit to 50 ug/m^3 (43 FR 52952 and 43 FR 54354) and set an action level of 30 ug/m^3 (an action level is based on the same criteria as a tolerance). At this action level, the industry must initiate environmental monitoring, recordkeeping, education, training, and medical surveillance. Medical removal protection (removing the employee to an area with exposure below the action level) is directed by the medical surveillance findings (109).

[4]CPSC's authority in this area comes from the Consumer Product Safety Act, which gives the Commission the power to ban as hazardous any consumer product that presents an unreasonable risk of injury (15 U.S.C. 2057). The current regulations state that paint may contain no more than 0.06 percent lead.

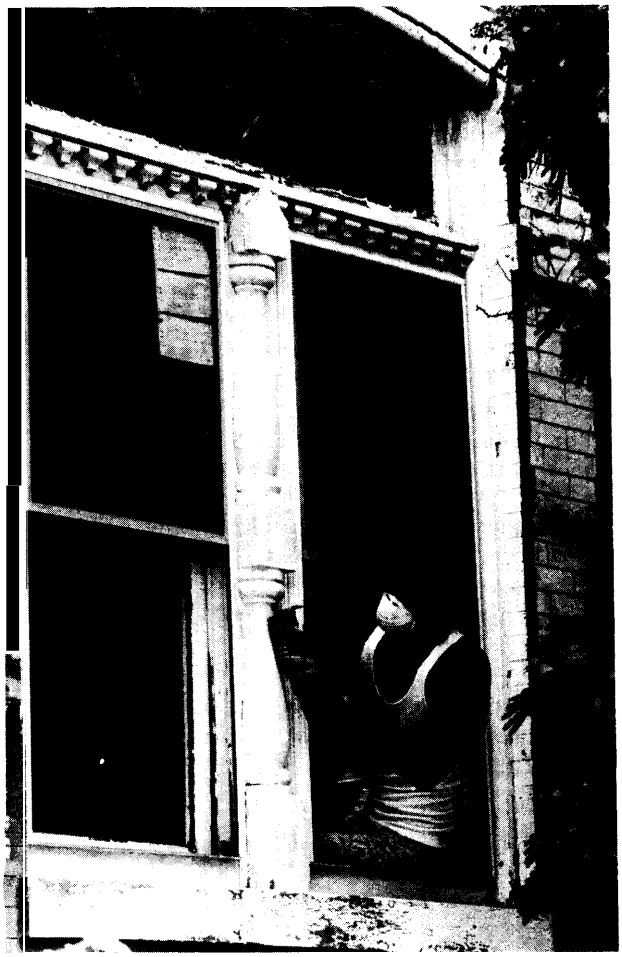


Photo credit: U.S. Environmental Protection Agency

The paint that remains on the walls of older housing is a significant source of lead poisoning.

erties (109). Removal of lead-based paint from walls is dangerous in itself. Workers can be exposed to lead dust if not adequately protected, and dust and paint chips can be released into the nearby environment if not properly disposed of, resulting in markedly increased exposure of inhabitants. HUD is currently conducting a study to determine the extent of the lead-based paint problem in public housing and to study the efficacy of alternative abatement procedures.

The Lead-Based Paint Poisoning Prevention Act also created a Federal program to fund lead poisoning prevention programs for children. Initially funded through the Bureau of Community Environmental Management, the program was transferred to the CDC in 1973, and until 1981 the CDC administered grants to the States for prevention programs. In 1981, the Omnibus Budget Reconciliation Act rolled a number of categorical health programs, including the lead poisoning prevention program, into the Maternal and Child Health Services Block Grant. Thus, the allocation of money among the various health programs, previously dictated by the Federal Government, became the decision of each individual State. Accordingly, States now choose how much money, if any, to apply to lead poisoning prevention programs (see box 10-C). Because many of these programs have been reorganized at the State level and because reporting of lead poisoning prevention expenditures is now voluntary, it is difficult to determine how expenditures on lead poisoning prevention programs have changed. According to a 1984 General Accounting Office study on the Maternal and Child Health Block Grant, lead screening projects have received "the greatest reduction in emphasis' (179), and a 1987 survey by the National Center for Education in Maternal and Child Health indicated 10 States have no lead poisoning prevention activities at all (1 11). In 1988, the Lead Poisoning Prevention Act authorized $66 million for community screening between 1989 and 1991 in order to compensate for deficits in lead poisoning prevention programs at the State level. Lead-based paint remains a significant source of lead poisoning, despite the laws and regulations that specifically address this problem.

Lead in Drinking Water

Both EPA and Congress are currently addressing the problem of lead in drinking water. In 1986, EPA estimated that 42 million Americans drank tap water containing more than 20 parts of lead per billion parts of water, the proposed drinking water standard (which has since been lowered). The Agency further estimated that exposure to lead in drinking water is keeping more than 240,000 children from realizing their full intellectual potential (171).

Lead rarely originates from source water but leaches out of plumbing containing lead pipes and fixtures or lead solder. EPA estimates that there are approximately 4.4 million lead service lines in use in the United States and that approximately 25 percent of water suppliers have some lead service lines within their distribution system (53 FR 31521). Since more acidic water leaches more lead out of plumbing systems, lead in drinking water may be regulated by controlling its pH (a measure of

Box 10-C-State Lead Poisoning Prevention Programs

Some States do nothing about lead poisoning, largely because it is not considered a significant problem. Others identify children with high blood lead levels through mandatory reports from laboratories that conduct blood tests, then follow up by treating the children and removing the environmental source of lead, if possible. Other States have an outreach program, whereby children in high-risk areas are screened and appropriate follow-up action is taken. Some communities have lead poisoning prevention programs.

A number of States have either passed legislation or are considering legislation addressing the issue of childhood lead poisoning. Massachusetts, for example, has extensive legislation that requires statewide screening of children under age 6, reporting of cases of childhood lead poisoning by physicians, and art education campaign about the dangers and sources of lead poisoning. The law also outlines lead-based paint abatement standards and a program for removing or covering lead in soil, among other provisions. Generally, areas of the country with industrial pollution, older housing, and large cities appear to have the most active lead poisoning prevention efforts.

Given the variability of these prevention efforts, it is difficult to characterize the extent of screening at the State and local levels. However, a survey conducted by the Public Health Foundation in 1983 yields some relevant data. Of the 48 State and territorial health agencies surveyed, 33 operated lead poisoning prevention services. Thirty of these programs reported screening 676,600 children ages 1 to 5. Of the children screened, 9,317, or 1.6 percent, had confined lead toxicity (defined as blood lead levels greater than 30 ug/dl and erythrocyte protein levels greater than 50 ug/dl, the CDC standard at that time). Of these children, 92 percent received medical care,[1] and environmental investigations were conducted for 96 percent. The source of lead was determined in 80 percent of the cases of confirmed lead toxicity, and 98 percent of those sources were lead-based paint. Of the children with identified hazards, the hazards were abated for 91 percent.

In one sense, these data are encouraging, since the majority of children with elevated blood lead levels evidently obtained medical treatment and hazard abatement. On the other hand, the number of children identified and treated is only a small percentage of the 200,000 children estimated to have elevated blood lead levels. Thus, a large number of children with potentially dangerous exposure to lead are not being helped.

[1]From this point on, percentages are based on data reported by those State and territorial health agencies that could provide both the numerator and the denominator for their percentages. As not all agencies reported all the relevant data, not all are represented in these numbers.

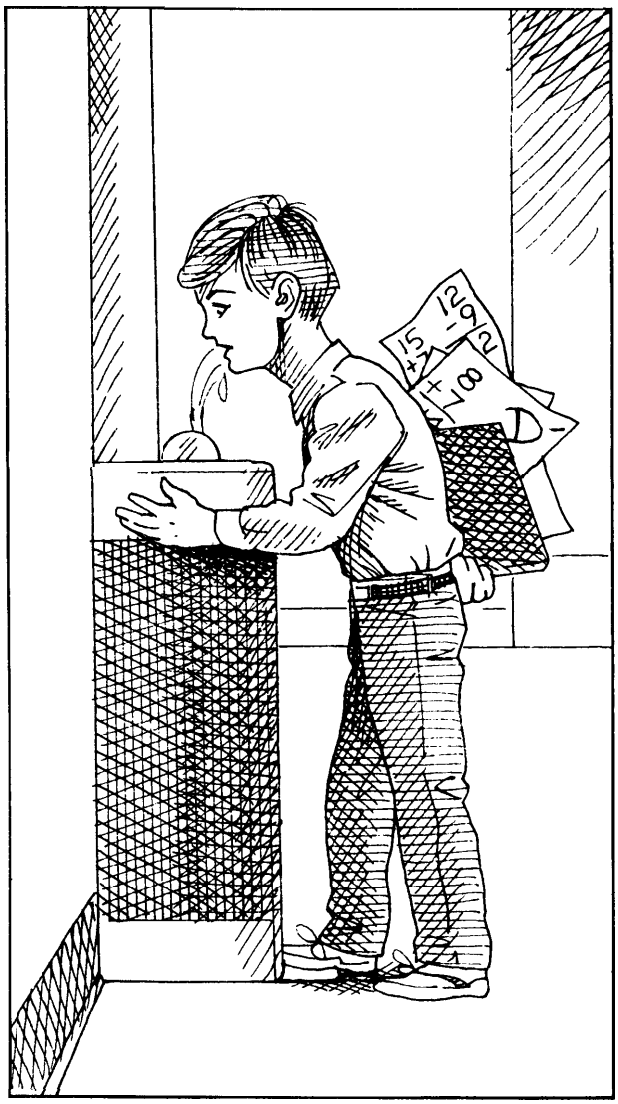
SOURCES: Public Health Foundation, ***Special Report: State Health Agency Lead Poisoning Prevention Activities, 1983*** (Washington, DC: 1986); U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, *The Nature and Extent of Lead Poisoning in **Children** in the United States: A Report to Congress* (Washington, DC: 1988).

acidity), and EPA argues that the least expensive method for reducing lead in drinking water is central corrosion control treatment (84,171).

Under the Safe Drinking Water Act (1974), EPA must establish maximum contaminant level goals (MCLGs) and national primary drinking water regulations (NPDWRs) for contaminants that may have an adverse effect on the health of the population drinking the water. While MCLGs are nonenforceable health goals, NPDWRs are enforceable standards. NPDWRs include maximum contaminant levels (MCLs) or treatment technique requirements, or both. In 1986, amendments to the Safe Drinking Water Act listed 83 contaminants, including lead, for which EPA had to develop MCLGs and NPDWRs.[5]

In 1988, EPA proposed an MCLG of zero for lead. The proposed NPDWRs establish an MCL of 0.005 milligram of lead per liter of water (mg/l) for water entering the distribution system (to replace the current MCL of 0.05 mg/l); require corrosion control treatment techniques if specified levels of lead, copper, and water acidity are not met (the Agency issued regulations for copper and lead simultaneously); and require public education if other meas-

[5]The 1986 amendments to the Safe Drinking Water Act also banned the use of lead solder or flux and lead-bearing pipes and fittings. This ban was effective in 1986, and States were required to implement and enforce it as of June 1988. EPA is currently developing a program to withhold Federal grants for programs to improve the quality of drinking water from States that fail to enforce the ban (53 FR 31516).



Illustrated by: Ray Driver

ures fail.[6] Some argue that the proposed regulations are not strict enough and claim that EPA has both the authority and the responsibility to set MCLs at the tap.[7] Water suppliers, on the other hand, find the corrosion control program to be unwarranted and expensive.

The debate over regulation of lead in drinking water focuses on whether the public water supplier or the consumer is ultimately responsible for preventing high levels. Public water systems control the quality of the water they distribute, including the parameters that determine how much lead will leach from plumbing into the water. On the other hand, the water passes through a distribution system that is owned partially by the water supplier and partially by the consumer. If the regulation is enforced at the tap, the water supplier must assume responsibility for some lead contributions from the consumer's plumbing. If lead levels are enforced at the beginning of the distribution system, the consumer must assume responsibility for some of the water supplier's plumbing or the corrosivity of the water supplied by the water system, or both. Undercurrent EPA regulations, the supplier is responsible both for lead levels in the water in the distribution system and for the water quality at the tap.

Lead in drinking water remains a serious problem in some water supplies, especially in schools. The efficacy of the regulations promulgated by EPA will be crucial in determining how serious a problem it remains. (Another widely discussed issue concerns lead in water coolers-see box 10-D.)

Lead in Incinerator Ash

The United States produces approximately 160 million tons of solid waste every year. Currently, approximately 83 percent of this waste is put in landfills, 11 percent is recycled, and 6 percent is incinerated (86). As landfills are rapidly being filled, there is much discussion concerning other methods of disposing of this waste. EPA estimates there will be a sixfold increase in the capacity for waste incineration in the United States over the next 15 years (76).

Incineration has both advantages and disadvantages. Its major advantage is that it reduces the volume of waste by 75 to 80 percent. Furthermore, it can be used to generate electricity and can be linked with recycling methods to remove such solids as iron, steel, glass, and paper from the waste stream

[6]Under these proposed relations, all water leaving the treatment plant would have to meet the 0.005 mg/l standard. To regulate how much lead the water can pick up as it travels from the distribution point to the consumer, EPA proposed that targeted samples be taken from consumers' taps. If the average lead level is less than or equal to 0.01 mg/l, the average copper level less than or equal to 1.3 mg/l, and the pH greater than or equal to 8.0 in at least 95 percent of the samples, then the supplier is not required to take any further action. If any of these three standards is not met, the water supplier would be required to implement or improve its corrosion control. If the lead levels are above 0.02 mg/l, the supplier would have to launch a public education program to encourage consumers to reduce their exposures to lead in drinking water (53 FR 31516).

[7]There is some concern that EPA's measures do not adequately treat the problem, since: 1) the NPDWR of 0.005 mg/l does not reflect the MCLG of O mg/l; 2) the tap standard is not enforceable; and 3) limited sampling at the tap will necessarily overlook some households with high lead levels (1 16).

Box 10-D-Lead in Water Coolers

Another source of lead in drinking water, water coolers, has received considerable attention in the press and is the subject of legislation passed in the 100th" Congress. Some water coolers may contain lead-lined tanks or lead solder that comes into contact with the water. Data solicited by Congress from manufacturers reveal that close to 1 million water coolers currently in use contain lead (U.S. Congress, Committee on Energy and Commerce, 1988). These water coolers are of special concern because they are frequently used in schools.

The Lead Poisoning Prevention Act of 1988 addresses this situation through the following provisions: 1) recalling all water coolers with lead-lined tanks; 2) banning the manufacture or sale of water coolers that contain lead; 3) setting up a Federal program to assist schools in evaluating and responding to lead contamination problems; and 4) making funds available for the initiation and expansion of lead poisoning prevention programs (for all sources of lead poisoning). This last provision is designed to expand on Federal funds for lead screening from the Maternal and Child Health Services Block Grants. The legislation also requires that the Environmental Protection Agency publish a list of water coolers that are not lead-free within 100 days of enactment (U.S. Congress, Committee on Energy and Commerce, 1988). The Agency released a proposed list in April 1989. The original draft of the legislation contained a section that set a Safe Drinking Water Act maximum contaminant level at the tap, but this section was eventually deleted because of political pressure (''House Staffers, ' 1988).

SOURCES: "House Staffers Scrap Lead Standard to Speed Drinking Water Bill's Passage," *inside EPA 9:6, 1988;* U.S. Congress, Committee on Energy and Commerce, Subcommittee on Health and the Environment, *Lead Contamination* (Washington, DC: U.S. Government Printing Office, 1988).

(76). However, byproducts of incineration may have adverse effects on the environment and on human health. Residue remaining from incineration (bottom ash), particles removed from the air after combustion (fly ash), and airborne emissions (stack emissions and fugitive emissions) may contain high concentrations of toxic substances, including lead and other toxic heavy metals (76). Compared to landfills, stack and fugitive emissions may greatly increase exposure. On the other hand, when ash is placed in landfills, the lead may leach out of the ash into the groundwater, eventually ending up in lakes, ponds, and rivers that may be used for recreation or drinking water.

EPA has the authority to regulate incinerator ash under the Resource Conservation and Recovery Act, but there is some debate as to whether incinerator ash should be considered a hazardous substance because the municipal solid waste which is burned to create it is not designated hazardous waste. Some environmentalists call for testing all incinerator ash and treating it as hazardous waste if the tests indicate it has hazardous properties.

Congress has been interested in this issue as well. Legislation has been introduced in the 10lst Congress to amend the Clean Air Act, directing EPA to promulgate regulations that would control emissions of specified air pollutants, including lead, from municipal waste incineration sites and ensure safe management of municipal incinerator ash.

Although the amount of human exposure to lead from municipal waste incinerators is not large now, the projected increase in the number of such incinerators indicates that it could become a problem in the future.

Lead in Soil

EPA is conducting a project under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, or Superfund) to determine whether abatement of soil lead (by removal or some form of isolation) will reduce



Photo credit: National Archives

Lead may be released into the air through the weathering of structures painted with lead-based paint.

childhood exposure to lead (as determined by the amount of lead measured on the hands and in the blood of children). Studies are being conducted in Boston, Cincinnati, and Baltimore. The studies will not focus on high-lead areas, such as areas near lead smelters, or on children who need clinical attention. Instead, the focus is on intermediate lead levels, which are more typical urban exposures (42).

Summary and Conclusions

Public health measures have achieved a substantial decrease in human exposure to lead in recent years; lead poisoning, however, remains a significant problem, especially in children. As tests become more sensitive, studies indicate that neurobehavioral dysfunction is associated with lower blood lead levels than previously believed. The precise level of exposure which causes impairment is controversial: there may be no threshold level for adverse effects, in which case the more sophisticated our ability to detect impairments from lead poisoning becomes, the lower the levels at which impairments may be found. Since 10 to 15 ug/dl is the limit most recently proposed as a maximum blood lead level and the medical treatment techniques now available are not able to reduce blood lead levels below approximately 20 ug/dl, prevention is crucial.

Since lead poisoning was clearly identified as a public health problem, it has received a great deal of attention from Congress and a number of Federal agencies. EPA's reduction of lead in gasoline has greatly reduced the amount of lead in the air; FDA and the food industry have together reduced the amount of lead in food; and EPA has recently implemented a regulatory program to control the amount of lead in water. OSHA regulations have reduced lead exposure in most large lead-using industries. Federal and State programs have begun to remove lead paint from older housing. The regulatory framework that now exists, if properly enforced, could continue to reduce many sources of exposure to lead.

Despite these areas of success, progress remains to be made. Not everyone is satisfied with the steps that have been taken. Some argue that the existing regulations fail to treat the problem of lead in drinking water adequately. Some feel the OSHA regulations for lead exposure in the workplace are not properly enforced and have too many exceptions. Also, there are no Federal programs to remove lead-based paint in old houses or to establish mandatory, centralized reporting of lead poisoning.

Many argue for stronger measures to prevent lead toxicity. Prevention might be improved by a general screening program for all children and by adopting alternatives to incineration of waste, thus avoiding increased exposure to lead in the air. Federal programs to improve conditions in the workplace and remove lead-based paint from all houses could be implemented. Lead content in water could be monitored strictly, and if need be, regulations could be revised. Public education programs could be introduced in high-risk areas near industrial or waste-disposal sites. Federal money could be designated for specific lead poisoning prevention programs rather than including lead poisoning programs under the block grant umbrella.

Designing programs to remove lead from the environment is most problematic when responsibility for removing contamination is not clear. A baby poisoned by lead from canned milk is clearly the food industry's responsibility, therefore that industry was prompt and thorough in its response to the lead poisoning problem. In many cases, however, such as controlling lead in drinking water, responsibility for lead poisoning cannot be so clearly ascertained: some public water suppliers question whether they or consumers are responsible for plumbing with lead pipes or lead solder. The Nation must address difficult questions such as this if continued progress is to be made in reducing public exposure to lead.

EXPOSURE TO NEUROTOXIC PESTICIDES IN AGRICULTURE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947 defines a pesticide as:

> . . . any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any insects, rodents, nematodes, fungi, or weeds or any other form of life declared to be pests. . . and any substance or mixture of substances intended for use as a plant regulator,[8] defoliant or dessicant.

[8] Alar (daminozide), for example, is called a pesticide for regulatory purposes, even though it does not kill pests. It is used as a growth regulator to promote a uniform red color in apples and to prolong shelf-life.

Human exposure to pesticides can occur in a number of ways—through contaminated drinking water, through eating foods containing pesticide residues (see box 10-E), through pesticides used in the yard, home, and office, and through exposure in various occupational and agricultural settings. Besides field workers and pesticide applicators, those at risk in agricultural settings include nursery, greenhouse, forestry, and lawn care workers. Although pesticides are a major health concern in the home and for exterminators, highway workers, grain elevator operators, and pesticide manufacturing and formulating employees, this section focuses on pesticide exposure in the agricultural setting.

Approximately 1 billion pounds of pesticides are used annually in agriculture in the United States, and approximately 4 billion pounds are used annually worldwide (102,174). Approximately $7 billion is spent annually on pesticides in the United States. Agriculture accounts for more than two-thirds of the expenditures and approximately three-fourths of the quantity used (174).

Agricultural workers who may be exposed to pesticides include pesticide handlers (handling is defined as mixing, loading, applying, flagging,[9] and equipment cleaning, repairing, and disposal), who work with concentrated forms of pesticides; workers performing hand labor in fields treated with pesti-

Box 10-E—Pesticides in Food

A report released in February 1989 by the Natural Resources Defense Council (NRDC), *Intolerable Risk: Pesticides in Our Children's Food,* has spurred considerable debate about the risks to humans, particularly children, of pesticide residues in food. The report analyzed the extent of children's exposure and attempted to determine the potential hazards, focusing on increased risk of cancer and neurobehavioral damage. Data analyzed in the study were obtained from the Environmental Protection Agency (EPA), the Food and Drug Administration, and the Department of Agriculture.

After examining 23 pesticides known to have adverse health effects, the report concluded that preschoolers are being exposed to hazardous levels of pesticides in fruits and vegetables. Twenty of these pesticides were found to be neurotoxic. NRDC estimated that, from raw fruits and vegetables alone, at least 17 percent of the preschool population, or 3 million children, are exposed to neurotoxic organophosphorous pesticides above levels the Federal Government has described as safe.

NRDC criticized EPA for setting legal limits for pesticides in foods based on data collected 20 years ago and on adult consumption of fruit and vegetables (children generally eat more produce than adults). A few of NRDC's primary recommendations follow:

Congress must clarify EPA's authority to change tolerance levels quickly.
. EPA must consider risks from ''inert' ingredients when regulating pesticides.
. Neurotoxicity testing should be required for all pesticides used on food.
. Congress should establish national definitions of "integrated pest management" and ''organic" farming technologies and develop a national certification process for goods grown using these technologies.

The report also includes recommendations to the public to reduce their exposure to pesticides.

EPA believes that the NRDC study overstates the risks from pesticides. The Agency stated that the benefits of pesticide use outweigh the minimal risks and that EPA routinely takes into account the potentially higher exposure of children. However, EPA officials do concede that the report raises valid questions. In a news release distributed the same day as the NRDC study, the National Food Processors Association (NFPA) stated that pesticides are virtually nonexistent in packaged foods and that, when detected, they are far below allowable levels. The NFPA attributes this absence of residues mainly to the NFPA Pesticide Protective Screen Program, which spells out proper pesticide control and monitoring practices for growers producing crops for the food industry.

SOURCES: Office of Technology Assessment, 1990; D. Duston, ''Hotline Helps Growers Find Alternatives to Pesticides,' Associated Press, Mar. 22, 1989; D. Duston, "Eight in 10 Americans Prefer Chemical Free Food; Half Would Pay More," Associated Press, Mar. 19, 1989; A.K. Naj, "Panel Assails Pesticide Study, Calls Food Safe," *Wall Street Journal,* Apr. 6, 1989, sec. B, p. 3; Natural Resources Defense Council, intolerable *Risk: Pesticides in Our Children's Food* (Washington, DC: 1989).

[9]Flaggers are workers who direct crop dusters as they spray pesticides on fields.

cides (called farmworkers in this report); and workers in forests, nurseries, and greenhouses where pesticides are used.

Extent of Exposure of Agricultural Workers

Agriculture is the primary source of income for an estimated 4 to 5 million Americans, a significant proportion of whom are children under the age of 16 (102). Many of these persons are exposed to higher levels of pesticides than the general public. Approximately 2.7 million agricultural workers in the United States are migrant and seasonal farmworkers (164), and most seasonal work involves contact with pesticide residues on crops such as cotton, vegetables, fruits, and nuts. Another group with significant exposure to pesticides is pesticide handlers: EPA estimates there are approximately 1.3 million certified pesticide applicators in the United States (176). The number of agricultural workers performing other pesticide-handling jobs is unknown.

The seventy of illnesses caused by pesticides depends mostly on the dose absorbed and the inherent toxicity of the product. Farmworkers are exposed to pesticides primarily through residues on foliage and crop surfaces, during aerial and hand spraying, picking, packing, and sorting, but also during hoeing and other field work. Forest, greenhouse, and nursery workers are exposed by similar means. Mixers, loaders, and applicators may be exposed to concentrated doses of pesticides in the course of their daily work. Exposure usually occurs by absorption through the skin, except in the case of fumigants, which are inhaled. The amount of pesticide absorbed depends on the nature of the work being performed, the clothing the worker is wearing, the part of the body exposed, and the condition of the worker's skin (absorption increases with dermatitis, cuts, and abrasions). Another relevant factor in exposure is the rate at which pesticides degrade, which varies with conditions such as heat and moisture.

Estimates of the incidence of pesticide-related health problems among workers vary. The annual worldwide incidence of pesticide poisonings is estimated to be between 500,000 (192) and 2.9 million (69), with a fatality rate of approximately 1 percent (102). In the United States, the prevalence of pesticide-related illness among farmworkers may be as high as 300,000 cases,[10] only 1 to 2 percent of which are thought to be reported (31). The majority of reported cases of pesticide-related illness involve exposure to neurotoxic pesticides (102,185), but the lack of reporting of most cases complicates the assessment of any persisting neurological and psychiatric problems. Some observers have estimated that in developed countries 4 to 9 percent of acutely poisoned individuals suffer long-term neurological and psychiatric effects (46).

Special Risks to Children

Pesticides are thought to pose a considerably higher risk to children than to adults (106,114). Children can be exposed in a number of ways: through prenatal maternal exposure, from being in the fields where their parents work, contact with pesticide residues on parents' clothing, living in migrant camps next to fields being treated, and working in the fields themselves. Since they absorb more pesticide per pound of body weight, children may receive substantially higher doses of pesticides than adults, and their immature development may make them more susceptible to neurotoxic effects. EPA and OSHA standards for worker safety are based on adult exposure only.[11] Many organ systems, including the nervous and reproductive systems, are still developing in infants and young children. The effects of pesticides on these developing systems are largely unknown. There are important lessons to be drawn from the case of lead, which has severe effects on the developing nervous system and other organs of children.

Documented Adverse Effects on the Nervous System

Although many pesticide-induced illnesses among agricultural workers are thought to be severe and acute, some evidence suggests that they are in fact moderate and chronic (31). The full effects on learning and perception and the emotional changes associated with pesticide exposure are not known because of the difficulty of testing these functions and establishing a normal range (5). Failure to report illness and the lack of comprehensive studies of the agricultural worker population may result in under-

[10]This figure is based on extrapolation of data collected in California. Tracking the prevalence of farmworkers' pesticide-related illnesses is difficult because of the lack of reporting requirements in most States and the limitations of those that do exist. These limitations are discussed later in this chapter,

[11]The National Academy of Sciences recently initiated a 2-year study to assess the risk of exposure of children to pesticides.



Photo ***credit: U.S. Environmental Protection Agency***

Current EPA regulations establish basic protective clothing requirements for agricultural workers who enter treated fields. However, recent studies document significant pesticide exposures despite the use of typical protective clothing.

estimation of the true extent of both short- and long-term neurological effects. Organophosphorous insecticides, which make up approximately 40 percent of all pesticides used in the United States, are currently the most commonly reported source of worker illness. The more persistent organochlorine pesticides, used extensively in the 1940s through 1970s, are now either banned or restricted in the United States and thus do not contribute as much to worker illness. What is known about the effects on worker health of a few commonly used classes of pesticides is examined later in this chapter.

Short-Term Effects on the Central Nervous System

Some cases of worker illness are mild and persist for a few hours. In more severe cases, symptoms may not peak until 4 to 8 hours after onset and may persist from 1 to 6 days. Some recovery periods are longer (90):

- In a moderately severe poisoning of 24 field workers, including children, exposed to residues of two pesticides, mevinphos (Phosdrin) and phosphamidon (Dimecron), in California, anxiety and other symptoms were reported after 70 days (98,184). In this case, farmworkers were working in cauliflower fields prior to the legal reentry interval.
- There have been several documented poisonings of entire crews who entered fields after the permissible reentry interval. In 1987,78 farmworkers in three different crews developed moderate to severe pesticide poisoning from contact with phosalone (Zolone), used in California vineyards, long after it was thought safe to reenter. Because of its persistence and risk to farmworkers, phosalone is no longer used on grapes in California (23).
- In 1988, two crews were poisoned by a highly toxic insecticide, methomyl, in California. In the first case, 34 orange harvesters went into a methomyl-treated orchard 1 day after application, and 17 developed symptoms of pesticide poisoning that required hospital treatment. In the second case, grape workers were hospitalized after exposure to methomyl. As a result of these poisonings, the reentry interval for methomyl in California was increased from 2 to 14 days (23).

Long-Term Effects on the Central Nervous System

The nature of long-term neurobehavioral effects of exposure to organophosphorous insecticides is unresolved and deserves further investigation. The evidence supporting the existence of delayed, persistent, or latent effects in humans includes case reports, epidemiological studies of agricultural workers with and without histories of acute poisoning, and deaths resulting from neurobehavioral disease among agricultural workers.

Case Studies—The pesticides parathion, mevinphos (Phosdrin), and malathion are frequently reported as causing health problems. Case reports and studies of acute poisonings of agricultural and other workers indicate that 4 to 9 percent of the acutely poisoned individuals experienced delayed or persistent neurological and psychiatric effects (46). These effects include agitation, insomnia, weakness, nervousness, irritability, forgetfulness and confusion, and depression (56,64,65,1 55); persistent mental disturbances—reported as delirium, combativeness, hallucinations, or psychoses—are noted in some cases of pesticide poisonings (62). Occupations most frequently mentioned in case reports include mixers, loaders, applicators, pilots, flaggers, nursery and greenhouse workers, pesticide manufacturing workers, agricultural and pest control operators, and inspectors. Farmworkers tend not to appear in the reports, for reasons that are discussed later in this chapter.

Epidemiological Studies-Although few epidemiological studies of agricultural workers have been done, approximately 500 subjects from various cohorts have been subjected to standardized neurobehavioral assessments examining memory, reaction time, behavior, visual ability, and mood. Subjects tend to be young, mostly male, and employed in agricultural occupations for unspecified periods. In field studies, quantitative data on exposure are lacking.

In general, this research demonstrates that pesticide poisoning can lead to poor performance on tests involving intellectual functioning, academic skills, abstraction, flexibility of thought, and motor skills; memory disturbances and inability to focus attention; deficits in intelligence, reaction time, and manual dexterity; and reduced perceptual speed. Increased anxiety and emotional problems have also been reported. Exposed groups included farmers without symptoms (73), industrial workers with accidental exposures (97), pest control workers (90), and a wide variety of agricultural workers tested an average of 9 years after an acute poisoning was diagnosed by a physician (140).

Neurobehavioral Disorders, Mortality, and Accidents—Analysis of occupation and causes of death reported on death certificates suggests that agricultural workers are at risk of dying from neurobehavioral disorders and accidents. Approximately twice the expected mortality from behavioral disorders (i.e., those resulting from altered perception or judgment) has been reported among white male farmworkers and orchard laborers from Washington (99) and among California farmworkers (154).

Both of these studies and one of British Columbia farmworkers (55) found disproportionate mortality due to external causes, particularly motor vehicle accidents. The precise role of pesticides, if any, in the mortality patterns is unknown. Based on worker reports of feeling "fuzzy" at the end of the work day, researchers have speculated that farmworker exposure to pesticides impairs judgment and coordination and may contribute to motor vehicle accidents (155). There are numerous case reports of near misses and fatal workplace accidents involving farm machinery and crop-dusting aircraft in which behavioral effects of pesticides are implicated (38,62, 135,136,149,191).

Suspected Adverse Effects and Limitations of Existing Data

The occurrence of neurobehavioral disorders after chronic low-level exposure in the absence of acute poisoning has not been adequately studied. Neuropsychological assessments of occupational groups have yielded inconsistent results, perhaps reflecting differences among pesticides and differences in the type and scope of tests used. Subtle neurobehavioral effects have been observed most consistently in young, asymptomatic male workers who have been employed for a long time (19,194), who have been previously diagnosed as having acute pesticide poisoning, or who are recovering from an acute exposure (38,73,140). Few studies have assessed the duration of impairment. Field studies have not provided sufficient data on exposure levels or duration to understand dose-response relationships, nor have most studies controlled for age, education, or other potential confounding factors. Few studies have examined exposed workers prospectively, subgroups of women or aging workers, interactions between pesticides, or interactions between pesticides and pharmacological agents (including ethanol or common medications).

Federal Regulation

Most workers in the United States are protected by the Occupational Safety and Health Act, which affords them certain rights, including permissible exposure limits, personal protective equipment and clothing, access to medical and exposure records, training about the risks of exposure, and protection against employer retaliation. Pesticide handlers and workers in forests, nurseries, and greenhouses are covered under these regulations. OSHA requires that field workers be provided with toilets, drinking water, and water for hand washing; however, handling of pesticides is covered under FIFRA, which is administered by EPA. Since 1983, manufacturing workers have had the right to information on the hazards of the chemicals with which they work under OSHA's Hazard Communication Right-to-Know Standard. Since 1988, other industrial workers have also had this right.

FIFRA was enacted in 1947 to protect farmers from ineffective and dangerous pesticides by requiring that a pesticide be registered before it is marketed. The legislation was amended extensively in 1972 (Public Law 92-516), with new provisions

allowing for direct controls over the use of pesticides, classification of selected pesticides into a restricted category, registration of manufacturing plants, a national monitoring program for pesticide residues, the inclusion of environmental effects in the cost-benefit analysis of the pesticide regulation process, and the required reregistration of older pesticides to ensure that they meet new data requirements (2).

Since FIFRA was amended in 1972, controversies about its implementation and its ability to protect farmers and farmworkers have received repeated congressional attention. In 1988, after considerable political debate, a compromise bill (dubbed "FIFRA lite" because of its restricted scope) was passed by Congress and signed by the President.



Photo credit: Douglas Watts/Christophar Brady

The new law requires EPA to review within the next decade the 600 active pesticide ingredients and to charge manufacturers for some of EPA's costs (under previous law, the government was responsible for virtually all of the cost). The bill also partially repeals the indemnification provision that required the government to pay manufacturers or users of pesticides for existing stock whose registration was canceled by the Agency. This provision was a major obstacle to EPA's cancellation or suspension of some of the most toxic pesticides.[12] Many issues, however, were lost in the final bill, including farmworker protection standards and specific requirements for EPA review and testing of pesticides. Two efforts to strengthen Federal authority were defeated: 1) synchronization of data requirements, which would have prevented States from requiring additional data before registering pesticides, and 2) preemption of States from setting more stringent tolerances for pesticide residues in food.

EPA promulgated regulations under FIFRA in 1974. Of particular interest here are those regulations dealing with the occupational safety and health of agricultural workers (40 CFR 170 and 156). The 1974 regulations apply only to workers performing hand labor in fields during or after pesticide application. Their main provisions are a prohibition against spraying workers; specific reentry intervals (i.e., the time that must elapse between application of a pesticide and the return of workers to the treated area) for 12 pesticides and a general reentry interval for all other agricultural pesticides; a requirement that protective clothing be worn by any worker who has to reenter a treated area before the reentry interval has expired; and a requirement for "appropriate and timely" warnings to workers when they are expected to work in fields that have been or will be treated with pesticides.

FIFRA has been criticized as inadequate to protect workers and the public from pesticides known to cause or suspected of causing serious chronic effects, including cancer, reproductive problems, and neurological damage (178). EPA has set reentry intervals for only 68 of more than 400 active ingredients currently used to manufacture thousands of agricultural pesticide products.

In addition, FIFRA requires a balancing of risks and benefits to determine whether a hazardous pesticide should be canceled or suspended. This provision can delay or prevent EPA from regulating pesticides that are potentially neurotoxic, depending on whether the perceived benefits of its use outweigh the perceived risks. Risk-benefit analysis, however, rarely includes the costs of ill health to those exposed, including lost work time, hospital care, and other medical care.

In 1983, EPA reviewed the regulations under FIFRA and determined that they were inadequate to protect workers occupationally exposed to pesti-

[12]Chlordane was originally proposed for cancellation in 1974 because of its adverse health effects. There is some feeling that the considerable cost to EPA of indemnifying chlordane's manufacturers and users may have influenced its decision not to cancel the registration. While agricultural uses of chlordane were canceled in 1984, it was still used widely to kill termites until 1988. On Feb. 3, 1989, the U.S. Court of Appeals overturned an earlier decision and permitted the sale of existing chlordane stocks (112).

cides. The Agency proposed new regulations in 1988. These regulations would cover workers in forests, nurseries, and greenhouses; pesticide handlers; and workers performing hand labor in treated fields. Some of the key items of the proposed regulations follow:

- General pesticide safety information must be placed in a prominent location at each farm, forest, nursery, and greenhouse during the growing season. Workers who do not speak English must be given a written warning in their own language to obtain a translation of this information. Training must be provided for all persons who handle agricultural pesticides and for all persons who enter treated areas before the reentry interval has expired. Any person who handles a pesticide must be provided, on request, all information from the labeling of that pesticide.
- All workers must be clearly and adequately notified about pesticide application and relevant reentry intervals. The methods of notification will vary according to the site, but will include a requirement that warning signs be posted outside pesticide-treated areas with a reentry interval of more than 48 hours.
- All pesticide handlers and early reentry workers must wear minimum personal protective equipment, as specified by pesticide labels. Determination of the appropriate equipment must take into account the toxicity of the pesticide, the handling technique, and the route and type of exposure.
- The minimum reentry interval will be "until sprays have dried, dusts have settled, or vapors have dispersed. " Reentry intervals will be set at 48 hours for organophosphorous and n-methyl carbamate insecticides in toxicity category I (most acutely toxic) and 24 hours for the same pesticides in toxicity category II and all other pesticides in toxicity category I.
- Workers must be provided with water, soap, and disposable towels after exposure to pesticides or pesticide residues. Information about and transportation to nearby medical facilities must be provided to workers in emergency cases of pesticide poisoning or injury.
- Commercial handlers who are exposed to toxicity category I or II organophosphorous insecticides for 3 consecutive days or any 6 days in a 21-day period must be monitored for cholinesterase inhibition (177).

The proposed regulations have been criticized by farmworkers' and farmers' groups, growers, and pesticide users and producers. Critics argue that the standards fail to address many needs, including those for mandatory education of all farmworkers concerning the neurotoxic and other health effects of pesticides and safety training in the use of pesticides; telling workers what pesticides they have been exposed to; more protective reentry intervals; and consideration of the additive and synergistic effects of exposure to multiple pesticides. Critics also argue that the proposed standard could increase farmworkers' risks by permitting early reentry into treated fields as long as workers are given protective equipment.

Pesticide regulation and policy have historically been made at the Federal level, yet the Office of Pesticide Programs has consistently had one of the smallest budgets of any EPA program. Resources for the review of toxicological data, monitoring programs, and worker protection standards have been limited. EPA currently provides no funds to State agencies to conduct worker and public health evaluations. Indeed, EPA officials have stated that farmworker protection standards are not part of current State enforcement grants under FIFRA (105).

Areas of Particular Concern

Pesticide Registration-An important obstacle to protecting farmworkers from neurotoxic pesticides is the major gaps in data in many pesticide registration files. In 1984, the National Academy of Sciences found that 67 percent of pesticides studied had undergone no neurotoxicity testing at all, and all of the neurotoxicity tests performed were judged inadequate (108). The 1988 FIFRA amendments gave EPA 9 years to complete its pesticide registration review, but the battery of tests currently required by EPA for pesticide registration is geared toward detecting only the most obvious neurotoxic effects. Only one type of test specifically intended to detect nervous system impairments is currently included in EPA's pesticide assessment guidelines, although new test guidelines are being devised (see ch. 5). EPA was petitioned by a group of consumer advocates and professional organizations to develop more extensive neurotoxicity test guidelines (26).

Another gap in protection is the lack of data on effects of exposure to the so-called inert ingredients in pesticides. These ingredients are used as carriers of the active ingredient and do not appear on pesticide labels because of their trade secret status.[13] They are inactive only to the extent that they are thought to have no effect on the targeted pest. Hence, they may be defined as inert yet be toxic to humans. Of the 1,200 substances designated as inert, EPA concludes that 55 are "toxicologically significant," with another 65 structurally related to substances known to be toxic. As of 1987, EPA did not know the toxicity of some 800 inert ingredients contained in pesticide products and regarded some 200 as generally safe (2); the Agency has since incorporated inert ingredients into its ongoing review of the toxicity of pesticide ingredients.

FIFRA permits States to register for 5 to 8 years pesticides needed to fill "special local needs" and "crisis" situations. This may, under certain conditions, provide a substantial loophole in farmworker protection, because it allows States to register pesticides that have not met Federal testing requirements. There has been considerable criticism of this practice.

Public attention was drawn to the issue of the quality of data submitted for the registration of new products by the discovery that one of the major laboratories providing data to EPA had falsified findings (31,143). In 1984, EPA's internal review process for evaluation of toxicological data was criticized because of cases in which EPA reviewers had incorporated information provided by manufacturers, apparently without any independent analysis. In 1989, the Senate Environment and Public Works committee initiated an oversight review of EPA's registration standards when it was learned that seven of the eight members of EPA's Science Advisory Panel had apparently served as consultants to the chemical industry (93,163). Thus, although EPA is working to fill the data gaps in pesticide registration, there remain questions about the impartiality of the Agency's regulation process.

Reentry 1ntervals-Unlike industrial workers, farmworkers are not protected by specific maximum levels of exposure to chemicals. Rather, they are protected by reentry intervals, which restrict entry to a field after pesticide application (40 CFR 1988 ed. 170). When they were first instituted in 1974, specific reentry intervals were set only for the 12 chemicals with the highest observed toxicity; access to all other active ingredients was restricted only "until sprays have dried or dusts have settled." Currently, specific reentry intervals have been set for 68 active ingredients for which animal studies demonstrated need. These 68 active ingredients are used in about 90 percent (by volume) of pesticides used in agriculture.

EPA claims that these reentry intervals protect workers from the most toxic active ingredients used in pesticides, but many observers are concerned that the existing regulations do not adequately protect farmworkers from neurotoxic pesticides. Farmworker protection advocates argue that the blanket reentry interval which covers other pesticides improves farmworker safety somewhat, but more adjustments need to be made for specific chemicals. There have been episodes of worker poisoning and even fatalities, particularly involving parathion, due to inadequate reentry intervals (102,151). Toxic residues can persist on foliage for weeks after application and are known to persist longer in dry climates (102). In California, most farmworker poisonings from neurotoxic pesticides have occurred because of inadequate reentry intervals (185). Several States have gone beyond EPA's standard and imposed longer reentry intervals based on local conditions. California, for example, has set many longer reentry intervals based on local conditions. Texas has set a minimum 24-hour reentry for all labor-intensive activities and has set longer reentry intervals for a number of pesticides. New Jersey and North Carolina require a 24-hour reentry interval for all toxicity category I pesticides. Other States, too, are revising their standards for reentry intervals.

The 1988 FIFRA amendments address some of the shortcomings of piecemeal regulation. EPA is currently drawing up proposals for stricter regulations, including longer reentry intervals for more chemicals.

Protective Clothing-current EPA regulations establish a basic protective clothing requirement for workers who must enter treated fields before the reentry interval has elapsed. Proposed EPA regula-

[13]Pesticides are not generally applied in a pure form. The pesticide (also known as the active ingredient) is usually diluted by a solvent or an inactive solid (known as the inert ingredient).

tions would specify particular items to be worn, depending on the task being performed, the circumstances of potential exposure, and the toxicity class of the pesticide. However, some persons argue that protective clothing and equipment are not adequate to protect workers from harmful exposures. All too frequently, employers do not provide protective clothing and equipment or employees do not wear them because of the excessive heat or their constraints on movement. Furthermore, recent studies document the significant exposures workers may receive even while using an approved respirator or wearing typical protective clothing (48).

Lack of Pesticide Illness Reporting—Because there are inadequate reporting mechanisms for acute pesticide poisoning episodes and none for adverse chronic effects among farmworkers in the United States, the true rate of pesticide-related illness among farmworkers may be underestimated. Even if there were more centralized reporting, physicians often have little training in occupational medicine and thus may not recognize instances of pesticide poisoning, and patients rarely have access to information about the pesticides to which they are exposed. The lack of occupational histories and accurate exposure data make proper diagnosis and treatment difficult, if not impossible (103). Furthermore, many ill workers never actually see a doctor.

Farmworkers, especially migratory farmworkers, whose immigration status and language barriers make them especially vulnerable, are often not represented by unions that influence standards of health and safety in the workplace. On a State level, most migrant farmworkers are excluded from workers' compensation and unemployment insurance (103). These exclusions from governmental protections prevent accurate estimates of pesticide illness, lost work time, and medical costs. Persons who advocate greater protection for farmworkers argue that reporting requirements for national pesticide illness and pesticide use would enable regulators to target pesticides for regulatory action and better assess their effects on health (134).

Monitoring Methods and Needs

There is no regular or required biological monitoring of agricultural workers exposed to pesticides in the United States, except for periodic cholinesterase tests for a small group of certified applicators exposed to organophosphorous and carbamate insecticides on a regular basis in California. Proposed EPA regulations would require monitoring of commercial pesticide handlers under certain circumstances. One direct means of assessing workers' exposure to chemicals is by measuring the parent substance or its metabolizes in the blood or urine; however, this methodology is available for only a limited number of pesticides (101). A promising new field cholinesterase test has been developed and used in Central America to identify workers suffering adverse effects (88); such a test might improve worker awareness and enhance preventive medical care (157) if workers can be induced to participate.

Monitoring programs are most effective when they are based on an understanding of the nature of farmworker exposure and the patterns of pesticide use. More extensive monitoring would allow better assessment of the extent of neurobehavioral problems caused by pesticide exposure among farmworkers; but conducting assessments of non-English-speaking, migratory populations may be difficult, there may not be qualified medical personnel and adequate equipment in rural areas, and the availability of monitoring devices may be a disincentive for employers to prevent exposures in the first place.

State Regulation

Under current law, States may set more stringent requirements for pesticide use than those provided in Federal statutes. Several States, notably Texas, California, and Washington, have initiated their own worker and public programs to fill the gaps in Federal regulations. Other States, for example, Iowa, Minnesota New Jersey, New York, North Carolina, and Wisconsin, have also taken steps to address critical needs at the State level. Nine States have laws requiring reporting systems for pesticide illness or pesticide use, although most of them are unenforced; 16 other States have limited forms of data collection; and 16 States have mandatory worker compensation programs for agricultural workers (53 FR 25973).

California has an extensive and well-funded pesticide registration and worker safety program that exceeds EPA standards in addressing local conditions and patterns of pesticide use. As mentioned earlier, California and Washington require reporting of pesticide illness. California enacted the Birth Defects Prevention Act of 1984 to require adequate data on the 200 most widely used pesticides

suspected to be hazardous to humans. This law prohibits the conditional registration of any new pesticide without complete and valid data on health effects. It also requires cancellation of any pesticide containing an active ingredient that causes significant adverse effects on health.

Texas has adopted several farmworker protection measures, including a 24-hour minimum reentry interval for all pesticides used on labor-intensive crops and certain prior notification and posting provisions for workers and other persons adjacent to treated fields. The most far-reaching development is Texas' Agricultural Hazard Communication (right-to-know) Law, the first such law in the Nation. It requires agricultural employers to provide their workers with information about the health risks of pesticides and ways to minimize these risks. Employers are required to maintain a list of all pesticides used and to make it accessible to workers, their physicians, and other designated representatives. Farmworker training (in a form and language understood by workers) is also guaranteed by this law, through crop sheets and other written and audiovisual materials (185,187).

New Approaches to Pest Control

The simplest way to protect farmworkers is to reduce the overall use of pesticides, particularly the most toxic ones. Movements to build sustainable agricultural systems based on limited use of pesticides and fertilizers and on integrated pest management (IPM) systems have been initiated in several States (see box 10-F). IPM relies on the coordination of a number of control tactics. It attempts to minimize the use of pesticides by making maximum use of biological controls (e.g., natural predators and parasites, disease-causing microorganisms, pheromones, and pest-resistant plants) and cultural controls (e.g., crop rotation and removal of crop residues that shelter pests after harvest). Chemical controls are used prudently, in conjunction with these other methods (176). IPM practices can potentially reduce pesticide use by as much as 50 percent (161).

Research on IPM techniques is slowly spreading to the more labor-intensive crops, but limited Federal funding has delayed implementation of this promising technology (187). The U.S. Department of Agriculture is researching and developing sustainable agriculture strategies which include IPM [14 U.S.C. 1463(C)]. In 1988, an estimated 8 percent of crop land (27 million acres) was enrolled in some 30 State IPM programs (104).

Examples of Neurotoxic Pesticides

The following discussion introduces several of the most common classes of pesticides known to have neurotoxic effects.

Cholinesterase-Inhibiting Insecticides

Organophosphorous and carbamate insecticides, the cholinesterase-inhibiting pesticides, represent a large and important class of neurotoxic substances (see table 10-3). Because of their widespread use and high toxicity at acute exposures, they are the most common cause of agricultural poisonings. Both affect target insects and humans by inhibiting acetylcholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine. Inhibiting this enzyme creates a build-up of the transmitter, which causes nervous system dysfunction.

Some cholinesterase-inhibiting pesticides cause hyperactivity, neuromuscular paralysis, visual problems, breathing difficulty, abdominal pain, vomiting, diarrhea, restlessness, weakness, dizziness, and possibly convulsions, coma or death (see table 10-4) (102,141,195). The extensive literature on neurobehavioral toxicology in laboratory animals exposed to pesticides has been reviewed by others (14,29,34,41,71,189). The onset and duration of symptoms in acute poisoning of workers depends on the inherent toxicity of the insecticide, the dose, the route of exposure, and preexisting health conditions. Deaths have occurred in the past when workers were not treated properly for their exposure. The inhibition of acetylcholinesterase by both organophosphorous insecticides and n-methyl carbamates is reversible; however, inhibition caused by n-methyl carbamates is generally considered more readily and rapidly reversible than that caused by organophosphorous insecticides. For several of the organophosphorous insecticides, inhibition of acetylcholinesterase is so slowly reversible that an accumulation of the effect can occur. Once exposure ceases, however, full recovery usually results (102,106).

Some researchers have found delayed effects after an episode of acute organophosphorous insecticide poisoning: these include irritability, depression, mood swings, anxiety, fatigue, lethargy, difficulty concentrating, and short-term memory loss. These symptoms may persist for weeks and months after

Box 10-F-Organic Farming and Alternatives to Chemical Pesticides

In response to growing consumer demand, the cost of chemical fertilizers and pesticides, and evidence of risk to human health and the environment more farmers are turning to organic production. There is no single definition of organic farming, but it generally requires some degree of abstinence from use of chemical fertilizers and pesticides. In Texas, a farm is only certifiably organic if no pesticides have been used for 3 years and no chemical fertilizers have been used for 2 years, but standards may vary from State to State. Where there is no State regulation of organic farming, responsibility for setting standards usually falls to trade organizations, and there is frequent controversy over how strictly to limit pesticide use.

Organic farming is gaining the attention of consumers, growers, and legislators. A California trade organization reported that sales of organic produce in the United States doubled between 1983 and 1988, to $1 billion. A 1989 Harris poll reported that 84,2 percent of Americans would buy organic food if it were available, with 49 percent of those willing to pay more for it (organic produce currently costs between 5 and 15 percent more than crops on which pesticides are used). This public concern is reflected by distributors such as Sunkist Growers, Inc., and Dole Foods Co., who are beginning to grow organic produce, and by supermarkets, which are beginning to issue written policies requiring chemical-free produce from suppliers. State legislatures have been slower to address the pesticide problem. To date, only a small percentage of States has any regulations for organic farming, and only a few of these have certification programs.

Historically, organic farming has been more expensive because it is more labor-intensive, it is done on smaller farms, and it results in smaller yields. The resulting products, however, tend to have a higher profit margin than the more abundant crops grown on large farms where pesticides are used, As biological alternatives to pesticides are researched and developed, costs of alternative farming might be reduced further.

Despite the promises organic farming offers for human health and the environment there is awareness of its drawbacks even within the organic farming community. Complete rejection of chemical pesticides may reduce crop yields. Even some environmentally aware and health-conscious farmers agree that chemical pesticides are occasionally required.

Insufficient regulation of organic foods and farming methods is another drawback to organic farming. Apart from the lack of precise definition of what organic farming is, public safety maybe threatened by lack of enforced regulation of so-called organic produce, as well as a lack of testing at the supplier level to confirm that foods are free of toxic substances. According to the Consumers Union, most grocery stores rely on their suppliers' word that produce is pesticide-free, yet when that organization tested apples bought in stores which claimed not to sell apples treated with Alar, 55 percent of the apples contained it.

Rather than attempting to end all use of chemicals in agriculture, a solution may be found in integrated pest management or other alternative agriculture systems, which use chemicals discriminately, if at all, in conjunction with biological controls designed to fit local conditions. A National Research Council report released in September 1989 concludes that Federal farm subsidy programs encourage the use of chemical pesticides when nonchemical alternatives may be as or more effective. The report recommends that at least $40 million be allocated annually for research on alternative farming.

SOURCES: "Apple Grower Says Chemicals Sometimes Needed When All Else Fails," Associated Press, Apr. 3, 1989; D. Duston, "Eight in 10 Americans Prefer Chemical Free Food; Half Would Pay More," Associated Press, Mar. 19, 1989; "Entomologists Defend Chemicals as Necessary in Food Production," Associated Press, Mar. 25, 1989; "Farmers Hope to Replace Chemicals with Biological Fertilizers,' Associated Press, Apr. 3, 1989; P. Fikac, "Consumers Union: Ask Grocers About Reduce," Associated Press, Mar. 30, 1989; National Academy of Sciences, National Research Council, *Alternative Agriculture* (Washington, DC: National Academy Press, 1989); S.L. Nazario, "Big Firms Get High on Organic Farming: Pesticide Scare Reinforces Shift in Techniques,' *Wall Street Journal,* Mar. 21, 1989; ''Pesticide Scares Fuel Already Growing Organic Food Popularity," Associated Press, Apr. 10, 1989.

the initial exposure (17,82,83,137,147). Whether there are significant chronic effects of exposure to low-level organophosphorous and n-methyl carbamate insecticides (and, indeed, of exposure to pesticides in general) is a matter currently under debate. A number of researchers have observed persistent alteration of brain function (36,56,59,97, 141), while others have noted no long-term effects (10,13,29,153,155).

Some organophosphorous insecticides can produce delayed and persistent neuropathy by damaging certain neurons in the spinal cord and peripheral

Table 10-3-Organophosphorous and Carbamate Insecticides

Highly toxic[a]	Moderately toxic[a]
Organophosphorous insecticides	
tetraethyl pyrophosphate (TEPP)	bromophos-ethyl (Nexagan)
dimefox (Hanane, Pestox XIV),	leptophos (Phosvel)
phorate (Thimet, Rampart, AASTAR)	dichlorvos (DDVP, Vapona)
disulfoton[b] (Disyston)	ethoprop (Mocap)
fensulfothion (Dasanit)	demeton-S-methyl[b] (Duratox, Metasystox (i))
demeton[b] (Systox)	triazophos (Hostathion)
terbufos (Counter, Contraven)	oxydemeton-methyl[b] (Metasystox-R)
mevinphos (Phosdrin, Duraphos)	quinalphos (Bayrusil)
ethyl parathion (E605, Parathion, Thiophos)	ethion (Ethanox)
azinphos-methyl (Guthion, Gusathion)	chlorpyrifos (Dursban, Lorsban, Brodan)
fosthietan (Nem-A-Tak)	edifenphos
chlormephos (Dotan)	oxydeprofos[b] (Metasystox-S)
sulfotep (Thiotepp, Bladafum, Dithione)	sulprofos (Bolstar, Helothion)
carbophenothion (Trithion)	isoxathion (E-48, Karphos)
chlorthiophos (Celathion)	propetamphos (Safrotin)
fonofos (Dyfonate, N-2790)	phosalone (Zolone)
prothoate[b] (Fac)	thiometon (Ekatin)
fenamiphos (Nemacur)	heptenophos (Hostaquick)
phosfolan[b] (Cyolane, Cylan)	crotoxyphos (Ciodrin, Cypona)
methyl parathion (E 601, Penncap-M)	phosmet (Imidan, Prolate)
schradan (OMPA)	trichlorfon (Dylox, Dipterex, Proxol, Neguvon)
mephosfolan[b] (Cytrolane)	cythioate (Proban, Cyflee)
chlorfenvinphos (Apachlor, Birlane)	phencapton (G 28029)
coumaphos (Co-Ral, Asuntol)	pirimiphos-ethyl (Primicid)
phosphamidon (Dimecron)	DEF (De-Green, E-Z-Off D)
methamidophos (Monitor)	methyl trithion
dicrotophos (Bidrin)	dimethoate (Cygon, DeFend)
monocrotophos (Azodrin)	fenthion (mercaptophos, Entex, Baytex, Tiguvon)
methidathion (Supracide, Ultracide)	dichlofenthion (VC-13 Nemacide)
EPN	bensulide (Betasan, Prefar)
isofenphos (Amaze, Oftanol)	EPBP (S-Seven)
endothion	diazinon (Spectracide)
bomyl (Swat)	profenofos (Curacron)
famphur (Famfos, Bo-Ana, Bash)	formothion (Anthio)
fenophosphon (trichloronate, Agritox)	pyrazophos (Afugan, Curamil)

nervous system. The resulting muscle weakness may progress to paralysis. Onset is usually 2 to 4 weeks after the acute exposure (27,70,150). The initial symptoms of peripheral neuropathy are usually cramps in the calves and numbness and tingling in the feet. Increased weakness and flaccidity of the legs follows, accompanied by varying amounts of sensory disturbance. The arms may also be affected (106). There is no specific treatment, and the rate and extent of recovery vary considerably.

Organochlorine Insecticides

The organochlorine insecticides are chlorinated hydrocarbon compounds that act as central nervous system stimulants (see table 10-5). Organochlorines accumulate in both the environment and the body. In general, they are considered less acutely toxic than organophosphorous and n-methyl carbamate insecticides, but they have a greater potential for chronic toxicity. The prototype organochlorine, DDT, was discovered in 1939 and was used extensively in agriculture and against mosquitoes and other insects that transmit human disease before it was banned from most uses in the United States in 1972.

From 1940 through the 1970s, a number of other organochlorine compounds, such as aldrin, dieldrin, toxaphene, mirex, endrin, lindane, heptachlor, and chlordane, were widely used as insecticides. Following recognition of their accumulation in the environment and in human and animal tissues, and observation of some adverse effects on wildlife, most have been banned or severely restricted in use. For example, chlordane, introduced in 1947 and since then one of the most widely used of this family, was originally targeted by EPA for restricted use in 1974. It was banned for most uses except termite control in 1978 (102). A decade later, EPA banned almost all uses of chlordane.

The organochlorines are easily absorbed by inhalation or ingestion and may also be absorbed through the skin. They are generally distributed to fatty

Table 10-3-Organophosphorous and Carbamate Insecticides-Continued

Highly toxic[a]	Moderately toxic[a]
dialifor (Torak)	naled (Dibrom)
cyanofenphos (Surecide)	phenthoate (dimephenthoate, Phenthoate)
dioxathion (Delnav)	IBP (Kitazin)
mipafox (Isopestox, Pestox XV)	cyanophos (Cyanox)
	crufomate (Ruelene)
	fenitrothion (Accothion, Agrothion, Sumithion)
	pyridaphenthion (Ofunack)
	acephate (Orthene)
	malathion (Cythion)
	ronnel (fenchlorphos, Korlan)
	etrimfos (Ekamet)
	phoxim (Baythion)
	merphos (Fo!ex, Easy off-D)
	pirimiphos-methyl (Actellic)
	iodofenphos (Nuvanol-N)
	chlorphoxim (Baythion-C)
	propyl thiopyrophosphate (Aspen)
	bromophos(Nexion)
	tetrachlorvinphos (Gardona, Appex, Stirofos)
	temephos (Abate, Abathion)
Carbamate Insecticide	
aldicarb[b] (Temik)	dioxacarb (Elocron, Famid)
oxamyl (Vydate L, DPX 1410)	promecarb (Carbamult)
methiocarb (Mesurol, Draza)	bufencarb (metalkamate, Bux)
carbofuran (Furadan, Curaterr, Crisfuran)	propoxur (aprocarb, Baygon)
isolan (Primin)	trimethacarb (Landrin, Broot)
methomyl (Lannate, Nudrin, Lanox)	pirimicarb (Pirimor, Abel, Aficida, Aphox, Fernos, Rapid)
formetanate (Carzol)	dimetan (Dimethan)
aminocarb (Matacil)	carbaryl (Sevin, Dicarbam)
cloethocarb (Lance)	isoprocarb (Etrofolan, Ml PC)
bendiocarb (Ficam, Dycarb, Multamat, Niomil, Tattoo, Turcam)	

[a]Compounds are listed in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD_{50} (median lethal dose) values (rat) less than 50 mg/kg; "moderately toxic" agents have LD_{50} values in excess of 50 mg/kg.
[b]These insecticides are systemic; they are taken up by the plant and translocated into foliage and sometimes into the fruit.

SOURCE: D.P. Morgan, *Recognition and Management of Pesticide Poisoning,* EPA pub. No. 540/9-S8-001 (Washington, DC: U.S. Government Printing Office, 19S9).

tissue, the liver, and the nervous system. Most are metabolized by the liver and excreted in urine. For some pesticides, accumulation in fat tissue occurs during chronic exposure, so elimination is slow. DDT, for example, is metabolized and excreted slowly and can still be found in the fat of most people exposed to it years after its use was terminated (62).

Acute intoxication from organochlorines can produce nervous system excitability, apprehension, dizziness, headache, disorientation, confusion, loss of balance, weakness, muscle twitching, tremors, convulsions, and coma. Uncontrolled seizures, respiratory problems, or both, may lead to brain or other organ damage. Children may be particularly sensitive to brain and nerve damage from organochlorine pesticides and may suffer from long-term behavioral and learning disabilities as a result of exposure (41).

One of the most serious cases of severe poisoning occurred in manufacturing workers handling chlordecone, commonly known as Kepone (see ch. 2). These workers suffered tremors, disturbances in vision, and difficulty in walking (156). As a result, this pesticide's registration was canceled by EPA in 1977 (42 FR 18855).

Fumigants

Fumigants-used to kill insects, insect eggs, and microorganisms-are the most acutely toxic pesticides used in agriculture. Because they are gases, fumigants are usually taken directly into the lungs, where they readily enter the blood and are distributed throughout the body. Although inhalation is the most serious source of exposure and can lead rapidly to death, absorption of fumigants through the skin can also be a significant hazard (103).

Table 10-4-Neurotoxic Effects of Acute Exposure to High Levels of Organophosphorous or Carbamate Insecticides

Function of nervous system when stimulated by acetylcholine	Effect of excessive stimulation of the nervous system
Activate salivary, sweat, and tear glands	Increased salivation, sweating, watering of eyes
Constrict bronchi	Tightness in chest, coughing and wheezing, difficulty breathing
Contract pupil of eye	Pinpoint pupils, blurring of vision
Control heart function	Abnormal heart beat, change in blood pressure
Increase spasms in digestive tract	Stomach cramps, nausea, vomiting, diarrhea
Increase spasms in urinary tract	Urinary frequency and incontinence
Activate skeletal muscles	Twitching, restlessness, tremulousness, impaired coordination, generalized muscle weakness, paralysis, and death or brain injury caused by asphyxiation after muscle paralysis
Alter brain function	Headache, giddiness, anxiety, emotional instability, lethargy, confusion; eventually severe central nervous system depression and coma

SOURCE: B.B. **Young, Neurotoxicity of Pesticides,"** *Journal of Pesticide* ***Reform 6:8-11,*** **1986.**

Table 10-5-Organochlorine Insecticides

Insecticide
endrin (Hexadrin)
aldrin (Aldrite, Drinox)
endosulfan (Thiodan)
dieldrin (Dieldrite)
toxaphene (Toxakil, Strobane-T)
lindane (gamma BHC or HCH, Isotox)
hexachlorocydohexane (BHC)
DDT (chlorophenothane)
heptachlor (Heptagran)
chlordecone (Kepone)
terpene polychlorinates (Strobane)
chlordane (Chlordan)
dicofol (Kelthane)
mirex (Dechlorane)
methoxychlor (Marlate)
dienochlor (Pentac)
TDE (DDD, Rhothane)
ethylan (Perthane)

SOURCE: D.P. Morgan, Recognition *and Management of Pesticide Poisoning,* EPA pub. No. 540/9-88-001 (Washington, DC: U.S. Government Printing Office, 1989).

Fumigants have caused severe illness and death in human beings (11,63,81,132). Poisoning initially causes headache, nausea, vomiting, and dizziness, followed by drowsiness, fatigue, slurred speech, loss of balance, and disorientation. In severe poisonings, seizures, loss of consciousness, respiratory depression, and death may occur. Tremors and generalized seizures may also occur, particularly from methyl bromide poisoning.

Methyl bromide, one of the most widely used pesticides in the United States, is a colorless gas at room temperature. It has a faint, somewhat agreeable odor, making it difficult to detect, even at toxic levels (127). This pesticide has caused death and severe neurotoxic effects in fumigators, applicators, and structural pest control workers. Acute exposure to methyl bromide can result in visual and speech disturbances, delirium, and convulsions. Both acute and chronic poisoning from methyl bromide may be followed by prolonged, and in some cases permanent, brain damage marked by personality changes and perception problems. Chronic exposure can result in progressive peripheral neuropathy, with loss of motor control, numbness, and weakness (4,63).

Chlorophenoxy Herbicides

Chlorophenoxy herbicides include 2,4-dichlorophenoxyacetic acid(2,4-D),2,4~-trichlomphenoxyacetic acid (2,4,5-T), 2-methyl-4 -chlorophenoxyacetic acid (MCPA), and 2,4,5 -trichlorophenoxypropionic acid (Silvex). These herbicides were among the most widely used until EPA suspended many of their uses because of potential adverse effects on human health (43 FR 17116). The chlorophenoxy herbicides continue to be used widely in forestry and weed control in agricultural and urban settings. Farmworkers can be exposed to these pesticides during mixing and loading or by drift from nearby applications. Although these compounds are readily metabolized and excreted and are of relatively low toxicity to mammals, they are often contaminated with dioxins, which may be toxic themselves (102). There are more than 75 different dioxin isomers, but TCDD, a contaminant of 2,4,5-T, is believed to be the most toxic (68).

Most current knowledge of the effects of TCDD on humans comes from overexposures of workers manufacturing 2,4,5-T or the compound from which it is derived (61,66,68). Acute exposure to high doses has led to peripheral neuropathy, sometimes accompanied by difficulty in walking and coordinating the legs. Irritability, insomnia and hypersomnia, lethargy, impotence, and psychiatric disturbances have also been reported in cases of acute exposure (102). Peripheral neuropathy resulting from dermal

absorption and death resulting from ingestion have been reported for 2,4-D (102).

The most notorious chlorophenoxy herbicide is the defoliant Agent Orange. Agent Orange consists of a 1:1 mixture of 2,4,5-T and 2,4-D and was widely used in Vietnam from 1962 to 1970. A number of adverse effects on Vietnamese and on American soldiers in Vietnam have been alleged. A recent report indicates that the probability of exposure of U.S. veterans was small (162), and whether Agent Orange was the cause of the alleged health effects is still unresolved (102).

Pyrethroids

Pyrethroids, a group of insecticides, are highly toxic to insects but less toxic to mammals, which metabolize and excrete them quickly. Pyrethroids act by altering the flow of sodium ions through the nerve cell membrane, resulting in repeated firing of the nerve cell (106).

Because pyrethroids appear to be less acutely toxic than other insecticide groups, their use is likely to increase. In response to the observation of axonal swelling in rats subsequent to pyrethroid ingestion, EPA requires a special new pathological evaluation as part of the 90-day rodent feeding study from all companies attempting to register a pyrethroid (37).

Summary and Conclusions

Approximately 1 billion pounds of pesticides products, made up of 600 active pesticide ingredients, are used annually in agriculture in the United States (102). Many of these active pesticide ingredients have never been tested for potential neurotoxic or neurobehavioral effects, damage to the reproductive system, or other effects on human health. Historically, few pesticides have been banned or restricted by EPA.

Although everyone is exposed to low levels of pesticides in food and water, an estimated 2.7 million migrant and seasonal farmworkers face greater risk because they are regularly exposed to higher levels of pesticides and because existing protections do not always cover them adequately. Pesticide applicators, loaders, and mixers, as well as nursery, greenhouse, forestry, and lawn care workers, may be exposed to particularly high levels of pesticides as well. Children, who constitute a significant proportion of the agricultural work force, are especially vulnerable because their nervous systems are not fully developed. The majority of pesticides used are organophosphorous and n-methyl carbamate insecticides, both of which are neurotoxic. They can produce acute effects (ranging from moderate symptoms to death) and perhaps chronic effects as well, although the data are inconclusive. Some organophosphorous insecticides can also cause delayed damage to the peripheral nervous system.

It is not possible to estimate accurately the extent of illness among farmworkers because there is no national pesticide illness reporting system or worker monitoring program. Extrapolations by others from available data suggest a prevalence of more than 300,000 pesticide-related illnesses among farmworkers, although only a small percentage of these cases are reported (31). The total number of worker deaths and the extent of chronic health problems caused by exposure to pesticides are also unknown.

Limiting the use of neurotoxic pesticides would be a straightforward way to control exposure. Integrated pest management systems offer alternative approaches to pest control and minimize the use of pesticides.

More research is needed to understand the neurotoxic effects of new and existing chemicals and to protect agricultural workers from them. EPA's pesticide registration review should require information on pesticide neurotoxicity based on the most current knowledge of dose-response relationships, mechanisms of action, and structure-activity relationships. Premarket testing could include effects on learning, memory, conditioned behavior, and emotional disorders, rather than being limited to motor function. More information is needed on the long-term effects of pesticides on the fetus, on children, and on the aged.

The need for epidemiological studies of the effects of pesticides on agricultural workers is critical. Reporting and monitoring procedures could be established and enforced to provide more accurate information on the prevalence and incidence of pesticide illness; furthermore, to facilitate reporting, both physicians and workers could be better educated in the signs and symptoms of pesticide illness.

In the near term, several actions could be taken to provide greater protection to agricultural workers. Establishing more specific reentry intervals, which take into account the chemical and neurotoxic properties of certain chemicals, would be a positive

step forward. EPA might also adjust its risk-benefit assessment criteria for pesticide registration to include the costs of pesticide poisoning of workers. Workers could be regularly monitored for exposure to pesticides, provided with appropriate protective clothing, trained in safe application for specific circumstances, educated about the health effects of exposure, and better informed about the chemicals they use under right-to-know laws. Mandatory recordkeeping on pesticide application could be included in the latter to ensure that workers can obtain information about previous exposures. EPA has proposed decontamination facilities and emergency provisions for all workers, but more could be done to prevent pesticide poisoning. Since the chronic effects of pesticide poisoning remain unknown, efforts may be best directed toward prevention.

EXPOSURE TO ORGANIC SOLVENTS IN THE WORKPLACE

According to the National Institute for Occupational Safety and Health (NIOSH), approximately 9.8 million workers are exposed to solvents every day through inhalation **or skin contact (166).** Acute exposure to organic solvents can affect an individual's manual dexterity, speed of response, coordination, and balance; it can also produce feelings of inebriation. Chronic exposure to some organic solvents can result in fatigue, irritability, loss of memory, sustained changes in personality or mood, and decreased learning and concentration abilities; in some cases, structural changes in the nervous system are apparent.

Organic solvents are a group of simple organic liquids that are volatile; that is, in the presence of air they change from liquids to gases and therefore are easily inhaled. Figure 10-6 illustrates the general classes of organic solvents. Solvents usually serve one of two general functions. They may be used in separation processes to selectively dissolve one material from a mixture, or they may act as a processing aid, facilitating fabrication of a material (usually a polymer) by reducing its viscosity (188). They are components of a variety of products, including paints, paint removers and varnishes; adhesives, glues, coatings; decreasing and cleaning agents; dyes and print ink; floor and shoe creams, polishes, and waxes; agricultural products; pharmaceuticals; and fuels. In 1984, approximately 49 **million tons of industrial organic solvents were produced in the United States (167).**

There are many occupations in which workers are exposed to solvents. For example, painters may come in contact with methyl alcohol, acetone, methylene chloride, toluene, and complex mixtures of petroleum products. Depending on the exposure levels in air, house painters may experience a variety of adverse effects, including fatigue, impaired memory, difficulty in breathing, slurred speech, nausea, dizziness, difficulty in concentrating, and dermatitis. Some researchers believe that painters may develop a "psycho organic syndrome" from exposure to chronic low levels of solvents (49,58). The syndrome is characterized by fatigue, difficulty concentrating, learning, and remembering, and personality changes (32).

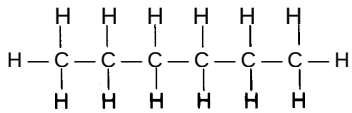
In order to protect workers, NIOSH recommends that employers educate them about the materials to which they are exposed, the potential health risks involved, and work practices that will minimize exposure to these substances (166). NIOSH also recommends that employers assess the conditions under which workers may be exposed to solvents, develop monitoring programs to evaluate the extent of exposure, establish medical surveillance for any adverse health effects resulting from exposure, and routinely examine the effectiveness of the control methods being employed in order to reduce exposures to the permissible exposure limits (PELs) mandated by OSHA. There are three basic methods for minimizing worker exposure to organic solvents: using effective engineering controls, isolating workers from the source of exposure, and using personal protective equipment (8).

Organic solvents are of particular concern because most are toxic in different ways and to varying degrees and many are also flammable. The increase in the number of available organic solvents and the development of new processes utilizing them present major occupational health challenges (8,166).

Some organic solvents are also subject to abuse by inhalation. The extent of this abuse is much greater than is generally recognized. The National Institute on Drug Abuse reports that the lifetime incidence of solvent abuse among seniors in high school (thus excluding dropouts) is exceeded only by alcohol, tobacco, marijuana, and stimulants (113). The abuse of solvents by Hispanic and Native Americans is widespread in some regions, exceeded only by

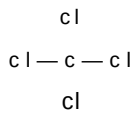
Figure 10-6-Classes of Organic Solvents

Allphatic hydrocarbons
(Acyclic)
Straight or branched chains of carbon and hydrocarbons



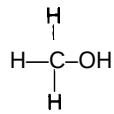
n- Hexane

Halogenated hydrocarbons
A halogen atom has replaced one or more hydrogen atoms on the hydrocarbon



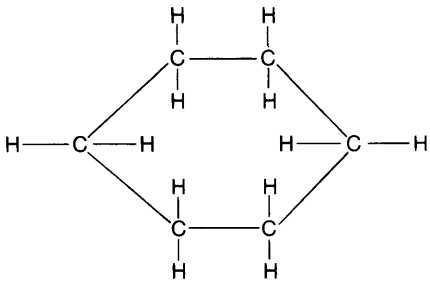
Carbon tetrachloride

Alcohols
Contain a single OH group



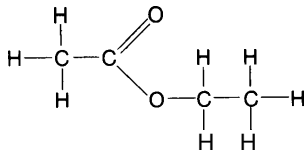
Methyl alcohol

Cyclic hydrocarbons
(cycloparaffins, naphthenes)
Ring structure saturated and unsaturated with hydrogen



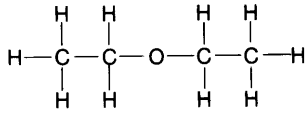
Cyclohexane

Esters
Formed by interaction of an organic acid with an alcohol



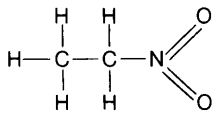
Ethyl acetate

Ethers
Contain the C–O–C linkage



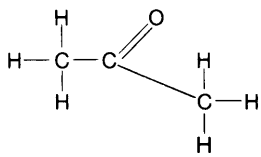
Ethyl ether

Nitrohydrocarbons
Contains an NO, group



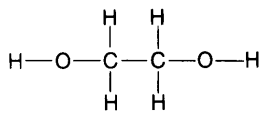
Ethyl nitrate

Ketones
Contain the double bonded carbonyl group, C = O, with 2 hydrocarbon groups on the carbon



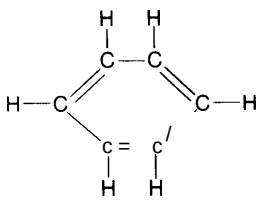
Acetone

Glycols
Contain double OH groups



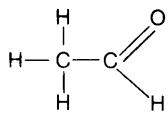
Ethylene glycol

Aromatic hydrocarbons
Contain a 6-carbon ring structure with one hydrogen per carbon bound by energy from several resonant forms



Benzene

Aldehydes
Contain the double bonded carbonyl group, C = O, with only one hydrocarbon group on the carbon



Acetaldehyde

SOURCE: Alliance of American Insurers, ***Handbook of* Organic *Industrial Solvents,* 6th** edition, 1987, pp. 1-20.

alcohol abuse (l). Such exposures greatly exceed those encountered in the workplace and can be associated with severe and irreversible toxicities.

Uptake, Distribution, and Elimination of Solvents

Solvents may enter the body by inhalation, dermal contact, or ingestion. The hazards associated with dermal exposure and ingestion can be severe; in fact, numerous fatalities have resulted from exposure to methanol by these routes. However, because of the volatility of these chemicals, a major route of exposure is inhalation. Exposure to the skin is another important route. For example, immersion of hands in methylene chloride causes neurological damage (159), and carbon disulfide produces shaking of the hands and loss of feeling (89).

The amount of the solvent entering the body depends on such factors as route of exposure, the concentration of the solvent in the air, the volubility of the solvent in blood, and the amount of physical work being performed at the time of exposure. A sedentary worker on a factory floor will absorb less solvent than a worker engaged in a vigorous physical task because the latter will be inhaling more rapidly and deeply (thereby moving more solvent to the site of uptake in the lungs) and more blood will be traveling through the lungs (carrying the solvent throughout the body).

Some solvents tend to be distributed unequally among the organs of the body. This is both because the volubility of a particular solvent varies with different tissues and because the blood supply to tissues varies greatly. Thus, an organ like the brain, with its high fat content and very rich blood supply, achieves high levels of solvents quickly. Given a constant concentration of solvent in the air, the amount of solvent present in body tissues eventually reaches a plateau in each tissue, but the time required to achieve that plateau varies among tissues and among individuals.

At the same time that the body is absorbing solvents, it is working to eliminate them. If exposure ceases or is reduced, the solvent begins to be exhaled, or "blown off. " Enzymes may change the structure of the solvent, making it more water soluble and enabling the kidneys to eliminate it. The metabolism of solvents can be a two-edged sword, however, since the metabolize may be more toxic than the parent solvent. Mixtures of solvents or



Photo credit: United Automobile, Aerospace, and Agricultural Improvmnt Winkers of America-UAW Public Relations Department

Respirators may be useful in minimizing exposure to solvent vapors when engineering or work practice controls are inadequate.

industrial grade solvents may be more toxic than pure solvents, either because of toxic contaminants or because of chemical interactions.

Neurological and Behavioral Effects

All solvents are soluble in fat and will at some level of exposure produce effects on the central nervous system (35). For a wide variety of drugs and chemicals, the more soluble the chemical is in brain membranes, the more potent it is and the longer it acts.

Interest in the effects of solvents on the central nervous system dates back to the early search for anesthetics, when many agents were examined. Short-term exposures at low toxicity may produce mucous membrane irritation, tearing, nasal irrita-

tion, headache, and nausea (35). With repeated inhalation of high levels of solvents, a state of severe narcosis may be produced; at lower levels, the effects resemble those of alcohol. There may be initial euphoria, loquaciousness, and excitement, followed by confusion, dizziness, headache, motor incoordination, ataxia, unconsciousness, and death. These so-called nonspecific narcotic effects of solvents are the major reason they are regulated in the workplace; they can impair work performance and the ability to avoid hazards (35).

Toxicity studies and health problems in the workplace have revealed other effects that are specific to individual solvents or classes of solvents. For example, neuropathies may result from chronic exposure to hexane, methyl-n-butyl ketone, and related solvents. This disorder (sometimes referred to as hexacarbon neuropathy) is characterized by numbness in the hands and feet and may progress to muscle weakness and lack of coordination (152). Some solvents produce seizures and convulsions on acute exposure, for example, such alkylcycloparaffins as methylcyclopentane and methylcyclohexane (79, 80,129). Indeed, epileptic seizures in the workplace may be mistakenly attributed to an undiagnosed neurological defect of the worker rather than to a chemical exposure.

Adverse effects on the inner ear may also be caused by exposure to solvents. For example, exposure to high levels of alkylbenzenes such as toluene and xylene can damage the inner ear, leading to high-frequency hearing loss (128,130,133). Dizziness and vertigo have been reported following acute exposure to a variety of solvents. Exposure may also adversely affect various visual functions and the sense of smell (43,94,95).

Some solvents may cause emotional disorders. Carbon disulfide can produce a raging mania and has been associated with increased risk of suicide (92). In 1902, Thomas Oliver described his visits to India-rubber factories in London and Manchester, noting "the extremely violent maniacal condition into which some of the workers, both female and male, are known to have been thrown. Some of them have become the victims of acute insanity, and in their frenzy have precipitated themselves from the top rooms of the factory to the ground" (122).

Other disorders associated with exposure to solvents include sleep disturbances, nightmares, and insomnia (18,190). Trichloroethylene or its contaminants may damage facial nerves and produce facial numbness (20). Severe brain injuries (chronic encephalopathies) have been documented following prolonged exposures to high levels of solvents, such as during deliberate self-administration of solvents. This has produced concern about the likelihood of such effects occurring in the workplace. Prolonged exposure to styrene may produce impairments in perceptual speed and accuracy, memory, and cognitive performance (60).

The Solvent Syndrome: A Current Controversy

There is considerable evidence that toxic encephalopathy may be caused by high-level, prolonged, and repeated exposure to some organic solvents (158). Encephalopathy consists of a wasting of brain matter, which leads to expansion of the fluid-filled cavities in the brain. The syndrome is associated with motor disorders and impaired mental function. Several Scandinavian countries have identified a new disease entity, a toxic encephalopathy following chronic solvent exposure, and compensate workers who develop it at the workplace (52). However, the studies used to document the syndrome's existence are the subject of controversy (45,58). A multinational study of workers exposed to solvents is being funded by a consortium of industrial groups (158). In studies of this type, many variables may obscure the detection of an effect or erroneously suggest its existence. These include age, concurrent exposure to other chemicals, excessive alcohol intake, drug abuse, and socioeconomic status. In fact, a recent reanalysis of test data failed to confirm an earlier report of a ''chronic painters' syndrome" with dementia (54). Many studies suffer from not having extensive documentation of workplace exposure levels. It was having such information on exposure that enabled investigators to do landmark studies of carbon disulfide neurotoxicity. These studies revealed differences in suicide rates among workers in a rayon factory as a function of work assignment and associated carbon disulfide exposure within the plant (92).

Although painters are exposed for long periods of time to solvents, their exposure is moderate in comparison to that of solvent abusers, who routinely expose themselves to very high concentrations. The injuries to the nervous system suffered by solvent abusers are unequivocal and severe (53,78,1 38,142). A scientific conference recommended directions that human and animal research should take (9). The

lack of an animal model inhibits the normal regulatory process of hazard identification, risk assessment, and risk management. Just as prudent regulatory actions are undertaken to minimize the risk of cancer in humans when tumors are observed in laboratory animals, a nervous system injury or behavioral disorder identified in laboratory animals could be the basis for regulation to reduce the likelihood of injury to the human nervous system. To date, little effort has been devoted to developing an animal model of the solvent syndrome.

Health Protection

There are several methods for controlling worker exposure to organic solvents, including worker isolation, use of engineering controls, and personal protective equipment. Proper maintenance procedures and education programs are important ingredients of protection programs. OSHA regulations require that workers be informed about the hazards associated with the chemicals present in the workplace (29 CFR 1987 ed. 1910.1200). NIOSH recommends that employers establish a medical surveillance program to evaluate both the acute and chronic effects of exposure to organic solvents and that workers undergo periodic medical examinations (166). Both physicians and workers should be given information regarding the adverse effects of exposure to organic solvents and an estimate of the worker's potential for exposure to the solvents. This information should include the results of workplace sampling and a description of protective devices that the worker may be required to use (166).

Contaminant Controls, Worker Isolation, and Personal Protective Equipment

The primary means of preventing contamination is by applying appropriate engineering controls. These may be necessary to eliminate the potential for exposure and to prevent fires and explosions. Achieving an adequate reduction of exposure to a solvent depends on the construction and maintenance of the engineering control applied to the system, the exposed liquid surface, and the temperature and vapor pressure of the solvent. Closed system operations are the most effective method of minimizing worker exposure. Closed system equipment can be used for manufacturing, storing, and processing organic solvents. As an alternative, workers can be isolated from the process by being enclosed in a control booth.

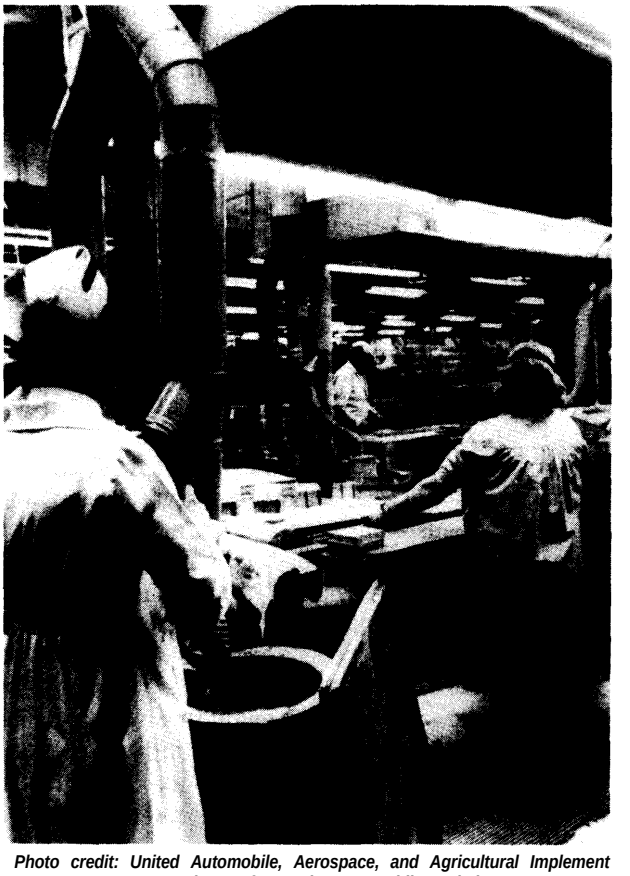


Photo credit: United Automobile, Aerospace, and Agricultural Implement Workers of America-UAWPublic Relations Department

Millions of workers come into contact with toxic substances every day through inhalation or skin contact, Many of the substances are known to be or are potentially neurotoxic.

When a closed system cannot be implemented, exhaust fans can be used to direct vapors away from workers and to prevent the contaminated air from recirculating in the workplace (166). In addition, personal protective equipment may be necessary (see box 10-G).

Respirators may be needed to minimize exposure when engineering or work practice controls are inadequate for this purpose. Respirator may be required for protection in certain situations such as implementation of engineering controls, some short-duration maintenance procedures, and emergencies. The use of respiratory protection requires that the plant or company institute a respiratory protection program (166). Direct contact of organic solvents with the skin can be prevented by wearing solvent-resistant gloves, aprons, boots, or entire work suits. Depending on the workplace and on the hazardous

Box 10-G-Engineering Controls v. Personal Protective Devices

The scientific and technical community has generally preferred engineering controls, that is, changes in the design of the physical environment and equipment used in the workplace, to personal protective devices, such as respirators, because:

- workers are erratic in their use of personal protective devices;
- such devices are cumbersome and, in the case of respirators, even the most conscientious worker may have difficulty ensuring an effective seal between face and mask;
- personal protective devices themselves require maintenance, such as periodic replacement of air filters; and
- it can be difficult to know when a personal protective device has failed.

The Occupational Safety and Health Act (OSH Act) was designed to decrease worker exposure to toxic substances and to provide information to employees about remaining occupational health risks. Maintaining low levels of toxic substances in the workplace through engineered controls has historically been given priority over the use of personal protective devices, except in those cases where it is not feasible to use engineering controls to reach the OSH Act exposure limit. Engineering controls are generally more expensive than personal protective equipment, and small plants and businesses often cannot afford to make expensive changes.

The mandate of the Act, however, has been to maintain a safe workplace, regardless of the size of the business. If it is not feasible to institute engineering controls or to engineer down to what the Act determines to be a safe level of exposure, then personal protective equipment is an acceptable choice. Recent changes in the existing rule on methods of compliance (54 FR 23991) allow respiratory protection to be used in lieu of administrative or engineering controls under the following circumstances **(54 FR 23991):**

1. during the time necessary to install or implement feasible engineering controls;
2. where feasible engineering controls result in only a negligible reduction in exposures;
3. during emergencies, recovery operations, unscheduled repairs, shutdowns, and field situations where there are no utilities for implementing engineering controls;
4. operations requiring added protection where there is a failure of normal controls; and
5. entries into unknown atmospheres (e.g., entering vessels, tanks, or other confined spaces for cleaning).

In addition to regulatory requirements, there are important ethical arguments about engineering controls versus personal protective devices. What are the important values at stake? The health, well-being, and autonomy of the worker are obviously important. (Autonomy refers to behaviors that reflect the capacity of competent adult individuals to formulate life plans and make decisions freely, without coercive influences.)

The Act is designed to ensure a safe and healthful workplace by setting exposure levels and establishing standards on behalf of the worker. One can argue that the option of using personal protective devices gives the worker a choice in determining the extent of exposure to hazardous substances. Yet it is difficult to imagine why a worker would prefer to use a cumbersome device like a respirator rather than have the workplace and equipment engineered to be safer. In situations in which it is not feasible to engineer safe levels of exposure, the use of personal protective devices may be the only option for working safely. On occasion, employees may decide to work in an area that requires the use of personal protective equipment in order to gain a particular type of work experience or to make more money. From an ethical standpoint however, circumstances in which there exists some coercive element are objectionable.

On balance, the interests of the worker seem to be best served by the use of engineering controls that lower levels of exposure to toxic substances for most workers most of the time. Some employers, however, can and do continue to argue that the greatest good for the greatest number requires at least some reliance on the use of personal protective devices.

SOURCE: Office of Technology Assessment, 1990.

properties of the substance, face shields and safety goggles may be required.

OSHA Regulations

The principal reason for the enactment of the Occupational Safety and Health Act of 1970 was to protect workers from occupational safety and health hazards. To accomplish this goal, OSHA sets minimum standards for working conditions. Hazards not mentioned in the standards are covered by the "general duty clause," which requires each employer to maintain a workplace ''free from recognized hazards. " All work environments must meet the regulations and standards set by the law (29 CFR 1987 ed. 1900-1910). OSHA has the authority to conduct inspections, determine compliance with the standards, and initiate enforcement actions against employers who are not in compliance.

If an inspector documents a violation, it is reported to the OSHA area director, who then informs the employer of the citation or proposed penalty. If the employer disagrees with the action, he or she may contest it by informing the Department of Labor within 15 working days of the citation. When notification is received that an action is being contested, the Occupational Safety and Health Review Commission is notified, and this review commission assigns the hearing to an administrative law judge. Following the hearing, the judge may issue an order to affirm, modify, or vacate the citation or proposed penalty. The order is final after 30 days unless the commission reviews the decision. If the employer decides not to contest the citation, he or she must correct the situation that is in violation of the standards. If the employer cannot do so within the proposed abatement period, an extension maybe requested. The law provides for fines of up to $1,000 for each violation and up to $10,000 if the violation is willful or repeated (29 CFR 1987 ed. 1903).

The PEL Controversy

OSHA recently published a revised standard that increased the protection of workers by implementing new or revised PELs for 428 toxic substances, including a number of organic solvents (53 FR 20960-20991). The final standard was published in January 1989. According to the Department of Labor, the new limits will reduce considerably the risk of illness, including cancer, by using the force of law to ensure that workers are not exposed at levels above the new PELs. The final rule was effective in March 1989, and the start-up date for compliance with any combination of controls (e.g., personal protective equipment) was September 1989, whereas compliance with engineering controls is delayed until December 31, 1992, or in some cases a year later.

The PELs are listed in the so-called Z tables in the OSHA regulations (29 CFR 1910.1000). The recent changes include revising the PELs, adding short-term exposure limits (STELs) to complement the 8-hour time-weighted average (TWA) limits, and where necessary designating skin or ceiling limits for the substances (54 FR 2332-2403). According to the Department of Labor:

> OSHA has reviewed health, risk and feasibility evidence for all 428 substances for which changes to the PEL were considered. In each instance where a revised or new PEL is adopted, OSHA has determined that the new limits substantially reduce a significant risk of material impairment of health or functional capacity among American workers, and that the new limits are technologically and economically feasible. This determination has been based on further review of the material discussed in the Proposal, public comments and a detailed review of the entire record for this rulemaking (54 FR 2334).

The new rule established lower exposure limits for approximately 212 substances already regulated by OSHA. PELs would be established for the first time for another 164 substances. A large number of these are established to prevent adverse effects on the nervous system. According to the Department of Labor:

> . . . Benefits will accrue to approximately 4.5 million workers who are currently exposed in excess of the PEL and are expected to include over 55,000 occupational illness cases, including almost 24,000 lost workdays annually. If not prevented, these illnesses would eventually result in approximately 700 fatalities per year. . . . The annual cost is approximately $150 per worker protected, and is never more than a fraction of 1 percent of sales and less than 2 percent of profits (usually substantially less) except for a very few segments . . . (54 FR 2335).

The approach used to develop the regulations of the new PELs has been controversial (54 FR 3272-2377). In evaluating the PELs, OSHA used the threshold limit values (TLVs) published by the American Conference of Governmental Industrial Hygienists (ACGIH) published in 1988 and the

recommended exposure limits (RELs) developed by NIOSH as its starting point. The agency compared the PELs to the Z tables and to the TLVs. If the two differed, the PEL was evaluated for revision. The agency first determined if the TLVs and RELs were similar. If they were, or if there was no REL, then OSHA studied the TLVs. If the TLV and REL differed significantly, OSHA examined the scientific basis of each recommendation and determined which was more appropriate. According to OSHA:

> In its review, OSHA determined frost whether the studies and analysis were valid and of reasonable scientific quality. Second, it determined, based on the studies, if the published documentation of the REL or TLV would meet OSHA's legal requirements for setting a PEL. Thus, OSHA reviewed the studies to see if there was substantial evidence of significant risk at the existing PEL or, if there was no PEL, at exposures which might exist in the workplace in the absence of any limit. Third, OSHA reviewed the studies to determine if the new PEL would lead to substantial reduction in significant risk. If this was so, and if the new PEL was feasible, OSHA proposed the new PEL (54 FR 2372).

The TLVs, RELs, and old and new PELs of some selected solvents are listed in table 10-6.

Table 10-6-Representative Exposure Limits to Solvents

	Measure (ppm)			
Solvent	REL[a]	TLV[b]	Old PEL[c]	New PEL
Toluene	100	100	200	100
Xylene	100	100	100	100
Cresol	2.3	5d	5d	4
Acetone	250	750	1,000	750
Styrene	50	50	100	50
Tetrachloroethylene	—	50	100	25
Methyl chloroform	200	350	350	350
Allyl chloride	1	1[d]	1	1
Furfuryl alcohol	50	10	50	10
Ethylene dichloride	1	10	50	1
Benzene	0.1	10	10	10
Carbon disulfide	1	10	20	4
Trichloroethylene	25	50	100	50
Chloroform	—	10	50	2

[a]RELs (recommended exposure limits) are set by the National Institute for Occupational Safety and Health.
[b]TLVs (threshold limit values) are set by the American Conference of Governmental Industrial Hygienists.
[c]PELS (permissible exposure limits) are set by the Occupational Safety and Health Administration.
[d]The ACGIH designation "skin"(s) refers to the potential contribution Of exposure by the cutaneous route, including mucous membranes and eyes.

SOURCES: 54 FR 2332-2983; 29 CFR 1987 ad. 1910.1000; R.B. Dick, "Short Duration Exposures to Organic Solvents: The Relationship Between Neurobehavioral Test Results and Other Indicators," *Neurotoxicology and Teratology* 10:39-50, *1988;* U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, "Organic Solvent Neurotoxicity," *Current Intelligence Bulletin* 48:1-39, 1987.

The final standard has been controversial because it represents a substantially different approach to OSHA rule-making. Until this action, OSHA addressed toxic substances individually, a process that produced standards for only 24 substances in 17 years. In this single rule-making, however, OSHA established new exposure limits for 376 toxic substances by adopting the TLVs published by ACGIH. Industry and several unions expressed concern that OSHA was delegating its regulatory authority to a nongovernment organization and that in some cases TLVs are not based on recent studies (25,139). The extent of corporate influence on TLVs has also been the subject of debate (25). Some unions contended that ACGIH is dominated by industry and that OSHA's action subverts the activities of NIOSH (139).

NIOSH offers RELs for chemicals following careful review of available data and bases its recommendations solely on the chemical's effects on health. However, OSHA, by law, cannot enforce a standard with a recommended exposure limit (REL) that is not technologically or economically feasible. These constraints often prevent OSHA from lowering a limit on the basis of health considerations alone, that is, on NIOSH's recommendation.

Public comments submitted to OSHA on the PEL proposal were in broad agreement that the PELs needed updating; however, many thought the project was being undertaken hastily and that the public interest would not be well served by such a major procedural change. Some commentors recommended that periodic updates be conducted on a more frequent and less harried basis.

By using the ACGIH list of TLVs as the basis for its selection, OSHA was able to save a great deal of the time it would have taken to address these chemicals through the usual regulatory procedures. OSHA is constrained to conduct a number of analyses by statute or executive order, including extensive economic analyses. By its own admission, OSHA states that it follows more extensive and elaborate administrative procedures than other health regulatory agencies:

> ... Clearly an improved approach to regulation is needed to solve this problem in a reasonable time period. OSHA's traditional approach, which has

> permitted on the average less than two major health regulations per year, is not adequate to address the backlog of at least 400 chemicals generally recognized as needing new or lower exposure limits. OSHA has reviewed the law, Congressional intent, its history, and the recommendations of experts . . . [and has] concluded that this approach has a greater health benefit and will prevent more deaths and various deleterious health effects, than could be achieved by allocating the same resources to comprehensive rulemaking for a small group of substances. . . (54 FR 2370).

The advisability of using the recommended exposure standards of a private organization instead of NIOSH is likely to be a subject of continuing controversy in the occupational health arena.

Summary and Conclusions

Organic solvents and mixtures of solvents with or without other toxic substances are widely used in the workplace. It is estimated that 9.8 million workers come into contact with solvents every day through inhalation or skin contact. Some solvents may profoundly affect the nervous system. Acute exposure to solvents can affect an individual's manual dexterity, response speed, coordination, or balance. Chronic exposure may lead to reduced function of the peripheral nerves and such adverse neurobehavioral effects as fatigue, irritability, loss of memory, sustained changes in personality or mood, and decreased learning and concentration abilities.

In order to protect workers, OSHA requires that employers inform and educate workers about the potential health risks of the materials to which they are exposed and adopt work practices that minimize exposure to hazardous substances. NIOSH recommends that employers assess the conditions under which workers may be exposed to solvents, develop monitoring programs to evaluate the extent of exposure, establish medical surveillance for any adverse health effects, and routinely examine the effectiveness of the control methods.

OSHA recently updated the permissible exposure limits for 428 substances, many of them solvents. The new ruling established lower PELs for 212 substances already regulated by the agency. PELs were also established for the first time for another 168 substances, while existing limits for 25 substances were reaffirmed. This marks the first time in 17 years that a new set of exposure standards has been established. The mechanism by which the new PELs were set, however, is the subject of controversy.

For many companies, meeting the new standards may require stricter engineering controls or more frequent use of respirators and other personal protective devices, or both. OSHA requires companies to educate workers about the hazards of the substances to which they are exposed, to institute control methods to prevent exposure, and to formulate plans or procedures to maintain compliance with the new rulings.

There is insufficient information available to regulatory agencies to distinguish dangerous solvents from ones that are not dangerous. Creative approaches are needed to protect workers while avoiding unnecessary and overly burdensome regulations. To fill this need, research programs in academia, industry, and government will have to be expanded significantly. If NIOSH is to play an important future role in the development and analysis of information on safe exposure levels for solvents, then additional resources will be required and the Institute will have to make a commitment to focus more attention on the neurological and behavioral effects of solvents. Improvement in the development of toxicity standards will require a substantially closer working relationship between OSHA and NIOSH.

CHAPTER 10 REFERENCES

1. Adams, E.H., "An Overview of Drug Use in the United States and Along the U.S.-Mexico Border," paper presented at the United States-Mexico Border Public Health Association, Monterrey, Mexico, Apr. 28, 1986.
2. Aidala, J., *Pesticide Regulation: Legislative Debate About FIFRA in 1986* (Washington, DC: Congressional Research Service, 1987).
3. Alliance of American Insurers, *Handbook of Organic Industrial Solvents, 6th cd., 1987, pp.* 1-20.
4. Anger, W. K., *Neurobehavioral Toxicology, Z.* Annau (cd,) (Baltimore, MD: Johns Hopkins University Press, 1986).
5. Anger, W. K., and Johnson, B. L., "chemicals Affecting Behavior," *Neurotoxicity of Industrial and Commercial Chemicals,* vol. 1, J.L. O'Donoghue (cd.) (Boca Raton, FL: CRC Press, 1985).
6. Annest, J. L., Mahaffey, K.R., Cos, D.H., et al., "Blood Lead Levels for Persons 6 Months to 74 Years of Age," *NCHS Advanced Data 79,* 1982.

7. "Apple Grower Says Chemicals Sometimes Needed When All Else Fails," Associated Press, Apr. 3, 1989.
8. Association of Schools of Public Health and National Institute for Occupational Safety and Health, *Proposed National Strategies for the Prevention of Leading Wrote-Related Diseases and Injuries,* part 2, 1988.
9. Baker, E. L., Bus, J. S., Cranmer, J. M., et al., "Workshop on Neurobehavioral Effects of Solvents, Consensus Summary, *Neurotoxicofogy 6:99-*102, 1985.
10. Barnes, J. M., "Letter," *Lancet 2:102-103, 1961.*
11. Behrens, R. H., and Dukes, D. C., "Fatal Methyl Bromide Poisoning,' *British Journal of Industrial Medicine 43:561-562, 1986.*
12. Bellinger, D., Leviton, A., Waternaux, C., et al., "Longitudinal Analyses of prenatal and Postnatal Lead Exposure and Early Cognitive Development," New *England Journal of Medicine 316: 1037-1043, 1987.*
13. Bidstrup, P. L., "Letter," *Lancet* 2:103, 1961.
14. Bignami, G., and Gatte, G.L., "Neurotoxicity of Anticholinesterase Agents: Antagonistic Actions of Various Centrally Acting Drugs," *Proceedings of the European Society to Study Drug Toxicity 8:93-106, 1967.*
15. Billick, I. H., Curran, A, S., Shier, D. R., et al., "Relationship of Pediatric Blood Lead Levels to Lead in Gasoline,' *Environmental Health Perspectives 34:213-217, 1980.*
16. Bondy, S. C., "The Neurotoxicity of Organic and Inorganic bad, ' *Metal Neurotoxicity, S.C.* Bondy and K.N. Prasad (eds.) (Boca Raton, FL: CRC Press, 1988).
17. Bowers, M. B., Goodman, E. M., and Sire, V. M., "Some Behavioral Changes in Man Following Anticholinesterase Administration," *Journal of Nervous and Mental Disorders 138:383-389, 1964.*
18. Braceland, F. J., "Mental Symptoms Following Carbon Disulfide Absorption and Intoxication," *Annals of Internal Medicine 16:246-261, 1942.*
19. Burkart, J.A., Gehrich, J. L., Smith, T.J., et al., *Assessment of Measurement Techniques for Worker Exposure to Pesticides,* NIOSH contract 210-76-0153 (Cincinnati, OH: National Institute for Occupational Safety and Health, 1978).
20. Buxton, P. H., and Hayward, M., "Polyneuritis Cranialis Associated With Industrial Trichloroethylene Exposure, " *Journal of Neurology, Neurosurgery and Psychiatry 30:511,* 1967.
21. Byers, R. K., '' Introduction,' Low *Level Lead Exposure: The Clinical Implications of Current Research,* H.L. Needleman (cd.) (New York, NY: Raven Press, 1980).
22. Byers, R.K., and Lord, E., "Late Effects of Lead Poisoning on Mental Development," *American Journal of Diseases of Children 66:471-494, 1943.*
23. California Department of Food and Agriculture, Worker Health and Safety Branch, *Summary of Illnesses and Injuries Reported in California by Physicians as Potentially Related to Pesticides for 2986* (Sacramento, CA: 1988).
24. Can Manufacturers Institute, Washington, DC, personal communication, June 1989.
25. Castleman, B. I., and Ziem, G.E., "Corporate Influence on Threshold Limit Values, " *American Journal of Industrial Medicine 13:531-559, 1988.*
26. Center for Science in the Public Interest, "Petition To Develop Testing Methods To Assess Neurotoxic and Neurobehavioral Effects of Pesticide Active and Inert Ingredients, ' testimony by Michael F. Jacobson, before the U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances, Scientific Advisory Panel, FIFRA subpanel, Oct. 13, 1987.
27. Cherniak, M. G., "Organophosphorus Esters and Polyneuropathy," *Annals of Internal Medicine 104:264-266, 1986.*
28. Christofferson, J.O., Schultz, A., Ahlgren, L., et al., "Lead in Finger-Bone Analyzed In Vivo in Active and Retired Lead Workers, " *American Journal of Industrial Medicine 6:447-457, 1984.*
29. Clark, G., "Organophosphate Pesticide and Behavior: A Review, " *Aerospace Medicine 42:735-740, 1971.*
30. Corwin, E., "On Getting the Lead Out of Food," *FDA Consumer,* pp. 19-21, March 1982.
31. Coye, M.J., "The Health Effects of Agricultural Production: I. The Health of Agricultural Workers," *Journal of Public Health Policy 6:349-370, 1985.*
32. Cranmer, J., and Goldberg, L. (eds.), "Proceedings of the Workshop on Neurobehavioral Effects of Solvents," *Neurotoxicology 7:45-56, 1987.*
33. Davis, J. M., and Svendsgaard, D.J., "Lead and Child Development," *Nature 329:297-300, 1987.*
34. *Desi,* I., ''Neurotoxicological Investigation of Pesticides in Animal Experiments, " *Neurobehavioral Toxicology and Teratology 5:503-515, 1983.*
35. Dick, R. B., ''Short Duration Exposures to Organic Solvents: The Relationship Between Neurobehavioral Test Results and Other Indicators, ' *Neurotoxicology and Teratology 10:39-50, 1988.*
36. Dine, J. R., and Smith, P. W., "Central Nervous System Effects of Chronic Exposure to Organophosphate Insecticides," *Aerospace Medicine 35:475-478, 1964.*
37. Dougherty, J., toxicologist, Office of Pesticide Programs, Health Effects Division, Environmental

Protection Agency, personal communication, Nov. 13, 1989.
38. Durham, W.F., Wolfe, H.R., and Quinby, G.E., 'Organophosphorous Insecticides and Mental Alertness," *Archives of Environmental Health 10:55-66, 1965.*
39. Duston, D., "Eight in 10 Americans Prefer Chemical Free Food; Half Would Pay More, " Associated Press, Mar. 19, 1989.
40. Duston, D., "Hotline Helps Growers Find Alternatives to Pesticides," Associated Press, Mar. 22, 1989.
41. Ecobichon, D.J., and Joy, R. M., *Pesticides and Neurological Diseases* (Boca Raton, FL: CRC Press, 1982).
42. Elias, R., biologist, Environmental Criterion Assessment Office, Environmental Protection Agency, personal communication, May 2, 1989.
43. Emmet, E.A., "Parosmia and Hyposmia Induced by Solvent Exposure," *British Journal of Industrial Medicine 33:196-198, 1976.*
44. "Entomologists Defend Chemicals as Necessary in Food Production, " Associated Press, Mar. 25, 1989.
45. Errebo-Knudsen, E. O., and Olsen, F., "Organic Solvents and Presenile Dementia (The Painters' Syndrome) A Critical Review of the Danish Literature," *Science of the Total Environment 48:45-67, 1986.*
46. Eskenazi, B., and Maizlish, N., "Effects of Occupational Exposure to Chemicals on Neurobehavioral Functioning," *Neuropsychologica! Disorder in Medical Illness,* E.E. Tarter and D.H. Van Thiel (eds.) (New York, NY: Plenum Press, 1987).
47. "Fanners Hope to Replace Chemicals With Biological Fertilizers, " Associated Press, Apr. 3, 1989.
48. Fenske, A., and Spear, R,, "Correlation of Fluorescent Tracer Measurements of Dermal Exposure and Urinary Metabolize Excretion During Occupational Exposure to Malathion," *Journal of American Industrial Hygiene Association 49:438-444, 1988.*
49. Fidler, A.T., Baker, E.L,, and Letz, R, E,, 'Neurobehavioral Effects of Occupational Exposure to Organic Solvents Among Construction Painters, " *British Journal of Industrial Medicine 44:292-308, 1987.*
50. Fikac, P., "Consumers Union: Ask Grocers About Produce," Associated Press, Mar. 30, 1989.
51. Fischbein, A., "Enviromnental and Occupational Lead Exposure,' *Environmental and Occupational Medicine,* W.N. Rom (cd.) (Boston, MA: Little, Brown, 1983).
52. Flodin, U., Edling, C., and Axelson, O., "Clinical Studies of Psychoorganic Syndromes Among Workers With Exposure to Solvents, *American Journal of Industrial Medicine 5:287-295, 1984.*
53. Fornazzari, L., Wilkinson, D. A., Kapur, B. M., et al., ''Cerebella, Cortical and Functional Impairment in Toluene Abusers, " *Acta Neurological Scandinavia 67:319-329, 1983.*
54. Gade, A., Mortenson, E. L., and Bruhn, P., "Chronic Painter's Syndrome: A Reanalysis of Psychological Test Data in a Group of Diagnosed Cases, Based on Comparisons With Matched Controls," *Acta Neurological Scandinavia 77:293-306, 1988.*
55. Gallagher, R.P., Threlfall, W.J., Spinelli, J.J., et al., "Occupational Mortality Patterns Among British Columbia Farm Workers," *Journal of Occupational Medicine 26:906-908, 1984.*
56. Gershon, S., and Shaw, F.H., "Psychiatric Sequelae of Chronic Exposure to Organophosphorous Insecticides," Lancet 1:1371-1374, 1%1.
57. Goyer, R. A., "Toxic Effects of Metals," *Casarett and Doull's Toxicology,* C.D. Klaassen, M.O. Amdur, and J, Doull (eds.) (New York, NY: Macmillan, 1986).
58. Grasso, P., Sharratt D., Davies, D.M., et al., "Neurophysiological and Psychological **Disorders** and Occupational Exposure to Organic Solvents," *Food and Chemical Toxicity 22:819-852, 1984.*
59. Grob, D., and Harvey, A. M., "The Effects and Treatment of Nerve Gas Poisoning," *American Journal of Medicine 14:52-63, 1953.*
60. Gutewort, T., Haublein, H.G., et al., "Biochemical, Neurological, and Psychological Signs of the Effects of Styrene on Functions of the Nervous System and Liver," presented at the XIX International Congress on Occupational Health, Dubrovnik, 1978.
61. Hay, A. W.M., "Tetrachlorodibenzo-p-dioxin Release at Seveso," *Disasters 1:289, 1977.*
62. Hayes, W.J., *Pesticides Studied in Man* (Baltimore, MD: Williams & Wilkins, 1982).
63. Hine, C, H., "Methyl Bromide Poisoning,' *Journal of Occupational Medicine* 11:1-10, 1969.
,64. Hirshberg, A., and Lerman, Y., "Clinical Problems in Organophosphorus Insecticide Poisoning: The Use of a Computerized Information System," *Fundamentals of Applied Toxicology 4: S209-S214, 1984.*
65. Holmes, J. H., and Gaon, M.D., "Observations on Acute and Multiple Exposures to Anticholinesterase Agents," *Trans American Clinical Climatology Association 68:86-101, 1956.*
66. Holmstedt, B., ''Prolegomem to Seveso: Ecclesiastes I: 18," *Archives of Toxicology 44:211, 1980.*
67. "House Staffers Scrap Lead Standard to Speed Drinking Water Bill's Passage," *Inside EPA 9:6, 1988.*
68. Huff, J. E., Moore, J. A., Saracci, R., et al., "Long-term Hazards of Polychlorinated Dibenzodioxins

and Polychlorinated Dibenzofurans, *Environmental Health Perspectives 36:221, 1980.*

69. Jeyaratnam, J., "Health Problems of Pesticide Usage in the Third World," *British Journal of Industrial Medicine 42:505-506, 1985.*
70. Johnson, M.K., ''The Mechanism of Delayed Neuropathy Caused by Some Organophosphorus Esters: Using the Understanding To Improve Safety," *Journal of Environmental Science and Health B15:823-841, 1980.*
71. Karczmar, A. G., "Acute and Long Lasting Central Action of Organophosphorus Agents,' *Fundarnentals of Applied Toxicology 4: S1-S17, 1984.*
72. Klaassen, C. D., Amdur, M. O., and Doull, J. (eds.), *Casarett and Doull's Toxicology (New* York, NY: Macmillan, 1986).
73. Korsak, R.J., and Sate, M. M., "Effect of Chronic Organophosphate Pesticide Exposure on the Central Nervous System," *Clinical Toxicology 11:83-95, 1977.*
74. Krigman, M. R,, Bouldin, T.W., and Mushak, P., "had," *Experimental and Clinical Neurotoxicology,* P.S. Spencer and H.H. Schaurnburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980).
75. "Landrigan Calls OSHA Standard Success: Warns on Construction Industry Exposures, ' *Chemical Regulation Reporter 12:1529-1530, 1989.*
76. Landrigan, P.J., "The Incompletely Studied Hazards of Waste Incineration," *American Journal of Industrial Medicine 15:243-244, 1989.*
77. Landrigan, P. J., "Strategies for Epidemiologic Studies of I-cad in Bone in Occupational Exposure Populations," *Environmental Health Perspectives,* in press.
78. Lazar, R. B., Ho, S. U., Melen, O., et al., "Multifocal Central Nervous System Damage Caused by Toluene Abuse," *Neurology 33:1337-1340, 1983.*
79. Lazerew, N. W., "Toxicity of Various Hydrocarbon Vapors," *Naunyn-Schmiedebergs Archiv Fur Experirnentelle Pathologic und Pharmakologic 143:223-233, 1929.*
80. Lazerew, N. W., and Kramneva, S. N., "Berkungen Uber Die Giftigkeit Der Darnpfe Des Zyklopentans und Siener Homogen, ' *Naunyn-Schniedebergs Archiv Fur Experimentelie Pathologic und Pharmacologic 149:1 16-118, 1930.*
81. *htz,* G. A., Pond, S. M., Osterloh, J. D., et al., "Two Fatalities After Acute Occupational Exposure to Ethylene Dibromide," *Journal of the American Medical Association 252:2428-2431, 1984.*
82. I..evin, H. S., and Rodnitzky, R. L., "Behavioral Effects of Organophosphate Pesticides in Man," *Clinical Toxicology 9:391-405, 1976.*
83. bvin, H. S., Rodnitzky, R. L., and Mick, D. L., "Anxiety Associated With Exposure to Organophosphate Compounds,' *Archives of General Psychiatry 33:225-228, 1976.*
84. Levin, R., senior water analyst, Environmental Protection Agency, personal communication, June 12, 1989.
85. Lin-Fu, J. S., "Lead Poisoning and Undue Lead Exposure in Children: History and Current Status," Low Level Lead *Exposure: The Clinical Implications of Current Research,* H.L. Needleman (cd.) (New York, NY: Raven Press, 1980).
86. McCarthy, J. E., *Waste Management,* CRS Issue Brief (Washington, DC: Congressional Research Service, 1989).
87. McMichael, A.J., Baghurst, P. A., Wigg, N. R., et al., ''Port Pirie Cohort Study: Environmental Exposure to Lead and Children's Abilities at the Age of Four Years,' *New England Journal of Medicine 319:468-475, 1988.*
88. Magnotti, R. A., Dowling, K., Eberly, J., et al., "Field Measurement of Plasma and Erythrocyte Cholinesterases,' *Clinica Chimica Acta 176:315-332, 1988.*
89. Magos, L., ''The Clinical and Experimental Aspects of Carbon Disulfide Intoxication, " *Reviews on Environmental Health 2(1):65-80, 1975.*
90. Maizlish, N., Schenker, M., Weisskopf, C,, et al., ''A Behavioral Evaluation of Pest Control Workers With Short-Term, Low-Level Exposure to the Organophosphate Diazinon, " *American Journal of Industrial Medicine 12:153-172, 1987.*
91. Major, R. H,, "Some Landmarks in the History of Lead Poisoning, '' *Annals of Medical History 3:218-227, 1931.*
92. Mancuso, T. F., and Locke,B.Z.,''Carbon Disulfide as a Cause of Suicide, Epidemiological Study of Viscose Rayon Workers,' *Journal of Occupational Medicine 14:595-606, 1972.*
93. Marshall, E., "Science Advisers Need Advice," *Science 245:20-22 1989.*
94. Mergler, D., "Solvent Related Color Vision Imss: An Indicator of Acural Darnage?" *lnternational Archives of Occupational and Environmental Health 59:313-321, 1987.*
95. Mengan, W. H., Wood, R.W., Zehl, D., et al., "Carbon Disulfide Effects on the Visual System, I. Visual Thresholds and Ophthalmoscopy," *Investigative Ophthalmology and Visual Science 29:512-518, 1988.*
96. Merrill, S., Simpson, M. M., and Johnson, W., *Lead Exposure: Health Effects, Regulatory Actions, and Congressional Options* (Washington, DC: Congressional Research Service, 1984).
97. Metcalf, D. R., and Holmes J. H., "EEG, Psychological and Neurological Alterations in Humans With Organophosphate Exposure," *Annals of the New York Academy of Science 160:375-385, 1%9.*

98. Midtling, J. E., Barnet, P. G., Coyle, M.J., et al., "Clinical Management of Field Worker Organophosphate Poisoning," *Western Journal of* Medicine 142:514-518, 1985.
99. Milham, S., "Occupational Mortality in Washington State 1950-1979, " U.S. DHHS (NIOSH) ccmtract No. 210-80-0088, 1983.
100. Monmaney, T., "The Dangers in Dinnerware: Gauging the Lead Threat," *Newsweek,* Oct. 31, 1988, p. 66.
101. Morgan, D.P., *Recognition and Management of Pesticide Poisoning,* EPA pub. No. 540/9-88-001 (Washington, DC: U.S. Government Printing Office, 1989).
102. Moses, M., "Pesticides," *Environmental and Occupational Medicine,* W.N. Rom (cd.) (Boston, MA: Little, Brown, 1983),
103. Moses, M., "Pesticide-Related Health Problems and Farmworkers,' *American Association of Occupational Health Nurses Journal 37:1 15-130, 1989.*
104. Mueller, W., "lPM's Future," *Agrichemical Age 10:22-23, 1988.*
105. Murphy, R. V., acting chief, Pesticides and Toxics Branch, Environmental Protection Agency, Region VI, Dallas, TX, personal communication to Ellen Widess, June 10, 1988.
106. Murphy, S., "Pesticides," *Casarett and J. Doull's Toxicology,* C.D. Klaassen, M.O. Amdur, and J. Doull (eds.) (New York, NY: Macmillan, 1986).
107. Naj, A. K., "Panel Assails Pesticide Study, Calls Food Safe, " *Wail Street Journal,* Apr. 6, 1989, sec. B, p. 3.
108. National Academy of Sciences, *Toxicity Testing: Strategies To Determine Needs and Priorities* (Washington, DC: National Academy Press, 1984).
109. National Academy of Sciences, National Research Council, Lead *in the Human Environment* (Washington, DC: National Academy Press, 1980).
110. National Academy of Sciences, National Research Council, *Alternative Agriculture* (Washington, DC: National Academy Press, 1989).
111. National Center for Education in Maternal and Child Health, *Childhood Lead Poisoning Prevention: A Resource Directory* (Washington, DC: 1989).
112. *National Coalition Against the Misuse of Pesticides v. EPA,* U.S. Court of Appeals, District of Columbia circuit [case No. 88-5147], 1989.
113. National Institute on Drug Abuse, *National Trends in Drug Use and Related Factors Among American High School Students and Young Adults, 1975-1987,* DHHS pub. NO. (ADM) 89-1638 (Washington, DC: U.S. Government Printing Office, 1988).
114, Natural Resources Defense Council, *Intolerable Risk: Pesticides in Our Children's Food* (Washington, DC: 1989).
115. Nazario, S. L., "Big Firms Get High on Organic Farming: Pesticide Scare Reinforces Shift in Techniques," *Wall Street Journal,* Mar, 21, 1989,
116. Needleman, H. L,, ''The Persistent Threat of Ixmd: A Singular Opportunity," *American Journal of Public Health 79:643-645, 1989.*
117. Needleman, H.L. (cd.), Low Level *Lead Exposure: The Clinical Implications of Current Research (New* York, NY: Raven Press, 1980).
118. Needleman, H. L., and Bellinger, D., "The Develop mental Consequences of Childhood Exposure to Lead: Recent Studies and Methodological Issues," Advances *in Clinical Child Psychology,* vol. *7,* B,B, Lahey and A.E. Kazdin (eds.) (New York, NY: Plenum Press, 1984).
119. Needleman, H. L., Gunnoe, C., Leviton, A., et al., "Deficits in Psychologic and Classroom Performance of Children With Elevated Dentine Lead *Levels,''NewEnglandJournal of Medicine 300:689-695, 1979.*
120. Needleman, H. L., Leviton, A., and Bellinger, D., "had-Associated Intellectual Deficit" New *England Journal of Medicine 306:367, 1982.*
121. ''NIEHS Meeting Highlights Research on Neurobehavioral Effects of bad, " *Chemical Regulation Reporter 12:1528-1529, 1989.*
122. Oliver, T., *Dangerous Trades* (London: Murray, 1902).
123. Otto, D., Robinson, G., Baumann, S., et al., "Five-year Follow-up Study of Children With Low-to-Moderate Lead Absorption: Electrophysiological Evaluation," *Environmental Research 38: 168-186, 1985.*
124. "Pesticide Scares Fuel Already Growing Organic Food Popularity,' ' Associated Press, Apr. 10,1989.
125. Pirkle, J. L., Schwartz, J., Landis J. R., et al., "The Relationship Between Blood Lead Levels and Blood Pressure and Its Cardiovascular Risk Implications, " *American Journal of Epidemiology 121: 246-258, 1985.*
126. Pocock, S. J., Shaper, A. G., Ashby, D., et al., "The Relationship Between Blood Lead, Blood Pressure, Stroke, and Heart Attacks in Middle-Aged British Men, " *Environmental Health Perspectives 78:23-30, 1988.*
127. Politis, M. J., Schaumberg, H. H,, and Spencer, P. S., "Neurotoxicity of Selected Chemicals," *Experimental and Clinical Neurotoxicoiogy* (Baltimore, MD: Williams & Wilkins, 1980).
128. Pryor, G. T., Dickinson, J., Feeney, E., et al,, "Hearing Loss in Rats First Exposed to Toluene as Weanlings or Young Adults, " *Neurobehavioral Toxicology and Teratology 6:1 11-1* 19a, 1984.
129. Pryor, G. T., Howd, R, A., Malik, R., et al., "Biomedical Studies on the Effects of Abused Inhalant Mixtures, annual progress report No. 2, NIDA

contract No. 271-77-3402 (1978), pp. 62-67, 97-

130. Pryor, G. T., Rebert, C. S., Dickinson, J., et al., ''Factors Affecting Toluene-Induced Ototoxicity in Rats," *Neurobehavioral Toxicology and Teratology* 6:223 -238b, 1984.
131. Public Health Foundation, *Special Report: State Health Agency Lead Poisoning Prevention Activities, 1983* (Washington, DC: 1986).
132. Radimer, G. F., Davis, J.H., and Ackerman, A. B., "Fumigant-Induced Toxic Epidermal Necrolysis," *Archives of Dermatology 110:103-104, 1974.*
133. Rebert, C. S., Sorenson, S. S., et al., "Toluene-Induced Hearing Loss in Rats Evidenced by the Brainstem Auditory-Evoked Response," *Neurobehavioral Toxicology and Teratology 5:59-62, 1983.*
134. *Recommended Design for an Annual Survey of Hospital TreatedPesticide Poisonings, RTI/3094110-12F* (Research Triangle Park, NC: Research Triangle Institute, 1986).
135. Redhead, I. H., "Poisoning on the Farm," *Lancet* 1:686-688, 1968.
136. Reich, G. A., and Berner, W. H., "Aerial Application Accidents, 1963 -1965," *Archives of Environmental Health 17:776-784, 1968.*
137. Rodnitzky, R. L., Levin, H. S., and Mick, D. L., "Occupational Exposure to Organophosphate Pesticides: A Neurobehavioral Study," *Archives of Environmental Health 30:98-103, 1975.*
138(Rosenberg, N. L., Kleinschrnidt-DeMasters, B. K., Davis, K.A., et al., "Toluene Abuse Causes Diffuse Central Nervous System White Matter Changes," *Annuls of Neurology 23:61 1-614, 1988.*
139. Samuels, S., Industrial Union Department, AFL/CIO, testimony before PEL hearings at Department of Labor headquarters, Aug. 10, 1988.
140. Savage, E. P., Keefe, T. J., Mounce, L. M., et al., *Chronic Neurological Sequelae of Acute Organophosphate Pesticide Poisoning: An Epidemiologic Study, NTIS/PB86-179827 (Fort Collins, CO: Col*orado Epidemiologic Pesticide Studies Center, 1982).
141. Savage, E.P., Keefe, T.J., Mounce, L. M., et al., "Chronic Neurological Sequelae of Acute Organophosphate Pesticide Poisoning," *Archives of Environmental Health 43:38-45, 1988.*
142. Schikler, K.N., Seita, K., Rice, J. F., et al., "Solvent Abuse-Associated Cortical Atropy," *Journal of Adolescent Health Care 3:37-39, 1982.*
143. Schneider, K,, "Faking It: The Case Against Industrial Biotest," *Amicus Journal 4:14-26, 1983.*
144. Schwartz, J., "The Relationship Between Blood Lead and Blood Pressure in the NHANES II *Survey, ''Environmental Health Perspectives78:15-22, 1988.*
145. Schwartz, J., Landrigan, P., Silbergeld, E., et al., "Does had-Induced Neuropathy Exhibit a Threshold?" *Journal of Pediatrics* 112:12-17, 1988.
146. Schwartz, J., and Otto, D., "Blood Lead, Hearing Thresholds, and Neurobehavioral Development in Children and Youth," *Archives of Environmental Health 42:153-160, 1987.*
147. Sharp, D. S., Eskenazi, B., Harrison, R., et al., "Delayed Health Hazards of Pesticide Exposure," *Annual Review of Public Health 7441-471, 1986.*
148. Silbergeld, E. K., Schwartz, J., and Mahaffey, K., "Lead and Osteoporosis: Mobilization of lead From Bone in Postmenopausal Women,' *Environmental Research 47:79-94, 1988.*
149. Smith, P. W., and Stravinoha, W. B., "Cholinesterase Inhibition in Relation to Fitness to Fly," *Aerospace Medicine 39:754-758, 1968.*
150. Soliman, S. A., Farmer, J., and Curley, A., "Is Delayed Neurotoxicity a Property of all Organophosphorous Compounds? A Study With a Model Compound, Parathion," *Toxicology 23:267-279, 1982.*
151. *Spear,* R.C., Popendorf, W.J., Spencer, W. F., et al., "Worker Poisoning Due to Paroxon Residues," *Journal of Occupational Medicine 19:411, 1987.*
152. Spencer, P. S., Couri, D., and Schaumburg, H.H., ''n-Hexane, n-Methyl, and n-Butyl Ketone, ' *Experimental and Clinical Neurotoxicology, P.S.* Spencer and H.H. Schaumburg (eds.) (Baltimore, MD: Williams & Wilkins, 1980), pp. 456-475.
153. Stroller, A., Krupinski, J., Christopher, A.J., et al., "Organophosphorus Pesticides and Major Mental Illness: An Epidemiologica.1 Investigation, " *Lancet 1:1387-1388, 1965.*
154. Stubbs, H. A., Harris, J., and Spear, R.C., "A Proportionate Mortality Analysis of California Agricultural Workers, 1978 -1979," *American Journal of Industrial Medicine 6:305-320, 1984.*
155. Tabershaw, I. R., and Cooper, W. C., "Sequelae of Acute Organic Phosphate Poisoning," *Journal of Occupational Medicine 8:5-20, 1966.*
156. Taylor, J.R., SelhorsL J.B., Houff, S.A., et al., "Chlordecone Intoxication in Man," *Neurology 28:626-630, 1978.*
157. Thrupp, L., "Pesticides and Policies—Approaches to Pesticide Dilemmas in Nicaragua and Costa Rica," *Latin American Perspectives 15(59):37-70, 1988.*
158. Triebig, G., Bleecker, M., Gilioli, R., et al., "Congress Report, International Working Group on the Epidemiology of the Chronic Neurobehavioral Effects of Organic Solvents, " *International Archives of Occupational and Environmental Health 61 :423-424, 1989.*
159. Tsuruta, H., ''Percutaneous Absorption of Organic Solvents: Comparative Study of the In Vivo Percutaneous Absorption of Chlorinated Solvents in Mice," *Industrial Health 13:227-236, 1975.*

160. U.S. Congress, Committee on Energy and Commerce, Subcommittee on Health and the Environment *Lead Contamination* (Washington, DC: U.S. Government Printing Office, 1988).
161. U.S. Congress, Office of Technology Assessment *Technology, Public Policy, and the Changing Structure of American Agriculture, OTA-F-285* (Washington, DC: U.S. Government Printing Office, March 1986).
162. U.S. Congress, Office of Technology Assessment "Comparison of Serum Levels of 2,3,7,8-TCD With Indirect Estimates of Agent Orange Exposure in Vietnam Veterans, staff paper, Washington, DC, September 1987.
163. U.S. Congress, Senate Environment and Public Works Committee, "EPA Pesticide Panel in Potential Conflict: Science Advisory Panel Linked to Chemical Industry: Reid, Lieberman Call for Investigation," press release No. 89-116, May 15, 1989,
164. U.S. Department of Health and Human Services, 1978 *Migrant Health Program Target Population Estimates* (Rockville, MD: Health Services Administration, Bureau of Community Health Services, April 1980).
165. U.S. Department of Health and Human Services, *The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress* (Washington, DC: Public Health Service, Agency for Toxic Substances and Disease Registry, 1988).
166. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, "Organic Solvent Neurotoxicity," *Current Intelligence Bulletin 48: 1-39,1987.*
167. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Division of Standards development and Technology Transfer, "Organic Solvents in the Workplace," *Journal of the American Medical Association 257:3198, 1987.*
168. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry and Center for Environmental Health and Injury Control, "Childhood Lead Poisoning-United States: Report to the Congress by the Agency for Toxic Substances and Disease Registry, ' *Morbidity and Mortality Weekly Report 37:481-485, 1988.*
169. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, *Preventing Lead Poisoning in Young Children: A Statement by the Centers for Disease Control* (Atlanta, GA: 1985).
170. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Food Safety and Applied Nutrition, *FDA Total Diet Study* (Washington, DC: 1989).
171. U.S. Environmental Protection Agency, *Reducing Lead in Drinking Water: A Benefit Analysis* (Washington, DC: U.S. Government Printing Office, 1986).
172. U.S. Environmental Protection Agency, "Drinking Water Regulations; Maximum Contaminant Level Goals and National Primary Drinking Water Regulations for Lead and Copper; Proposed Rules" (53 FR 31565), 1988.
173. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, *Air Quality Criteria for Lead,* vols. I-IV (Washington, DC: U.S. Government Printing Office, 1986).
174. U.S. Environmental Protection Agency, Office of Pesticide programs, *Pesticide Industry Sales and Usage: 1987 Market Estimates* (Washington, DC: 1988).
175. U.S. Environmental Protection Agency, Office of Policy Analysis, *Costs and Benefits of Reducing Lead in Gasoline: Final Regulatory Analysis* EPA-230-05-85-006 (Washington, DC: U.S. Government Printing Office 1985).
176. U.S. Environmental Protection Agency, Office of Public Affairs, "EPA Proposes New Worker-Protection Standards for Agricultural Pesticides," press release, June 29, 1988.
177. U.S. Environmental Protection Agency, Office of Research and Development, *Research Summary: Integrated Pest Management, EPA-600/8-80-044* (Washington, DC: 1980).
178. U.S. General Accounting Office, *Pesticides: EPA's Formidable Task To Assess and Regulate Their Risks, GAO/RCED-86-125* (Washington, DC: U.S. Government Printing Office, 1986).
179. U.S. General Accounting Office, Health and Human Resources Division, *Maternal and Child Health Block Grant: Program Changes Emerging Under State Administration* (Washington, DC: U.S. Government Printing Office, 1984).
180. *U.S. Steelworkers of America v. Marshall, 647 F.2d* 1189 (D.C. Cir. 1980).
181. Waldron, H., "Lead Poisoning in the Ancient World," *Medical History 17:391-398, 1973.*
182. Wallace, D. M., Kalman, D.A., and Bird, T. D., "Hazardous Lead Release From Glazed Dinnerware: A Cautionary Note," *Science of the Total Environment 44;289-292, 1985.*
183. Weiss, B., and Clarkson, T. W., "Toxic Chemical Disasters and the Implications of Bhopal for Technology Transfer, ' *The Milbank Quarterly 64:216, 1986.*
184. Whorton, M.D., and Obrinsky, D.L., "Persistence of Symptoms After Mild to Moderate Acute Organophosphate Poisoning Among 19 Farm Field Workers, " *Journal of Toxicology and Environmental Health* 11:347-354, 1983.

185. Widess, E., "Neurotoxic Pesticides and the Farmworker," prepared for the Office of Technology Assessment, Washington, DC, December 1988.
186. Wielopolski, L., Rosen, J.F., Slatkin, D.N., et al., ''Feasibility of Noninvasive Analysis of Lead in the Human Tibia by Soft X-ray Fluorescence," *Medical Physics 10:248-251, 1983.*
187. Wilk, V. A., "Occupational Exposure, " *The Pesticides Crisis: A Blueprint for States, T.* Adams and J. Tryens (eds.) (Washington, DC: National Center for Policy Alternatives, 1988).
188. Witcoff, H., and Reuben, B., "Solvents,' *Industrial Organic Chemicals in Perspective-Part Two: Technology, Formulation, and Use (New* York, NY: John Wiley & Sons, 1980), pp. 280-303.
189. Wolthuis, O. L., and Vanwersch, R.A.P., "Behavioral Changes in the Rat After Low Doses of Cholinesterase Inhibitors," *Fundamental and Applied Toxicology 4: S195-S208, 1984.*
190. Wood, R., "Neurobehavioral Toxicity of Carbon Disulfide," *Neurobehavioral Toxicology and Teratology 3:397-405, 1981.*
191. Wood, W.W., Brown, H. W., Watson, M., et al., "Implication of Organophosphate Pesticide Poisoning in the Plane Crash of a Duster Pilot" *Aerospace Medicine 42:111 1-1113, 1971.*
192. World Health Organization, *Safe Use of Pesticides,* Technical Report Series No. 9 (Geneva: 1973).
193. World Health Organization, *Principles and Methods for the Assessment of Neurotoxicity Associated With Exposure to Chemicals,* Environmental Health Criteria 60 (Geneva: 1986).
194. Xintaras, C., Burg, J.B., TanaluL S., et al., NIOSH *Health Survey of VelsicolPesticide Workers, NIOSH* pub. No. 78-136 (Washington, DC: U.S. Government Printing Office, 1978).
195. Young, B.B., "Neurotoxicity of Pesticides," *Journal of Pesticide Reform 6:8-11, 1986.*

Appendixes

Appendix A
The Food Additive Approval Process: A Case Study

The primary responsibility of the Food and Drug Administration (FDA) is to ensure that the food and drugs Americans consume and the medical devices and cosmetics they use are safe. In so doing, it ties not to deny or delay unnecessarily Americans' access to new or more affordable foods, food additives, and therapeutics. To illustrate how FDA's review procedures work, this case study discusses the approval process for aspartame, a food additive for which questions about possible neurotoxic effects were raised.

Aspartame, more commonly known as Nutrasweet, is an artificial sweetener that is used by more than 100 million people (3). Users include persons with a medical need to reduce sugar intake, such as diabetics and obese individuals, as well as the general population. The sweetener is composed of phenylalanine and aspartic acid, two naturally occurring amino acids. Aspartame's extreme sweetness, 180 to 200 times that of sugar, was discovered serendipitously in 1965 by two G.D. Searle Corp. scientists, 8 years before submission of the first food additive petition for the compound, After aspartame's approval as an additive, the amount added to foods increased substantially each year until 1985, when it appeared to reach a plateau. Approximately 75 percent of all the aspartame used in the United States is used in carbonated diet beverages. An ongoing dietary survey of aspartame ingestion undertaken by FDA indicates that 35 percent of the population (40 percent of adults) are regular users of aspartame.

The Application Process

preapplication

The first step in the food additive approval process, an informal meeting with FDA staff, is optional. The staff of the Center for Food Safety and Applied Nutrition (CFSAN) encourage applicants to discuss with them the nature of the compound, available animal toxicity data and uses for which approval is sought before formally submitting a petition. In these meetings, potential problems can be identified, enabling applicants to begin any necessary research quickly. Although both CFSAN and the Center for Drugs and Biologics encourage these meetings, they occur much more frequently with drug-licensing applications, where problems are often more evident. G.D. Searle did meet informally with CFSAN staff before submitting its petition in February 1973.

Application

Searle petitioned FDA for permission to market aspartame as an additive for certain foods (38 FR 5921). Section 409 of the Federal Food, Drug, and Cosmetic Act requires FDA to evaluate and act on petitions for approval of food additives. Petitions are evaluated for toxicology, chemistry, probable consumption levels, and potential environmental and health impact. The applicable safety standard is the "reasonable certainty of no harm, " and the burden of proof is on the petitioner. This standard is less stringent than that for new drugs, which must be proven ''safe and effective" in human studies.

The Act does not require specific tests to measure the neurotoxic potential of any compound, and FDA generally assumes that adverse neurobehavioral effects will become apparent during routine toxicological studies in animals. However, if neurotoxic potential is suspected because a substance is structurally similar to a known neurotoxic substance or for any other reason, FDA may specifically require a neurotoxicological evaluation. Normally, only animal toxicity (preclinical) studies are required for foods and food additives. In contrast, new drug approval requires that the results from three phases of human studies be submitted for review.

Review

Following receipt of a petition, FDA personnel identify the types of reviews appropriate for the particular application. Reviews are frequently solicited from FDA staff in other divisions with relevant expertise.

Every application is reviewed for potential toxicity. The ancient Roman credo "moderation in all things" is the first principle of toxicology. Virtually every food and chemical in existence can be toxic in excessive quantities; therefore, the first step is to assess the chemical to which humans will be exposed and estimate the degree of exposure. This is done by testing what happens when the food additive is administered to laboratory-grown mammalian cell lines and animals and by analyzing the chemistry of the compound, including identifying the additive and products of its metabolic breakdown and estimating the likely level of human exposure. These studies identify the types of toxicity caused by the compound and determine the amounts required to produce the toxic effects.

Initially, concerns were raised that aspartame might lead to significantly higher concentrations of phenylalanine in the blood, which could lead to mental retardation in children with the genetic disease phenylketonuria (PKU). One in every 50 to 70 Americans carries the gene for PKU, and every year 200 children are born with this disease (1 of every 14,000 to 15,000 live births). PKU results only if a child has two copies of the gene, one from each parent. Fortunately, if PKU is identified at birth, mental retardation can be prevented by a diet that is restricted in phenylalanine. By law, all newborn babies in the United States must be tested for PKU.

Approval

Toxicological studies on animal models were determined to be sufficient, and Searle's petition to add aspartame to some foods was approved on July 26, 1974 (39 FR 27317-27319). It was approved for consumer use as a dry sugar substitute in granular and tablet form and for industry use as an addition to cold breakfast cereals, chewing gum, and dry bases for beverages, instant coffee and tea, gelatins, puddings, fillings, and nondairy toppings.

The toxicity research on which approval was based included 2-year feeding studies in rats and dogs as well as a lifetime feeding study in rats first exposed to aspartame as fetuses. Based on these studies, a no observed effect level (NOEL), or the largest amount of the additive that could be administered without evidence of toxicity in animals, was established-namely, 2 grams of aspartame per kilogram of body weight. The acceptable daily intake for humans is somewhat arbitrarily set at 100 times less than the NOEL for animals, thus the acceptable daily intake was set at 50 milligrams of aspartame per kilogram of body weight per day. For a 140-pound man, this is the equivalent of approximately 17 (12-ounce) diet sodas or 100 packets of coffee sweetener per day (4). Estimates of the probable maximum daily intake (1.3 to 1.7 grams) were sufficiently close to the acceptable daily intake to permit product approval. The petitioner submitted data from clinical (human) studies which showed that the approved levels of aspartame would not elevate concentrations of phenylalanine in the blood.

Appeal

Two parties objected to the approval of aspartame on grounds of questionable safety and, as is their right, requested a hearing before a judge. However, because of the scientific controversy surrounding the approval process, FDA decided instead to convene a Public Board of Inquiry (15). The board, consisting of three experts appointed by the FDA Commissioner, would hear evidence and make a recommendation to the Commissioner, who would then make the final decision. The board was asked to consider whether aspartame, alone or in combination with glutamate, an amino acid found in monosodium glutamate (MSG), could contribute to brain damage or mental retardation. In addition, if marketing approval were recommended, the board was to suggest appropriate labeling and use restrictions. In response to an additional objection, the board also evaluated evidence that aspartame ingestion resulted in cancer in rats. (The Delaney clause prohibits approval of any food or additive that is shown to be carcinogenic in animals following appropriate testing. If carcinogenic potential is demonstrated, the clause mandates that no level of usage for humans can be considered reasonably safe.)

Before the Public Board of Inquiry was convened, Searle voluntarily suspended plans to market aspartame, pending the resolution of an additional objection, a question about the role of diketopiperazine (DKP, a product of the metabolic breakdown of aspartame) in the development of benign growths in the uterus of female rats (5). (The eventual conclusion was that DKP did not promote the development of these benign growths.) An additional complication resulted from questions raised about the reliability of the animal testing data submitted by the petitioner. As a result, FDA stayed the approval, pending additional review and audit of the animal studies (40 FR 56907). The audit was performed both by the FDA and an independent organization, Universities Associated for Research and Education in Pathology. The process took more than a year and resulted in the conclusion that there were no discrepancies sufficiently significant to compromise the results of the studies.

This conclusion cleared the way for convening the Public Board of Inquiry in January 1980. The board was composed of three distinguished scientists with expertise in neurology, pathology, and nutrition. The role of this board, like other FDA advisory committees, was merely advisory; its conclusions were not binding on FDA, which has statutory responsibility for approval decisions. Solicitation of outside expert opinion, a regular procedure in the evaluation of drugs and biologics, occurs less often in CFSAN. This is presumably because most of their decisions are not controversial. In fact, this board was the first external advisory panel convened by CFSAN.

The panel heard 3 days of testimony, including new clinical data, from FDA staff, G.D. Searle staff, and interested scientists. To the consternation of both FDA and Searle staff, the board's report was not delivered until the fall of 1980. The new clinical data that were presented allowed the board to establish an estimate of the maximum daily intake of aspartame (34 milligrams) by an average-sized man. This step was essential for an evaluation of the toxic potential of aspartame use. The data also demonstrated that the ingestion of very large quantities of aspartame, equivalent to 12 liters of aspartame-sweetened beverage in a single sitting, raised phenylalanine concentrations in the blood to only slightly above normal [from the normal 6 to 12 micromole per deciliter of blood (uM/dl) to 20 uM/dl]. Studies of people with PKU have shown that only sustained, extremely elevated concentrations (above 100 uM/dl, or 50 uM/dl for pregnant women) are associated with developmental brain damage. This damage can be prevented by restricting dietary phenylalanine. **Therefore the board concluded, and FDA concurred, that aspartame use would not contribute to the type of brain damage associated with sustained high levels of phenylalanine in the blood. However, the board did recommend that all aspartame-containing products carry informational**

statements to alert people on phenylalanine-restricted diets.

Additional animal and clinical studies demonstrated that the products resulting from the metabolic breakdown of aspartame, alone or in combination with other dietary compounds, including glutamate, had no neurotoxic potential. Clinical studies **of possible toxicity are almost never required for the approval of foods or food additives. The aspartame application was unusual in that the sponsor voluntarily conducted clinical studies and submitted the results to** FDA during the review process. Indeed, ''extensive clinical safety studies were conducted under the (original) food additive petition with the awareness and encouragement of the FDA" in various populations with metabolic disorders (17). The resolution of questions of clinical toxicity requires that clinical studies be carried out, so these would presumably have been required by FDA even if they had not been provided by the sponsor.

The board also found, however, some questions about whether aspartame caused tumors in rats. This finding was based on an incidence of brain tumors, equivalent in the aspartame-treated and control rats, that was higher than the expected incidence of spontaneous tumors. This conclusion would result in automatic disapproval of the food additive petition, as required by the Delaney clause. FDA disputed the validity of the data and cited wide variations in the literature regarding spontaneous incidence of brain tumors in rats, as well as the lack of a statistically significant difference between the treated and control groups.

Final Approval

A decision on the merits of the aspartame application was further delayed to allow all interested parties to prepare exceptions to the findings of the board. In early March 1981, a number of FDA staff members were selected to serve as advisors to the Commissioner for this petition. This group's deliberations were perhaps hurried by Searle's intention to file suit in Federal court against the FDA for unreasonable delay (18). Searle's major concern was that its period of patent exclusivity was being significantly diminished. In 1982, the Senate passed an amendment to the Orphan Drug Act which extended the patent life of products that had experienced unusual regulatory delays in approval.

Following evaluation of additional studies on the question of whether aspartame induces tumors in rats, FDA issued its final ruling in July 1981, a year after the meeting of the board and 8,5 years after the original filing of the petition (see table A-1). The FDA report concluded



Illustrated by: Ray Driver

that there was no evidence that either aspartame or its breakdown product, DKP, contributed to the development of brain tumors in rats. This avoided the obligatory invocation of the Delaney clause,[1] FDA concluded that proper handling of foods containing aspartame would prevent this breakdown and that the consumption of a mishandled product, although possibly unsavory, would be safe.

An additional concern addressed by FDA was that methanol, a metabolize of aspartame, might cause adverse effects. A review of the data revealed that aspartame consumption resulted in the production of smaller amounts

[1] In 1977, FDA, on the basis of convincing evidence of the carcinogenic potential of saccharin in rats, had attempted to remove saccharin from the ''generally recognized as safe' list. The resultant public outcry caused Congress to specifically exempt saccharin from the requirements of the Delaney clause, but at the same time required that foods containing saccharin carry a prominent warning label (8).

Table A-l-Chronology of the Aspartame Petition Process

Date	Action
February 1973	Petition filed
July 1974	Petition approved
April 1975	Searle voluntarily suspends plans to market a response to objections
December 1975	FDA stay of approval to review and authenticate data
September 1976	Data audit initiated
December 1978	Data found acceptable
June 1979	Notice of public hearing
January 1980	Public Board of Inquiry covered
October 1980	Board report represented to FDA
January 1981	Deadline for comments on Board report
March 1981	FDA advisors to Commissioner selected
July 1981	Petition approved

SOURCE: Office of Technology Assessment, 1990.

of methanol than resulted from eating many fruits and vegetables and that this toxic potential was therefore negligible. A final concern was that aspartame, eaten alone or in combination with carbohydrates, might alter the activity of neurotransmitters. A study of infant monkeys fed large quantities of aspartame or phenylalanine continually for 9 months showed that their development and behavior were normal and that there was no evidence of seizures or irregularities in brain waves (1 1). Therefore, aspartame was finally approved as a food additive in July 1981 (46 FR 38285-38308; 40 FR 46394) and for use in carbonated beverages in July 1983 (48 FR 31376-31382).

In the case of aspartame, approval was **based on a massive amount of data derived from animal and human studies. However, the vast majority of food additive petitions are approved on the basis of animal studies alone. It has been repeatedly demonstrated that the effects of active chemicals in animals are not always predictive of their effects in humans.**

FDA has supported limited research on the development of neurobehavioral testing methods to assess potential neurotoxic effects of food additives. Indeed, a 1983 article written by FDA staff concludes with the statement:

> Within the general field of toxicological testing, the FDA Bureau of Foods views the development of behavioral teratological or neurotoxicological testing as one of the most important and urgent areas for future improvement. We await with keen interest the creation of testing paradigms that can be recommended for routine measurement of the neurotoxic potential of food additive substances (5).

Postmarketing Surveillance

Until recently, there was no formal **postmarketing, or Phase** IV, procedure for evaluating any adverse reactions to a newly approved food additive; however, aspartame's approval agreement of 1981 included the establishment of a postmarketing survey. The survey had two components: 1) a poundage survey, in which sales of aspartame to food and pharmaceutical industries were reported; and 2) a dietary survey, in which actual ingestion of aspartame by a sample population was reported. Partially in response to the publicity surrounding the approval of aspartame, FDA also established a passive system of review of consumer complaints. In 1985, FDA asked the Centers for Disease Control (CDC) to evaluate the complaints received. The CDC concluded, on the basis of interviews conducted with 517 complainants, that "although it may be that certain individuals have an unusual sensitivity to the product, these data do not provide evidence for the existence of serious, widespread, adverse health consequences attendant to the use of aspartame" (2).

A more extensive postmarketing reporting system, the Adverse Reaction Monitoring System, was implemented in July 1985 for all food additives as part of FDA's Plan for Action, Phase I. This monitoring system was strengthened in December 1985 with the publication of a "Request for Reports of Adverse Food Reactions" in the *FDA Drug Bulletin. This* announcement requested that physicians and other health professionals inform CFSAN of any severe, well-documented reactions associated with foods, food additives, or dietary practices. In the FDA Plan for Action, Phase II, announced in 1987, this system was expanded to incorporate data from other government agencies, industry, and professional organizations.

Besides monitoring adverse reactions, FDA conducted research in the postmarketing period on the safety of aspartame. A contract was awarded to Battelle Memorial Institute to evaluate the effects of altered amino acid balances on rodent brain function, with an emphasis on neurotransmitters. Also, FDA transferred funds to the National Institute of Environmental Health Sciences in February 1987 for study of the impact of amino acid imbalances on seizure thresholds and neurobehavioral function in rodents. This study is still under way, but preliminary results demonstrate that large doses of aspartame do not affect the sensory or motor functions, learning and memory, or seizure induction in rats (19). Another interagency agreement transferred funds to the Federal Aviation Administration to study the effects of aspartame on the performance of airplane pilots on a number of complex laboratory-based tests of physical and mental function.

Claims of Adverse Effects

Despite the preclinical evidence of safety, there have been numerous consumer complaints alleging that aspartame use resulted insignificant medical problems, including seizures, severe headaches, tremors, insomnia, dizziness, panic attacks, and moodiness. Many of the patients'

symptoms were reportedly reversed when use of aspartame was discontinued. In many of the anecdotal reports there may have been contributing factors, such as excessive dieting, fluid intake, and caffeine consumption. One study (partially supported by the Nutrasweet Co.) of people who claimed to get headaches following ingestion of aspartame demonstrated no difference in their headaches when they ingested aspartame or a placebo (12). However, another placebo-controlled study (in a very small number of patients) found that there was an association between aspartame ingestion and migraines for some patients (7). To date, these are the only controlled studies of the effects of aspartame on people who claim to be sensitive to it, A recent review of research on aspartame was conducted by the Nutrasweet Co., which concluded that ''available evidence confirms that, other than in individuals with homozygous phenylketonuria, who must consider aspartame as an additional source of phenykdanine, aspartame is a remarkably safe food additive" (l).

It is plausible that there may be a small portion of the population that is vulnerable to neurological side-effects following consumption of aspartame. Other "restaurant syndromes" afflicting subpopulations with unusual sensitivity include susceptibility to caffeine, MSG, red wine, and chocolate (13).

The Council on Scientific Affairs of the American Medical Association, in a report based on members' expertise and the scientific literature, concluded in 1985 that "Available evidence suggests that consumption of aspartame is safe except by individuals with homozygous phenylketonuria or other individuals needing to control their aspartame intake" (2). Similarly, in his November 3, 1987, statement to the Senate Committee on Labor and Human Resources, the FDA Commissioner expressed his confidence that no serious, reproducible adverse reactions can be associated with aspartame use. He added that widespread use of aspartame and the publicity regarding possible adverse effects would have guaranteed their identification had they existed (16). Nonetheless, he committed the FDA to continue the postmarketing monitoring of aspartame and to maintain close communication with aspartame's critics. He agreed that some people may be exquisitely sensitive to aspartame and that some people are allergic to the compound. FDA has the authority to remove substances from approved lists on the basis of new information (5). This occurred in 1970, when cyclamate was removed from the "generally recognized as safe" list.

Summary and Conclusions

Because of the continuing dispute about aspartame's safety (9), FDA's approval procedures have been the subject of careful scrutiny. The General Accounting Office and others have concluded that FDA acted entirely properly and according to established policy during the aspartame approval process, but it is not clear whether the established procedures are optimal, striking the best balance between consumer dietary wishes and public health. Critics argue that the procedures are only minimally sufficient and that products which have not been adequately tested are entering the marketplace.

Some of the safety questions emerged as a result of postmarketing passive surveillance, an activity that is optional for food additives but mandatory for drugs. In fact, this distinction between food additives and drugs is itself arbitrary. The acting director of the Bureau of Drugs recommended in an FDA memorandum (which was not issued) that ''safety evaluations of proposed new sugar substitutes be conducted as Phase I studies under the Investigational New Drug (IND) Regulations" (15), Postmarketing monitoring is nearly impossible unless the presence of additives is clearly noted on the food package. Some critics argue that, even when there are unsubstantiated anecdotal reports of toxicity due to ingestion of a food additive, people who feel they are vulnerable to these toxic effects have a right to know the identity and quantity of the suspect additive, This would allow concerned individuals to monitor their intake and would facilitate the reporting of adverse effects. Clearly, consumers cannot report an adverse effect if they are not aware of what they have ingested. This view is supported by some investigators who contend that ingestion of quantities exceeding the acceptable daily intake is possible in some individuals (such as children) and that increasing rates of consumption could lead to more frequent ingestions exceeding the acceptable daily intake (6,10). On the other hand, the Nutrasweet Co., although not opposing the labeling of all food ingredients, would not agree that sufficient scientific evidence of possible toxicity exists to warrant singling out aspartame for obligatory labeling (14).

The value of postmarketing surveillance for identification of neurotoxic effects has been demonstrated several times with new drugs; therefore, many persons argue that establishment of postmarketing surveillance-at least a passive system—should be required for all new products. Because of the difficulty of identifying and quantifying subtle neurological damage and because of the differences between the nervous systems of humans and other animals, an optimal approval process would require clinical studies.

Appendix A References

1. Butchko, H. H., and Kotsonis, F. N., "Aspartame: Review of Recent Research," *Comments in Toxicology, 1988.*
2. Council on Scientific Affairs, American Medical Association, "Aspartame, Review of Safety Issues," *Journal of the American Medical Association 254:40@* 401, 1985.

3. Dews, P. B., "Summary Report of an International Aspartame Workshop," *Food and Chemical Toxicology 25:549-552, 1987.*
4. Franz, M., "Is It Safe To Consume Aspartame During Pregnancy? A Review," *The Diabetes Educator 12:145-147, 1986.*
5. Hattan, D. G., Henry, S.H., Montgomery, S.B., et al., "Role of the Food and Drug Administration in Regulation of Neuroeffective Food Additives," *Nutrition and the Brain,* R.J. Wurtman and J.J. Wurtman (eds.) (New York, NY: Raven Press, 1983).
6. Janssen, P.J.C.M., and van der Heijden, C. A., "Aspartame: Review of Recent Environmental and Observational Data," *Toxicology 50:1-26, 1988.*
7. Koehler, S. M., and Glares, A., "The Effect of Aspartame on Migraine Headache," *Headache 28:10-*13, 1988.
8. Lecos, C., ' 'The Sweet and Sour History of Saccharin Cyclamate , . . Aspartame," *FDA Consumer 15(4):8, 1981.*
9. Maher, T. J,, and Wurtman, R. J., "Possible Neurologic Effects of Aspartame, a Widely Used Food Additive," *Environmental Health Perspectives 75:53-57, 1987.*
10. Partridge, W. M., "Potential Effects of the Dipeptide Sweetener Aspartame on the Brain," *Nutrition and the Brain,* R.J, Wurtman and J,J. Wurtman (eds.) (New York, NY: Raven Press, 1983), pp. 199-241.
11. Reynolds, W.A., Bauman, A. F., Stegink, L. D., et al., "Developmental Assessment of Infant Macaques Receiving Dietary Aspartame or Phenylalanine," *Aspartame,* L.D. Stegink and L.J. Filer, Jr. (eds.) (New York, NY: Marcel Dekker Press, 1984), pp. 405-423.
12. Schiffinan, S. S., Buckley, C. E., III, Sampson, H. A., et al., ''Aspartame and Susceptibility to Headache, ' New *England Journal of Medicine 317:1181-1185, 1987.*
13. Settipane, G. A., "The Restaurant Syndrome," New *England and Regional Allergy Proceedings 8;39-46, 1987.*
14. Shapiro, R. B., "Statement of Robert B. Shapiro, Chairman of the Board and Chief Executive Office of the Nutrasweet Company, Before the Committee on Labor and Human Resources, ' *Nutrasweet Health and Safety Concerns,* U.S. Senate hearing 100-567 (Washington, DC: U.S. Government Printing Office, 1988), pp. 412-423.
15. U.S. Congress, General Accounting Office, *Food and Drug Administration: Food Additive Approval Process Followed for Aspartame,* report to the Honorable Howard M. Metzenbaum, GAO/HRD-87-46 (Washington, DC: 1987), p. **38.**
16. U.S. Congress, Senate, *Nutrasweet Health and Safety Concerns,* hearings before the Committee on Labor and Human Resources, hearing 100-567 (Washington, DC: U.S. Government Printing Office, 1988), p. 227.
17. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, *FDA Medical Review of Clinical Safety Studies,* FAP No. 3A2885, Aug. 20, 1973,
8. U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, internal memorandum from the Acting Associate Commissioner for Health Affairs to the Commissioner, Apr. 24, 1981.
9. Young, F. E., "Statement of Frank E. Young, Commissioner, Food and Drug Administration, Before the Committee on Labor and Human Resources," *Nutrasweet-Health and Safety Concerns,* U.S. Senate hearing 100-567 (Washington, DC: U.S. Government Printing Office, 1988), pp. 74-77.

Appendix B

Workshop on Federal Interagency Coordination of Neurotoxicity Research and Regulatory Programs

Federally sponsored activities in neurotoxicology are diverse and highly decentralized. They involve more than 15 different institutes, centers, and independent agencies, such as the Environmental Protection Agency (EPA) and the Consumer Product Safety Commission (CPSC), as well as agencies in several departments, including the Department of Health and Human Services (DHHS), the Department of Energy (DOE), the Department of Labor, and the Department of Defense (DoD). Coordination of neurotoxicity research and regulatory activities tends to be informal within agencies and more formal but less extensively developed between agencies. Notable exceptions at the interagency level have included the coordinating efforts of at least two Federal organizations-the Interagency Regulatory Liaison Group and, within DHHS, the Committee to Coordinate Environmental Health and Related Programs.

Results of research into the mechanisms of neurotoxicity must be made available rapidly to risk assessors and other officials at regulatory agencies. This need is magnified by current budgetary constraints, which provide a considerable impetus for improving coordination of Federal research and regulatory activities. Improved coordination of Federal neurotoxicological research could well benefit not only the regulatory sector, but also industry and consumers.

With such considerations in mind, representatives from more than a dozen Federal organizations were convened on May 23-24, 1989, at a workshop, 'Federal Interagency Coordination of Neurotoxicity Research and Regulatory Programs," sponsored jointly by the congressional Office of Technology Assessment (OTA) and EPA (l).

Overview of Federal Neurotoxicology Research Programs

Federal research in neurotoxicology spans the spectrum from basic to targeted. Coordination of Federal research and regulatory programs in neurotoxicology varies widely—with informal communication being the dominant means, particularly among basic researchers. Much of the data developed in Federal programs-but certainly not all of it—is being made accessible by publication, through on-line computer networks, or both. However, some information, including a great deal of data developed in the private sector and furnished to Federal regulatory agencies to support drug, pesticide, and other product marketing applications, is often unavailable except through cumbersome means, such as requests via the Freedom of Information Act. Still other data submitted to Federal agencies by companies in the private sector are considered proprietary and therefore confidential. The following section provides a brief overview of Federal research and regulatory activities in this area.

Department of Health and Human Services

The responsibility for overseeing neurotoxicology-related activities within DHHS falls to the Office of the Assistant Secretary for Health. The Committee to Coordinate Environmental Health and Related Programs operates within that office.

National Institutes of Health

Several Institutes within the National Institutes of Health (NIH) sponsor a great deal, perhaps the majority, of the U.S. basic research effort in neurotoxicology. Most NIH research is investigator-initiated, and the data produced are published in the scientific literature. The principal Institutes with such programs are the National Institute on Neurological Disorders and Stroke (NINDS), the National Institute of Environmental Health Sciences (NIEHS), the National Institute on Aging (NIA), and the recently created National Institute on Deafness and other Communication Disorders (NIDCD). These Institutes support a broad range of basic studies of the nervous system, including development of model systems for the etiology of neurological diseases, particularly chronic degenerative conditions.

Neurotoxicological research within NINDS is divided into two areas of interest: exogenously applied and endogenously occurring neurotoxic agents, The action of synthetic neurotoxicants may cause damage that mimics neurodegenerative diseases. For instance, the synthetic compound MPTP, sometimes formed during the illicit synthesis of a meperidine-like drug, destroys dopamine-producing cells of the central nervous system, making the drug a powerful tool for studying Parkinson's disease. Among endogenous toxins, the reactive forms of oxygen that can damage membranes through lipid peroxidation are now being studied as possible mediators of damage when cell protective mechanisms go awry.

NIEHS, which supports the most targeted of the several NIH-sponsored neurotoxicity research programs, is now taking a "broader look" at toxicology than it did when carcinogen testing dominated its activities. The Institute conducts and supports research to identify environmental agents that may cause adverse reproductive, neurological, and other effects on human health in addition to cancer. NIEHS oversees a substantial extramural grants program in the neurotoxicology field.

The National Toxicology Program within NIEHS conducts tests of selected chemicals, including suspected neurotoxic agents, and develops databases on them.

Although the selection of chemicals for testing receives a great deal of attention, the program ' 'shouldn't be driven purely by the [chemical] nomination-based process,' said one NIEHS official. Compounds are selected on the bases of extent of human exposure, quantity produced, adequacy of existing toxicological data, and regulatory and research agency concerns regarding potential adverse effects.

Although NIEHS, EPA, and the National Institute for Occupational Safety and Health (NIOSH) have overlapping research interests and can use similar research and testing technologies, there is little direct formal interaction between the agencies, according to an official from NIEHS. The executive committee that oversees the program is composed of directors or administrators from NIEHS, the National Cancer Institute, NIOSH, the Agency for Toxic Substances and Disease Registry (ATSDR), the Food and Drug Administration (FDA), CPSC, EPA, and the Occupational Safety and Health Administration; the program is reviewed by nongovernment scientists.

Because of its mandate, NIA supports researchers investigating the "special vulnerability of the aging nervous system to toxins, '' noted an official from NIA. As with programs in NINDS, the emphasis is on "the basic neurobiology of the problem. " The Institute also sponsors epidemiological studies to identify populations with chronic exposures to toxic substances, such as aging residents of rural areas, who maybe exposed to pesticides.

Alcohol, Drug Abuse, and Mental Health Administration

The National Institute on Drug Abuse (NIDA), which is part of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), sponsors research to study the neurotoxicological effects of addictive drugs as well as drugs being developed to treat or prevent drug abuse. Researchers at NIDA are trying to determine what areas of the brain are affected by such drugs and whether their effects are reversible. FDA and NIDA have an interagency agreement to develop and validate methods of assessing the neurotoxic actions of drugs that are currently being prescribed or considered for treatment of neuropsychiatric disorders. NIDA researchers are also seeking avenues for coordinating some of their efforts with officials of the Drug Enforcement Agency, but that "gap is difficult to bridge,' according to an official from NIDA. Cooperative agreements with other Federal agencies to develop and validate neurotoxicity screening tests and a neurotoxicity database should become priority activities, noted another NIDA official.

The National Institute of Mental Health (NIMH), another agency within ADAMHA, also sponsors research on therapeutic agents that can exert neurotoxic effects on brain function. NIMH researchers are helping to develop a neurophysiological battery of tests for evaluating central nervous system impairment, particularly among patients with AIDS. Because NIMH and NIDA interact closely with the pharmaceutical industry, some neurotoxicology data they obtain may be kept confidential because it is considered proprietary information.

Centers for Disease Control

The Centers for Disease Control (CDC) act as a sentinel protecting the public health. Currently, CDC is updating its regulations for setting lead safety standards and thus is reexamining the concentrations in the blood at which this potent neurotoxic agent exerts adverse effects.

NIOSH studies a broad range of products through both intramural and extramural programs. Specifically, NIOSH considers substances to which individuals may be exposed in the workplace, including field studies of farmworkers and others exposed to pesticides. In addition, Institute researchers conduct studies using various animal models. The primary concern of the NIOSH intramural program is methods assessment.

NIOSH is participating in the National Health and Nutrition Survey, which is organized under the auspices of the National Center for Health Statistics. During the course of this study, about 6,000 people will be given three tests from the neurobehavioral evaluation system in order to develop baseline data to assess future exposures to neurotoxic agents. NIOSH is also participating with the International Program on Chemical Safety and the World Health Organization (WHO) invalidation of a neurobehavioral screening battery for rodents.

Agency for Toxic Substances and Disease Registry

Under Superfund auspices, ATSDR carries out applied research on health effects of exposures to hazardous substances, including neurotoxic agents. ATSDR is "looking at data gaps," according to an official of the Agency. By law, the Agency must make a list of the 200 most toxic substances found at Superfund sites and help determine which of them maybe toxic in general as well as neurotoxic. Officials also expect to develop a standard battery of tests that could be used not only for broad testing of the population, but also for workers and other individuals at Superfund sites who might be exposed to mixtures of neurotoxic agents. In December 1988, the ATSDR cosponsored the Third International Symposium on Neurobehavioral Methods in Occupational and Environmental Health with WHO and the Pan American Health Organization. Discussions at the symposium have helped ATSDR officials develop a list of scientific priorities.

Food and Drug Administration

FDA evaluates the adverse effects of drugs on the nervous system through its general toxicological evaluations. Such testing is designed not only to detect drugs with adverse effects on the central nervous system, but also to evaluate psychoactive drugs, which generally act directly on the nervous system. Before a drug is approved for marketing, general toxicity is evaluated by a battery of studies, ranging from short-term acute tests in several species by different routes of administration to chronic dosing studies in two species exposed at three dose levels for up to 2 years. Behavior in test animals is monitored periodically, and abnormalities are recorded. Mating, fertility, developmental abnormalities, maternal behavior, and survival are among the endpoints that are evaluated. However, officials of some agencies voiced concern that FDA's general toxicological testing approach may miss some neurotoxicological effects. Many neurotoxicologists believe that specific neurotoxicological testing is necessary to detect some adverse effects.

Elsewhere in FDA, officials are concerned about pesticides, contaminants, and additives in the food supply and how they may affect individuals of different ages, on various diets, or with other risk factors. In addition, the National Center for Toxicological Research is developing models and trying to enhance current risk assessment methods in general, as it begins to examine neurotoxic agents specifically.

Department of Energy

DOE sponsors a relatively small program to study toxic chemicals. The Department is also interested in central nervous system disorders such as Alzheimer's disease. DOE researchers typically are interested in the underlying mechanisms of such diseases. Historically, their efforts have led to the development of complex instruments for examining central nervous system functions. DOE has also conducted evaluations of Federal agency carcinogen risk assessment procedures—an exercise that could prove helpful as many agencies try to develop consistent risk assessment procedures for analyzing neurotoxic substances.

Environmental Protection Agency

EPA faces a broad mandate under several statutes in regulating neurotoxic agents. Throughout the Agency, officials are refining risk assessment methods. Other efforts focus more directly on neurotoxic substances. For instance, the Agency maintains files on hundreds of pesticides, many of which are neurotoxic. EPA sponsors a sizable research program within the Office of Research and Development, which focuses on development of methods and applied research questions, including hazard identification and characterization.

EPA is currently revising and adapting guidelines for animal tests to screen organophosphorous pesticides for neurotoxic activity. The Agency has found evidence that pesticide residues in foods cause neurotoxic effects in children, and the identification and characterization of neurotoxic pesticides is a high priority for EPA officials. An EPA Scientific Advisory Panel recommended that routine testing of pesticides include observation for signs of neurobehavioral abnormality and neuropathology.

Under Superfund legislation, EPA officials are cooperating with their counterparts at ATSDR to study chemical mixtures at toxic waste sites, where individuals may be exposed to complex mixtures of chemicals that might act synergistically on the nervous system.

In 1986, EPA established an intra-agency work group to look at substances that act as reproductive and developmental toxicants. Testing guidelines for develop mental neurotoxicity are now being drafted. According to EPA scientists, animal models have consistently proved useful for predicting human response to neurotoxic agents.

Consumer Product Safety Commission

CPSC is beginning to develop neurotoxicity guidelines for manufacturers. The Commission program is directed at developing new regulations for products such as paint thinners and art materials that may have neurotoxicological effects under certain conditions of use. Appropriate labeling to warn of hazards, advise against hazardous uses or exposures, and provide first-aid instruction is required under statutes administered by CPSC.

Although the Commission develops guidelines and regulations rather than conducting research, staff members are identifying areas where scientific research would help them better fulfill their mandate. Development of test methods for identifying toxicants that cause neurological damage after chronic low-level exposures, identification of key species differences to aid in extrapolating animal test results to appropriate endpoints in humans, and development of a better understanding of the relationship between high- and low-dose neurotoxic effects are research areas of particular interest to CPSC officials.

Department of Labor

Although charged with setting neurotoxicity health and safety standards, the Occupational Safety and Health Administration (OSHA) conducts no research of its own. Instead, scientists at NIOSH and elsewhere supply OSHA with information needed to promulgate health standards. For example, to help in regulating neurotoxic agents, OSHA officials would like to see research conducted on subclinical effects of neurotoxic substances and at what exposure levels such effects remain reversible. OSHA would also like Federal agencies to standardize means for

conducting risk assessments, develop quantitative methods for expressing subtle behavioral changes, devise simple tests to measure toxic effects on individual workers, and publish a standardized list of neurotoxic substances.

OSHA health standards become legal documents intended to ensure that employees not suffer "material impairment of health or functional capacity, ' which the courts interpret to include subclinical effects. Thus, in setting standards, OSHA can act to prevent relatively mild and reversible forms of potentially serious diseases, such as those caused by a particular neurotoxic substance. "Material impairment" can also mean workplace exposures to chemicals that cause temporary narcosis, which can lead to accidents and injuries. The courts give OSHA considerable latitude in determining "significant risk" and the consequences of resetting exposure limits to particular chemicals.

Department of Defense

DoD has carried out extensive testing of protective drugs designed to counteract neurotoxic chemical agents. Its current program involves 26 laboratories, including support of research at laboratories within NIDA. To evaluate such drugs, DoD has developed a four-part procedure for extrapolating their effects to human performance in real-world situations, noted an official from DoD. DoD has developed sophisticated performance evaluation test batteries, risk identification procedures, a computer-based task-analysis procedure, and a real-world contingency analysis package, which provides information about the use and potential neurotoxic effects of antidotes for chemical warfare agents.

Workshop Discussion Groups

Identifying Testing Needs

Although there are processes prescribed by the National Testing Program (within ATSDR) and by the Interagency Testing Committee for nominating chemicals for neurotoxicity testing and evaluation, the discussion group concluded that the processes need revising. A major difficulty in conducting evaluations that lead to a chemical's nomination is the inadequate number of people with expertise in neurotoxicology. Having more appropriately trained experts would also help in educating regulators who select chemicals for such testing. The notion that neurotoxicity is a valid endpoint for evaluating chemicals needs general reinforcement.

Moreover, the scientific criteria for defining neurotoxicity, setting priorities, and selecting chemicals, including structure-activity relationships and comparisons of chemicals and chemical classes, also should be reevaluated and strengthened. For example, the volume of production and likely extent of human exposure to a particular chemical could be taken into account when deciding whether it should be nominated for testing, an official from NIEHS noted.

Thus, establishment of an independent advisory group of experienced individuals to better define neurotoxicity, to evaluate the nomination process, to review chemicals going through it, and to act as an information "resource" seems warranted, the discussion group concluded. If established, such an advisory group would not "sup plant' the regulatory agency, but would help 'sanction" the decisions the agency makes, an EPA official said.

A battery of standardized human neurotoxicity tests is needed, particularly for use in evaluating the effects of environmental exposures to potentially hazardous agents. Because several test batteries, such as the field performance battery used by DoD as well as another test battery developed by NIOSH, have been developed for testing humans exposed to suspected neurotoxic substances, it may be possible to adapt existing procedures into a more broadly applicable test battery.

''If you're going to do a particular test, at what level do you consider that some adverse health effect has occurred?" asked an official from ATSDR. "What you'd like is not only some tests, but indications for when to use them. . . .The whole idea. . . is to get the biggest bang for the Federal buck. " In that context the lack of resources for funding research and testing of suspected neurotoxic substances is a critical "rate-limiting" step.

Development and Use of Standardized Neurotoxicity Tests

Many neurotoxicity tests are now in use. The discussion group agreed that representatives from various agencies could form a coordinating group to compare the specific tests each agency is using and to evaluate strategies for developing new tests.

Some effort to coordinate research involving animal and human neurotoxicity testing is also needed. Improved efforts to obtain relevant information, such as pharmacokinetic data about a chemical's behavior in a particular species, are part of this overall task, an FDA official said.

Despite differences in statutory authority, other agencies besides EPA need to acknowledge critical arenas, such as developmental neurotoxicity, for evaluating chemicals and drugs, noted an official from EPA. However, any effort to move toward uniformity in testing becomes challenging because so much depends on the regulatory context in which a particular test will be used. EPA, for example, is expected to set and observe standards for tests that are mandated under several legislative acts—particularly the Toxic Substances Control Act-that are unique to the Agency. Working under quite different legislative mandates, NIDA and FDA have

developed specific, highly sophisticated tests for particular categories of neuropharmacological agents. Whatever the tests being performed, noted another EPA official, the interpretation of results is "very dependent on the expertise of your reviewers, " For example, without adequate training in neuropathology, agency reviewers might overlook telltale signs of neurotoxicity in a particular animal model test.

A practical consideration arising from mission and statutory differences among regulatory agencies is that the costs of testing commodity chemicals, for instance, rather than drugs ''can very often not be supported by the anticipated market, ' an EPA official pointed out. Nonetheless, sharing of adequately reviewed information among agencies could help individual agencies in making decisions about neurotoxic substances to fulfill their particular legislative mandates. Whether test methods should be standardized or merely codified remains an unresolved issue.

Coordination of Federal Research Programs

Neurotoxicity research is defined broadly because the definition is driven by individual investigators as well as legislatively mandated regulatory agencies. Existing mechanisms for coordinating such research, particularly its more basic components, are largely informal and often fragmented. The discussion group did not reach a consensus on whether a central coordinating mechanism would be useful or desirable.

In particular, several representatives of the basic research community thought that such a committee might be viewed as an advocacy body trying to obtain a larger share of resources for conducting neurotoxicity research instead of studies in other areas. Thus, their misgivings about a formal neurotoxicity research coordinating body are based on an underlying fear that a central committee might interfere with research freedom "through budget leverage. '

In addition, noted an official from NIH, although other Federal activities involving neurotoxicity may well benefit from coordination, research "would be the least important to coordinate. . . .We're trying to solve a nonproblem. " Informal exchanges of information now ensure that research interests and opportunities are shared fairly freely between various Institutes within NIH, he said. Moreover, that exchange of information occurs outside the formal budget process. Sometimes it involves efforts to minimize overlap, but it also permits a degree of research 'redundancy'—i.e., overlapping or even repetitive research by different investigators. (Such redundancy, when it occurs, is usually justified as a vital part of the self-correcting, confirmatory aspect of basic research.) There are plenty of "knowledge gaps" in the neuroscience, he said. "Instead of feeling redundant, we're working to fill the knowledge gaps. "

Representatives from agencies that are purely regulatory or that also conduct research to support their regulatory responsibilities see a need for more deliberate efforts to coordinate research. "We need to identify gaps in the research database available to the regulatory agencies, " said an official from EPA. "We need. . .to transfer information [when] trying to develop research strategies, added another EPA representative, "We want to test their validity with other agencies. "

Historically, basic research findings have had an enormous impact on setting neurotoxicity-related regulations, The current effort within CDC, for instance, to reevaluate safe blood levels for lead "arose from basic research findings about lead's neurotoxicity, ' an EPA official pointed out. "How can we [convey] basic information about how the nervous system responds to various insults . . . to [officials] to protect public health?" He and many other participants at the workshop agreed that such information could be evaluated and disseminated more effectively than current mechanisms allow. They also agreed that, by making basic researchers more aware of the scientific challenges facing regulatory agencies, the nature of some research undertakings may change in valuable ways. "We want NIH aware of problems facing regulatory agencies ., , to see if it can give a different emphasis to basic research," an EPA official noted.

Coordination of Testing and Monitoring Programs

Several Federal agencies, including, EPA, OSHA, NIOSH, FDA, and CPSC, have both passive and active neurotoxicity monitoring capabilities and interests. Data **developed during the conduct of such activities typically are stored by the agencies, Members of the discussion group concluded that sharing such information among agencies would be** useful-as would identifying key contact people at each agency and making agency-specific databases compatible with one another.

The handling of data is seen as a challenge. Agencies now have different criteria for evaluating such data. EPA, for example, stringently reviews data before entering them into the Integrated Risk Information System, an Agency official noted. "These data have status. [As] an agency policy. . . .1 would have to ask what status other kinds of shared data would have. ' The expected uses for a "centralized database. , . to a large extent might dictate what kind of data you would put in it" another EPA official said.

Officials face serious questions in evaluating neurotoxicity test schemes. The development and validation of new tests and test batteries are a central challenge.

Moreover, there is no agreed-on basis for moving from a tier-one to a tier-two battery of tests. A concise definition of "significant biological effect" is needed, as are consistent strategies for using test data when conducting risk assessments, The exchange of information, sometimes at the early stage of description in grant applications, might expedite development of useful procedures. In the same vein, it would be useful to track what compounds are being tested by which agencies so that interested parties could be kept informed about the status of particular suspect neurotoxic agents, even during the earliest stages of examination. Similarly, it would be useful to reexamine past neurotoxicology data, in part to gain a greater understanding of what test endpoints have proved particularly reliable.

Coordination of Risk Assessment and Regulatory Programs

Of the regulatory agencies represented at the workshop, EPA apparently has the most stringent guidelines for risk assessment. This stringency is dictated in part by EPA's need for consistency throughout its diverse programs and across its regional offices. For example, engineers at Superfund sites may be called on to make $20-million decisions, pointed out an EPA representative, In such circumstances, guidance and consistency are essential—to support the on-site decision if it is subsequently challenged in court.

Although other regulatory agencies may not have such formal guidelines, they often have special offices for addressing risk assessment, scientific, and policy issues. OSHA, for instance, has promulgated guidelines for carcinogens, according to an agency official. However, developing those guidelines "was time-consuming and not an effective process, ' this same official noted, adding that having consistent practices across agencies seems more important than publishing specific guidelines. Informally, many agencies follow a process outlined in the National Research Council document *Risk Assessment in the Federal Government: Managing the Process (2).* It distinguishes between risk assessment, which is considered principally a scientific evaluation process, and risk management, which involves political, economic, and other considerations, Efforts to coordinate neurotoxicity risk assessment ought to emphasize "science and. . . risk assessment and not . . . risk management" an EPA official recommended.

"I don't think you can make that kind of clean distinction,' another discussion group participant responded. "I don't think you can live with that kind of artificial situation. . . it's the sort of thing that gets us into trouble. And, noted another participant, "There is a basic political premise that is involved in that separation decision. If it works well for an agency under a set of circumstances, great. But I don't think it's universally clear that is the way to proceed. "

The discussion group considered whether universal guidelines for conducting risk assessments might exert untoward effects, such as restricting scientific judgments and, ultimately, impeding regulatory actions. "Standardized guidelines tend to stagnate the discipline," said an official from DOE. "Formalizing them too soon is not good. The important part of risk assessment is [holding] a social dialogue, focusing on a problem, and stimulating research." However, an official from EPA responded, "What you say is very nice if the agency doesn't have a lawsuit accusing [it] of not making a regulatory decision.

There was general agreement that careful thought must be exercised lest risk assessment concepts be introduced too early. Nonetheless, some principles of risk assessment may be applicable to neurotoxicity data from all regulatory agencies. Moreover, research issues common to most, if not all, regulatory agencies can be addressed in a coordinated fashion. "Looking at common research issues could certainly be a marked advantage,' the discussion group agreed. However, concern was voiced that other agencies feel "their input into what EPA is doing in risk assessment is. . . retrospective." Thus, there is a need for them to have input earlier in the process so as to have greater impact.

"Rather than adopt [guidelines] uniformly, we may want to see how a particular agency's guidelines work out . . . and then learn from each other's mistakes and successes, " suggested an official from FDA. "EPA and FDA may start at the same point trying to detect neurotoxic drugs or environmental agents, Later on, the FDA decision on setting a neurotoxic threshold for a drug will be different from [the standard] EPA sets for an environmental agent. "

The group was divided over how risk assessment procedures for evaluating suspected carcinogens stand up against procedures for evaluating putative neurotoxic substances. "In some ways, we know more in the area of neurotoxicity, ' an EPA official argued. "We know about variety, reversibility, as much or more about mechanisms. . . . [In neurotoxicity] somehow we are able to accept a certain level of risk. . . .It's not that cancer risk assessment is more developed, [but] we put an arbitrary structure on [it] largely in response to a political need. " Added an official from FDA, "The key is that we are better able to set a safe limit for a neurotoxicant than. . . for carcinogens.'

Sometimes the "politics of the situation require us to say, 'We don't know enough about what we're doing here',' said another EPA official. However, both EPA and FDA "have a long empirical track record of dealing

with neurotoxic agents, of establishing safe levels. . . .So we shouldn't confuse ourselves.

Such considerations also have an impact on "risk communication' '—that is, notifying individuals of the risk posed by particular substances. "That whole area is under great scrutiny within the cognitive psychology community, " noted a participant. Research "to explain a complex concept" and efforts to "develop a special language" could help in getting the public to understand risks more clearly.

Models for Coordinating Federal Neurotoxicity Efforts

There are several models for coordinating interagency neurotoxicity activities. The Interagency Regulatory Liaison Group was established more than a decade ago and seemed to work well until it became too difficult to manage, according to a DOE official. Moreover, with a change in administrations came a change in activities among regulatory agencies and a decreased emphasis on coordination among them.

Within DHHS, the Committee to Coordinate Environmental Health and Related Programs (CCEHRP) could coordinate neurotoxicity activities. The committee "is authorized to establish subcommittees and could readily accommodate interests in neurotoxicity among DHHS agencies with liaisons to agencies outside the Department. CCEHRP has a policy board and counsel that are research- and program-directed, according to a representative from DHHS. CCEHRP is also integrated vertically, meaning its membership includes researchers who work at the bench as well as high-level managers.

Historically, the Office of Science and Technology Policy (OSTP) within the Office of the President has functioned as an organizing body for cooperative activities to establish risk assessment principles for carcinogens. The OSTP Chemical Carcinogens Document published in the *Federal Register* on March 14, 1985, is widely accepted as a model achievement. Moreover, with OSTP leadership, representatives from academia, industry, and the Federal Government can work together in developing acceptable policies. A risk in calling on OSTP to undertake Federal coordination of neurotoxicity activities is that the issue could become too political. Thus, some workshop participants argued that the coordination of neurotoxicity activities to fulfill research and data needs might prove more workable if organized from "the bottom up. " Once successful, agency officials then are better positioned to convince management of particular policy options to implement.

Proposal

Toward the close of the workshop, participants agreed that an "Interagency Working Group on Neurotoxicology " should be formed.[1] The proposed working group, which would be dedicated to improving the Federal response to human health issues related to neurotoxicology, would include members from all Federal agencies and organizations having research, regulatory, or other pertinent interests in neurotoxicology. Such a forum for exchanging information could help minimize duplication of efforts. The working group could also help ensure that negative as well as positive findings are shared by individuals interested in neurotoxicology.

Although workshop participants limited their proposal to a sketch of what such an interagency working group should undertake, they did outline key areas where such a body could fill gaps and help to coordinate otherwise isolated efforts in research, testing, monitoring, risk assessment, regulation, and other areas. The working group also might develop a "conceptual framework. . .to identify long-range needs related to neurotoxicology, " suggested an official from EPA. It might also "encourage the Library of Medicine to participate in the establishment of a neurotoxicology database."

Appendix B References

1. This summary of the OTA/EPA workshop was prepared by Jeffrey Fox under contract No. L3-2630.O.
2. National Research Council, *Risk Assessment in the Federal Government: Managing the Process* (Washington, DC: National Academy Press, 1983).

[1]On Oct. 26,1989, the name was changed to the Interagency Committee on Neurotoxicology (ICON). The committee is adrninisteredthrough the Neurotoxicology Division of EPA's Health Effects Research Laboratory in Research Triangle Park, NC.

Federal Interagency Coordination of Neurotoxicity Research and Regulatory Programs

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Appendix C
Decade of the Brain

Public Law 101-58, 101st Congress, Joint Resolution

Whereas it is estimated that 50 million Americans are affected each year by disorders and disabilities that involve the brain, including the major mental illnesses; inherited and degenerative diseases; stroke; epilepsy; addictive disorders; injury resulting from prenatal events, environmental neurotoxins, and trauma; and speech, language, hearing, and other cognitive disorders;

Whereas it is estimated that treatment, rehabilitation and related costs of disorders and disabilities that affect the brain represents a total economic burden of $305 billion annually;

Whereas the people of the Nation should be aware of the exciting research advances on the brain and of the availability of effective treatment of disorders and disabilities that affect the brain;

Whereas a technological revolution occurring in the brain sciences, resulting in such procedures as positron emission tomography and magnetic resonance imaging, permits clinical researches to observe the living brain noninvasively and in exquisite detail, to define brain systems that are implicated in specific disorders and disabilities, to study complex neuropeptides and behavior as well as to begin to learn about the complex structures underlying memory;

Whereas scientific information on the brain is amassing at an enormous rate, and the field of computer and information sciences has reached a level of sophistication sufficient to handle neuroscience data in a manner that would be maximally useful to both basic researches and clinicians dealing with brain function and dysfunction;

Whereas advances in mathematics, physics, computational science, and brain imaging technologies have made possible the initiation of significant work in imaging brain function and pathology, modeling neural networks and simulating their dynamic interactions;

Whereas comprehending the reality of the nervous system is still on the frontier of technological innovation requiring a comprehensive effort to decipher how individual neurons, by their collective action, give rise to human intelligence;

Whereas fundamental discoveries at the molecular and cellular levels of the organization of the brain are clarifying the role of the brain in translating neurophysiologic events into behavior, thought, and emotion;

Whereas molecular biology and molecular genetics have yielded strategies effective in preventing several forms of severe mental retardation and are contributing to promising breakthroughs in the study of inheritable neurological disorders, such as Huntington's disease, and mental disorders, such as affective illnesses;

Whereas the capacity to map the biochemical circuitry of neurotransmitters and neuromodulators will permit the rational design of potent medications possessing minimal adverse effects that will act on the discrete neurochemical deficits associated with such disorders as Parkinson's disease, schizophrenia and Alzheimer's disease;

Whereas the incidence of necrologic, psychiatric, psychological, and cognitive disorders and disabilities experienced by older persons will increase in the future as the number of older persons increases;

Whereas studies of the brain and central nervous system will contribute not only to the relief of necrologic, psychiatric, psychological, and cognitive, disorders, but also to the management of fertility and infertility, cardiovascular disease, infectious and parasitic diseases, developmental disabilities and immunologic disorders, as well as to an understanding of behavioral factors that underlie the leading preventable causes of death in this Nation;

Whereas the central nervous and immune systems are both signaling systems which serve the entire organism, are direct connections between the nervous and immune system, and whereas studies of the modulatory effects of each system on the other will enhance our understanding of diseases as diverse as the major psychiatric disorders, acquired immune deficiency syndrome, and autoimmune disorders;

Whereas recent discoveries have led to fundamental insights as to why people abuse drugs, how abused drugs affect brain function leading to addiction, and how some of these drugs cause permanent brain damage;

Whereas studies of the brain will contribute to the development of new treatments that will curtail the craving for drugs, break the addictive effects of drugs, prevent the brain-mediated "high" caused by certain abused drugs, and lessen the damage done to the developing minds of babies, who are the innocent victims of drug abuse;

Whereas treatment for persons with head injury, developmental disabilities, speech, hearing, and other cognitive functions is increasing in availability and effectiveness;

Whereas the study of the brain involves the multidisciplinary efforts of scientist, from such diverse areas as physiology, biochemistry, psychology, psychiatry, molecular biology, anatomy, medicine, genetics, and many others working together toward the common goals of

better understanding the structure of the brain and how it affects our development health, and behavior;

Whereas the Nobel Prize for Medicine of Physiology has been awarded to 15 neuroscientist within the past 25 years, an achievement that underscores the excitement and productivity of the study of the brain and central nervous system and its potential for contributing to the health of humanity;

Whereas the people of the Nation should be concerned with research into disorders and disabilities that affect the brain, and should recognize prevention and treatment of such disorders and disabilities as a health priority;

Whereas the declaration of the Decade of the Brain will focus needed government attention on research, treatment and rehabilitation in this area: Now, therefore, be it

Resolved by the Senate and House of Representatives of the United States of America in Congress Assembled, That the decade beginning January 1, 1990, hereby is designated the "Decade of the Brain," and the President of the United States is authorized and requested to issue a proclamation calling upon all public officials and the people of the United States to observe such decade with appropriate programs and activities.

Approved July 25, 1989.

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Appendix D

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Appendix E
List of Contractor Documents

For this report, OTA commissioned six papers on various topics in neurotoxicology. The manuscripts of all but one of these contract documents(*) are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161, telephone (703) 487-4650.

"Neurotoxic Pesticides and the Farmworker," E. Widess, 1988.
"The Federal Regulatory Response to the Problem of Neurotoxicity," J.B. Corteau, J.S, Young, and W. Muir, Hampshire Research Associates, Inc., 1988.
"International Neurotoxicity Research: Current Activities and Future Directions," Z. Annau, 1988.
"Assessing Human Risks Posed by Neurotoxic Substances," Environ Corp., 1988.
"Economic Considerations in Regulating Neurotoxic Substances," G. Provenzano, 1989.
*" Neurotoxicity Research-Current Activities and Future Directions," R. Wood, 1988.

Appendix F
Glossary of Terms and List of Acronyms

Glossary of Terms

Acceptable daily intake (ADI): See *reference dose.*

Acetylcholine: See *neurotransmitter.*

Acetylcholinesterase: An enzyme that catalyzes the breakdown of the neurotransmitter acetylcholine. See *neurotransmitter.*

Action level: The point at which steps must be taken to reduce the concentration of a toxic substance in or on food, air, or water. An action level is based on the same criteria as a tolerance, but the action level is temporary, until a tolerance level can be set and is not legally binding. Compare *tolerance level.*

Active ingredient (of a pesticide): The component of a chemical compound that produces the desired biochemical effect; specifically, the pesticide itself. Compare *inert ingredient.*

Acute exposure: See *duration of exposure, frequency of exposure.*

Administrative controls: Methods of reducing worker exposures to occupational hazards through administrative arrangements. For example, rotating a worker from areas of high exposures to areas of low exposures reduces that worker's average exposure level.

Axon: The long extension, or process, of the neuron along which nerve impulses travel.

Axonopathy: Degeneration of axons. In central-peripheral distal axonopathy, degeneration usually begins at the end of the axon and proceeds toward the cell body (the cell body itself is not affected). In central-distal axonopathy, a less common form, degeneration of the spinal cord, but not the peripheral nervous system, occurs, Compare *neuronopathy, neuropathy.*

Biotransformation: The biochemical processes by which a foreign substance is altered or metabolized by the body (e.g., by the action of enzymes). Although biotransformation usually results in less toxic compounds, it can result in more toxic compounds.

Blood-brain barrier: A layer of tightly juxtaposed cells in blood vessel walls that protects much of the central nervous system by selectively filtering out some substances while allowing others to pass from the blood into the brain,

Carbamate: A synthetic organic insecticide. As pesticides, carbamates are reversible inhibitors of cholinesterase.

Carcinogen: A substance that causes cancer.

Cell **body:** The relatively compact portion of the neuron that contains the nucleus. Compare *process.*

Cell **culture:** Growth in the laboratory of cells isolated from multicellular organisms. Although the cells proliferate, they do not organize into tissue. See pure cell culture, *mixed cell culture, cell line,* and *cloned cells.*

Cell **line:** A group of malignant cells derived from a primary culture at the time of first subculture; an established cell line has the potential for indefinite subculture in vitro.

Central nervous system: One of the two major divisions of the nervous system, made up of the brain and spinal cord. Compare *peripheral **nervous** system.*

Cerebellum: The part of the brain involved in coordination of muscles and the maintenance of equilibrium.

Cerebrum: The portion of the brain responsible for conscious mental processes.

Cholinesterase inhibition: See *acetylcholinesterase.*

Chronic exposure: See *duration of exposure, frequency of exposure.*

Classical neurotransmitter: See *neurotransmitter.*

Clinical test: Experimental use (as of drugs) on humans.

Cloned cells: Asexually produced cells, all of them genetically identical to the original cell.

Commodity chemical: A compound produced by several companies. Compare *specialty chemical.*

Consent decree: A legally binding mutual agreement between EPA and the manufacturer of a chemical under which the manufacturer will conduct EPA-specified tests and EPA will not require further testing,

Cost-benefit analysis: A determination of whether the costs of regulating a toxic substance exceed the benefits in reducing risk to health or the environment. Both costs and benefits are measured in monetary units. Compare *risk-benefit analysis, cost-eelectiveness analysis. See risk.*

Cost-effectiveness analysis: A determination of whether the costs of regulating a toxic substance exceed the effectiveness in reducing risks to health or the environment. Costs are measured in monetary units, effectiveness in natural units such as years of life saved, incidence of disease averted, and days of work loss avoided. Compare *cost-benefit analysis. See risk.*

Dementia: Loss of intellectual function.

Demyelination: Destruction of the myelin sheath of a nerve. See *myelin sheath.*

Dendrite: Any of the branched extensions, or processes, of the neuron along which nerve impulses travel toward the cell body.

Developmental neurotoxicity tests: Studies of the offspring of animals exposed to toxic substances during pregnancy and lactation in order to determine the nature and extent of structural or functional damage to the nervous system of the offspring.

Differentiation: The process of cells and tissues acquiring distinct characteristics during development.

Discounting: Relating costs or benefits that occur at different times to a common basis.

Dopamine: See *neurotransmitter.*

Dosage: The amount, frequency, and number of doses administered in a test.

Dose: The amount of a substance absorbed in a unit volume or in an individual. Dose rate is the dose delivered per unit of time.

Dose-response: The quantitative relationship between exposure to a substance, usually expressed as a dose, and the extent of toxic injury or disease.

Duration **of exposure:** The length of time a person or test animal is exposed to a chemical. Duration of exposure is divided into four categories: acute (exposure to a chemical for less than 24 hours), subacute (exposure for 1 month or less), subchronic (exposure for 1 to 3 months), and chronic (exposure for more than 3 months). See *frequency of exposure.*

Economic efficiency: The 'state in which the greatest direct and indirect gains (benefits) are derived from the resources expended (costs) to achieve a stated objective. Compare *net efficiency.*

Efficiency: See *economic efficiency.*

Electromyography, EMG: Recording and measuring the electrical activity of muscles by means of an electromyograph. Electromyography is used in testing the effects of neurotoxic substances on humans.

Electroneurography, ENG: Recording and measuring the electrical signals generated by nerves by means of an electromyograph. Electroneurography is used in testing the effects of neurotoxic substances on humans.

Electrophysiology: Measuring and recording the electrical activity of the brain or nerve cells by means of electrodes.

Encephalopathy: Degeneration of the brain.

Endpoint: The disease, conditions, or adverse effect resulting from exposure to a toxic substance (e.g., memory loss, paralysis, dizziness, anxiety).

Engineering **controls:** Methods of controlling worker exposure by modifying the source or reducing the amount of contaminants released into the workplace. These include process design and modification, equipment design, enclosure and isolation, and ventilation.

Environmental hypothesis: The theory that exposure to toxic substances contributes significantly to neurological disorders such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease).

Epidemiology: The study of the distribution of diseases and their precursors in human populations.

Evoked potentials, sensory evoked potentials (EPs): Electrical signals generated by the nervous system in response to a stimulus, whether auditory (brainstem auditory evoked responses, BAERs), visual (visual evoked potentials, VEPs, which include flash evoked potentials, PEPs, and pattern reversal evoked potentials, PREPs), or somatosensory (somatosensory evoked potentials, SEPs). EPs can be measured and the measurements used to identify which senses are affected by neurotoxic substances and how they are affected. See *electrophysiology.*

Explant culture: Tissue taken from its original site and placed in an artificial medium for growth.

Experimental use permit (EUP): An application to EPA by a manufacturer for permission to conduct fieldtests on a pesticide.

Exposure: The accidental or intentional contact of a person or animal with a substance, specifically a toxic substance. Exposure is measured by the amount of the substance involved (dose), how often and for how long contact took place (frequency and duration of exposure), and the means through which contact occurred (route of exposure). See *dose, duration of exposure, frequency of exposure, route of exposure.*

Frequency of exposure: The number of times a person or test animal is exposed to a chemical. Acute exposures "are generally single exposures, whereas subacute, subchronic, and chronic exposures are repeated exposures. See *duration of exposure.*

Functional observational battery (FOB): A collection of noninvasive tests to evaluate sensory, motor, and autonomic dysfunction in test animals exposed to substances or whose nervous systems have been damaged, FOBS are generally used to screen for neurotoxic substances. See *screening test.*

Ganglion: A collection of nerve cells outside the brain or spinal cord.

Glia, glial cells: The second basic cell type of the nervous system. Glia perform support functions for neurons: namely, nutrition, insulation (through the production of myelin), and structural support. Compare *neuron.*

Hazard: The likelihood that a pesticide will cause immediate or short-term adverse effects or injury under ordinary circumstances of use.

Hen test: An observational assay in which the observer ranks the animals' motor ability.

Hydrophilic: Having an affinity for water; that is, soluble in water. These substances may also be termed lipophobic, or insoluble in lipids.

Hydrophobic: Insoluble in water; these substances may also be termed lipophilic.

Inert ingredient (of a pesticide): The solvent or "inactive" solid that dilutes or carries a pesticide; inert ingredients are so called because they have no effect on the targeted pest, not because they are inherently inactive. An inert ingredient as defined by EPA *can,* in some cases, cause adverse effects on human health.

Inorganic: Matter generally not containing carbon (i.e., not animal or plant matter). Compare *organic.*

Integrated pest management (IPM): A system for controlling pests in which pesticides are used in conjunction with biological controls (natural predators and parasites, disease-causing microorganisms, pheromones, pest-resistant plants) and cultural controls (crop rotation, removal of pest-harboring crop residues

after harvest).

Investigational new drug (IND): Application to FDA by a manufacturer for permission to conduct clinical trials on a drug.

In vitro test: Experiment using cells, tissues, or explants grown in a nutritive medium as a model system in toxicity testing rather than using living animals or human beings. Toxicity is assessed by adding a test substance to the culture and observing any changes that occur. See cell *culture, tissue culture, explant culture.*

In vivo: Literally, in the living; pertaining to a biological process or reaction taking place in a living cell or organism.

Latent effect: A reaction to a toxic substance that is not immediately evident but that appears later in life; also referred to as a silent effect.

Lipids: Fat-like substances that are an important constituent of cell structure; the nervous system is composed of high concentrations of lipids.

Lipophilic: Having an affinity for lipids; that is, soluble in fat-like material, These substances may also be termed hydrophobic, or insoluble in water. Many toxic substances are lipophilic, making them especially dangerous to the nervous system. See *lipids.*

Margin of exposure: See *margin of safety.*

Margin of safety: Division of the NOEL or NOAEL by the current, desired, or most feasible human exposure level. See *NOEL, NOAEL.*

Maximum allowable concentration (MAC): The limit on atmospheric contaminants in manned spacecraft for missions of up to 7 days; set by the National Aeronautics and Space Administration.

Maximum contaminant level (MCL): An enforceable standard set by EPA for pollutants in drinking water, to be set as close as possible to the maximum contaminant level goals. See ***maximum*** *contaminant level goals, recommended maximum contaminant level.*

Maximum contaminant level goal (MCLG): Nonenforceable goal set by EPA for pollutants in drinking water. MCLGs for carcinogenic pollutants are set at zero; goals for noncarcinogenic pollutants are set by establishing the lowest dose at which harmful effects can be observed, compensating for uncertainties, and calculating predicted human exposure from food and air. See *maximum contaminant level.*

Me-too registration: A practice by which subsequent products that are identical to an initial, registered product can be registered without undergoing regulatory tests.

Mixed cell **culture:** A culture of more than one type of cell.

Mixed neuropathy: Degeneration of both sensory and motor neurons.

Motor activity tests: Observation and evaluation of the movements of test animals after acute or subchronic exposures to a substance; used as a screen for neurotoxic substances. See *screening test.*

Motor neuron: See *neuron.*

Mutagenic: Causing increases in the mutation of genes.

Myelin: A fatty substance (of which the myelin sheath surrounding axons is made) that acts as an electrical insulator to speed the conduction of nerve impulses. Myelin is formed in the peripheral nervous system by Schwann cells and in the central nervous system by glial cells.

Myelin sheath: Concentric layers of myelin surrounding the axons of some neurons. The myelin sheath speeds the conduction of electrical impulses.

Myopathy: Degeneration of muscle fiber.

Narcosis: Nonspecific, reversible depression of central nervous system function, marked by stupor or unconsciousness and produced by drugs.

National primary drinking water regulations (NPDWRs): Enforceable standards for contaminants in drinking water set by EPA that include maximum contaminant levels or required treatment techniques, or both. See *maximum contaminant level.*

Net efficiency: The difference between direct benefits and direct costs, generally in regard to regulation.

Neuromuscular junction: The site at which chemical or electrical information is transmitted from a nerve cell to muscle fiber. Compare synapse.

Neuron, nerve cell: The basic functional unit of the nervous system. The neuron is typically composed of a relatively compact cell body containing the nucleus, several short radiating processes (dendrites), and one long process (the axon) with branches along its length and at its end. Information in the form of electrical impulses travels from the cell body along these processes to other cells. Sensory neurons send information to the brain and spinal cord; motor neurons send instructions to the muscles. See axon, *dendrite.*

Neuronopathy: A primary damage to the nerve cell body which results in a rapid, but secondary, degeneration of nerve processes.

Neuropathological tests: Postmortem examination of test animals in order to determine changes in the structure and function of the nervous system as a result of exposure to a toxic substance. These tests may be used to screen for toxic substances. See *screening test.*

Neuropathy: Degeneration of nerve cells; a general description for any disease of the peripheral or central nervous system.

Neuropeptide: See *neurotransmitter.*

Neurophysiological tests: Techniques for measuring the electrical signals, or evoked potentials, of charged ions; the measured potentials reflect the functioning of the neuron or neurons that generated them. See *electrophysiology, evoked potentials.*

Neurotoxic esterase (NTE) assay: A procedure for

measuring the inhibition of the enzyme NTE in the brain or spinal cord of hens exposed to organophosphates. The test can be used to determine the delayed effects of acute and subchronic exposures to organophosphates. See *organophosphates.*

Neurotoxicant, neurotoxic substance: A chemical that adversely affects the nervous system.

Neurotoxicity, neurotoxic effect: An adverse change in the structure or function of the nervous system following exposure to a toxic substance.

Neurotoxicology: Study of the effects of toxic chemicals on the nervous system, including the modes by which neurotoxic substances enter the body, the effects these substances have on the nervous system, the biochemical and physiological mechanisms through which the effects occur, the prevention of damage to the nervous system, and the treatment of neurological and psychiatric disorders caused by exposure.

Neurotransmitter: Specialized chemical messenger synthesized and secreted by neurons to convey information from one nerve cell to another (serotonin, norepinephrine, dopamine) or from a nerve cell to muscle fiber (acetylcholine). Neurotransmitters act on the receptors of other cells: classical neurotransmitters (e.g., the four mentioned above) typically interact with receptors of adjacent cells; neuropeptides (e.g., the endorphins and vasopressin) may transmit messages to receptors on distant cells. See *receptor.*

New **drug application** (NDA): Submission of evidence, including results of clinical trials, to FDA by a manufacturer that a drug is both safe and effective. Approval of the NDA is required before the drug can be marketed. Compare *investigational new drug.*

NOAEL, **no observed adverse effect level:** That dose below which no adverse effect is observed. Compare *NOEL.*

No-effect levels: See *NOEL, NOAEL, threshold.*

NOEL, no **observed effect level:** That dose below which no effect of any sort is observed. Compare *NOAEL, threshold.*

Norepinephrine: See *neurotransmitter.*

No-threshold: The situation in which any dose greater than zero increases risk. Compare *threshold.*

Oligodendrocyte: A type of glial cell that appears to play a role in myelin formation in the central nervous system. Compare *Schwann cell. See glia.*

Opportunity cost: The value of alternative endeavors that might have been undertaken with the resources used for the particular endeavor chosen.

Organ culture: A type of tissue culture in which a whole organ is maintained in vitro.

Organic: Matter containing carbon (i.e., animal or plant matter). Compare *inorganic.*

Organic farming, organic production: Farming without **the** use of or with limited use of chemical pesticides or fertilizers.

Organic solvents: Generic name for a group of simple organic liquids that are volatile (that is, in the presence of air they change from liquids to gases) and therefore are easily inhaled.

Organoleptic: Stimulating any of the organs of sensation or susceptible to a sensory stimulus.

Organophosphates, organophosphorous pesticides: A class of pesticides with neurotoxic properties; organophosphates have also been used as nerve gases.

Organotypic culture: A type of primary tissue culture in which the structure of the original organ is maintained in vitro. This method is useful in neurotoxicity studies because the connections and spatial relations between neurons and glia can be maintained.

Pattern of exposure: The dose, duration, frequency, and route of exposure; used in risk assessment. See *dose, duration of exposure, frequency of exposure, route of exposure.*

Peripheral nervous system: One of the two major divisions of the nervous system, made up of the nerves connecting the spinal cord and sensory organs, glands, blood vessels, and muscles. Compare *central nervous system.*

Permissible exposure limit (PEL): The maximum exposure to a given chemical that an industrial worker is allowed during an 8-hour workday and 40-hour workweek, set by the Occupational Safety and Health Administration. Compare *reentry interval.*

Personal protective equipment: Equipment and clothing designed to control hazards: it includes hard hats, safety shoes, protective eyewear, and various types of respirators.

Pesticide: A generic term referring to toxic substances developed to control pests; it includes insecticides, fungicides, rodenticides, and herbicides.

Potentiation: The process through which a nontoxic substance increases the toxicity of another substance.

Preclinical test: Experimental testing (as of drugs) on animals.

Presumption of risk: The probability that an existing hazard, combined with the potential for human exposure to it, creates risk. Compare *risk assessment.*

Primary culture: Cell, tissue, or organ culture initiated directly from an organism rather than from another culture. Compare *explant culture.*

Prior informed consent (with respect to pesticides): Agreement on the part of one government to import a pesticide banned or severely restricted by another government in full knowledge of the reasons for that ban or restriction.

Processes, **nerve processes:** Extensions of the neuron, whether axons or dendrites, along which nerve impulses travel. Compare cell *body.*

Receptor: Sensory neuron terminal; also, a molecule in the cell membrane that recognizes and combines with a specific chemical substance, such as a neurotransmit-

ter. See neurotransmitter.

Recommended exposure limit (REL): Standard for maximum exposure of industrial workers to toxic substances, set by the National Institute for Occupational Safety and Health. Compare *permissible exposure limit, threshold limit value.*

Recommended maximum contaminant level (RMCL): Nonenforceable goals set by EPA for pollutants in drinking water; renamed maximum contaminant level goal. See *maximum contaminant level goal, maximum contaminant level.*

Red Book: Guidelines for toxicological testing of direct food additives and color additives used in food under the Federal Food, Drug, and Cosmetic Act published by the Center for Food Safety and Applied Nutrition of FDA,

Reentry interval: The time that must elapse between application of a pesticide and the return of agricultural workers to the treated area without special protection.

Reference dose (RfD): A term used to characterize risk and derived by applying safety factors to NOELs or NOAELs. If human exposure to a substance is below the RfD, no risk is assumed to exist; if exposure exceeds the RfD, risk is assumed to exist. The term may be used interchangeably with acceptable daily intake, although EPA uses the term RFD. See *NOEL, NOAEL.*

Reuptake: Process by which neurotransmitters andtheir metabolizes are recycled.

Right-to-know laws: State and local laws requiring companies to inform workers and communities of the chemical names and hazards of their products.

Risk: The probability of injury, disease, or death for persons or groups of persons undertaking certain activities or exposed to hazardous substances. Risk is sometimes expressed numerically (as a fraction) and sometimes qualitatively (e.g., high, moderate, or low).

Risk assessment: The analytical process by which the nature and magnitude of risk are identified. Four steps make up a complete risk assessment: hazard identification, dose-response assessment, exposure assessment and risk characterization. Compare *risk management, presumption of risk. See risk, exposure, dose-response.*

Risk-benefit analysis: A determination of whether the risks to health and the environment of using a chemical or drug exceed the economic benefits that accrue from its use. In the case of pesticides, benefits are measured in terms of the monetary value of crop yields; in the case of drugs, benefits are measured in terms of therapeutic efficacy.

Risk management: The process of determining whether or how much to reduce risk through regulatory action. Decisions depend on data from risk assessments and may also depend on political, social, ethical, economic, and technological factors.

Route of exposure: The means by which a person or animal comes into contact with a chemical: namely, intravenous (injected into the bloodstream), inhalation (through the lungs), oral (through ingestion), and dermal (through the skin).

Safety factor: Division of the NOEL or NOAEL and succeeding measures by a factor, typically 10, to yield a reference dose; used interchangeably with uncertainty factor. Safety factors account for uncertainties in the extrapolation of data from, for example, short- to long-term exposures, and animals to humans.

Scaling factor: Weighting disparate measures of health outcomes for cost-effectiveness analysis on the basis of value judgments concerning their relative worth.

Schedule-controlled operant behavior (SCOB): A test in which an experimental animal's response to a stimulus is reinforced on a predetermined schedule in order to produce a predictable pattern of behavior. SCOB is used to evaluate the effects of acute or chronic exposure to toxic substances on the rate and pattern of the animal's responses.

Schwann cell: A glial cell in the peripheral nervous system that produces myelin for the myelin sheath. Compare *oligodendrocyte.*

Screening test: Broad-based initial test of a chemical designed to detect adverse health effects. Screening can help determine what further tests should be performed to evaluate a substance's toxicity.

Sensitivity analysis: Deliberately varying the uncertainties in an assessment in order to examine their effects on the decision taken.

Sensory neuron: See *neuron.*

Serotonin: See *neurotransmitter.*

Silent effect: See *latent effect.*

Specialty chemical: A compound produced by only one company. Compare *commodity chemical.*

Structure-activity relationship: The relationship between a chemical's structure and the biochemical changes it induces.

Subchronic exposure: See *duration of exposure, frequency of exposure.*

Synapse: The site at which chemical or electrical information is transmitted from one nerve cell to another, typically by a neurotransmitter. Compare *neuromuscular junction. See neurotransmitter.*

Synaptic cleft: A narrow gap between two adjacent neurons into which neurotransmitters are secreted. See *neurotransmitter.*

Synergism: The state in which the combined adverse effects of a chemical exceed the sum of the effects of each chemical acting alone.

Teratogenic: Producing defects in the developing embryo. (A substance that causes physical defects in the offspring.)

Test rule: A statement written by EPA of what chemical or chemicals in a compound must be tested by the

manufacturer and how they are to be tested. Test rules are written under the Toxic Substances Control Act when it can be shown both that inadequate data on the effects of a compound exist and that testing is required to obtain such data.

Threshold: The highest dosage at which no effect is observed. Compare *no-threshold.*

Threshold limit value (TLV): That concentration (by volume in air) of a hazardous substance to which the majority of industrial workers may be repeatedly exposed every day without adverse effects; set by the American Conference of Governmental Industrial Hygienists. Compare *reference dose.*

Tiered testing: A strategy for identifying the toxicological effects of a substance by proceeding from general toxicity tests to progressively more specific and sophisticated tests.

Time-weighted average: An average over a given (working) period of a person's exposure, as determined by sampling at given times during the period.

Tissue culture: The maintenance or growth of tissue, organs, or cells in vitro. Tissue culture can be subdivided into cell culture and organ culture. See cell *culture, organ culture.*

Tolerance level: The maximum permissible concentration of a toxic substance in or on food, water, or air, as set by a regulatory agency. Compare *action level.*

Toxicology: The study of adverse effects of natural or synthetic chemicals on living organisms.

Uncertainties: Questions involved in risk assessment, ranging from fundamental questions (e.g., How useful are animals as predictors of toxicity in humans?) to specific questions arising from incomplete or imperfect data on a particular substance (e.g., Do responses differ with route of exposure? What exposures are likely for various populations?).

Uncertainty factor: See *safety factor.*

List of Acronyms

ACGIH —American Conference of Governmental Industrial Hygienists
ADAMHA —Alcohol, Drug Abuse, and Mental Health Administration
ADI —acceptable daily intake
AETT —acetylethyl tetramethyl tetralin
ALS —amyotrophic lateral sclerosis
ATSDR —Agency for Toxic Substances and Disease Registry
AZT —azidothymidine
BAER —brainstem auditory evoked response
BHC —benzene hexachloride
BHMH —Lucel-7
BPI —Bureau of Plant Industry (Philippines)
CAA -Clean Air Act
CAP -Consumers Association of Penang (Malaysia)
CBI -confidential business information
CDC -Centers for Disease Control
CEH —Center for Environmental Health
CERCLA -Comprehensive Environmental Response, Compensation, and Liability Act
CFSAN —Center for Food Safety and Applied Nutrition (FDA)
CIIT —Chemical Industry Institute of Toxicology
COHb -carboxyhemoglobin
CPDA -central-peripheral distal axonopathy
CPSA —Consumer Product Safety Act
CPSC —Consumer Product Safety Commission
CSA —Controlled Substances Act
CSPI —Center for Science in the Public Interest
CWA —Clean Water Act
DBCP -dibromochloropropane
DHHS —Department of Health and Human Services
DOE —Department of Energy
EDB --ethylene dibromide
EEC —European Economic Community
EEG -electroencephalograph
EMG -electromyography
ENG -electroneurography
EP -evoked potential
EPA —Environmental Protection Agency
EPN -ethyl-p-nitrophenyl phosphonothionate
EUP —Experimental Use Permit
FAO —Food and Agriculture Organization (United Nations)
FDA —Food and Drug Administration
FEA —Federal Environmental Agency (West Germany)
FEP —flash evoked potential
FFDCA —Federal Food, Drug, and Cosmetic Act
FHSA —Federal Hazardous Substances Act
FIC —Fogerty International Center
FIFRA —Federal Insecticide, Fungicide, and Rodenticide Act
FIOH —Finland Institute of Occupational Health
FLT —fenvalerate
FMSHA —Federal Mine Safety and Health Act
FOB —functional observational battery
FPA —Fertilizer and Pesticide Authority (Philippines)
FWPCA —Federal Water Pollution Control Act
GAO —General Accounting Office
GFAP —glial fibrillary acidic protein
HCH —hexachlorocyclohexane
HHANES —Hispanic Health and Nutrition Examination Survey
HUD —Department of Housing and Urban Development
IND —investigational new drug
IPM —integrated pest management
IRIS —Integrated Risk Information System

ITC —Interagency Testing Committee
LBPPPA —had-Based Paint Poisoning Prevention Act
LMIN —Laboratory of Molecular and Integrative Neuroscience (NIEHS)
MA —motor activity
MAC —maximum allowable concentration
MCL —maximum contaminant level
MCLG —maximum contaminant level goal
MCPA —2-methyl-4-chlorophenoxyacetic acid
MNAF —Ministry of Nutrition, Agriculture, and Forest (West Germany)
MnBK —methyl-n-butyl ketone
MND —motor neuron disease
MOE —margin of exposure
MOS —margin of safety
MPRSA —Marine Protection, Research, and Sanctuaries Act
MSHA —Mine Safety and Health Administration
MPTP —l-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine
MTBE —methyl-tert-butyl ether
NAPARE —National Association for Perinatal Addiction Research and Education
NAS —National Academy of Sciences
NASA —National Aeronautics and Space Administration
NBS —National Bureau of Standards
NBT —Neurobehavioral Toxicology Team
NCHS —National Center for Health Statistics
NCTB —Neurobehavioral Core Test Battery
NCTR —National Center for Toxicological Research
NDA —new drug application
NFPA —National Food Processors Association
NHANES —National Health and Nutrition Examination Survey
NHLBI —National Heart, Lung, and Blood Institute
NIA —National Institute on Aging
NIAAA —National Institute on Alcohol Abuse and Aging
NIAID —National Institute of Allergy and Infectious Diseases
MDA —National Institute on Drug Abuse
NIEHS —National Institute of Environmental Health Sciences
NIGMS —National Institute of General Medical Sciences
NIH —National Institutes of Health
NIMH —National Institute of Mental Health
NINCDS —National Institute of Neurological and Communicative Disorders and Stroke
NIOSH —National Institute for Occupational Safety and Health
NLM —National Library of Medicine
NOAEL —no observed adverse effect level
NOEL —no observed effect level
NPDWR —national primary drinking water regulations
NRC —National Research Council
NRDC —Natural Resources Defense Council
NTD —Neurotoxicology Division (EPA)
NTE —neurotoxic esterase assay
NTP —National Toxicology Program
OECD -Organization for Economic Cooperation and Development
OPP -Office of Pesticide programs (EPA)
OSH Act -Occupational Safety and Health Act
OSHA -Occupational Safety and Health Administration
OTA -Office of Technology Assessment
OTS -Office of Toxic Substances (EPA)
PAN —Pesticide Action Network
PCB —polychlorinated biphenyl
PCP —phencyclidine; pentachlorophenol
PDDP diisodecyl phenyl phosphite
PEL —permissible exposure limit
PIC —prior informed consent
PMN —premanufacture notice
PPPA —Poison Prevention Packaging Act
PREP —pattern reversal evoked potentials
RCRA —Resource Conservation and Recovery Act
REL —recommended exposure limit
RfD —reference dose
RMCL —recommended maximum contaminant level
RQ —reportable quantity
SAP —Science Advisory Panel
SARA —Superfund Amendments and Reauthorization Act
SCOB —schedule-controlled operant behavior
SDWA —Safe Drinking Water Act
SEP —somatosensory evoked potential
SMSA —Standard Metropolitan Statistical Area
SNUR —significant new use rule
STEL —short-term exposure limit
TDM —triadimeform
TLV —threshold limit value
TPT —triphenyltin
TRI —Toxics Release Inventory
TSCA —Toxic Substances Control Act
TWA —time-weighted average limit
USDA —U.S. Department of Agriculture
USDJ —U.S. Department of Justice
WHO —World Health Organization

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