Chapter 1

Summary, Policy Issues, and Options for Congressional Action

CONTENTS

Boxes

Figures

Tables

Chapter 1

Summary, Policy Issues, and Options for Congressional Action

SUMMARY

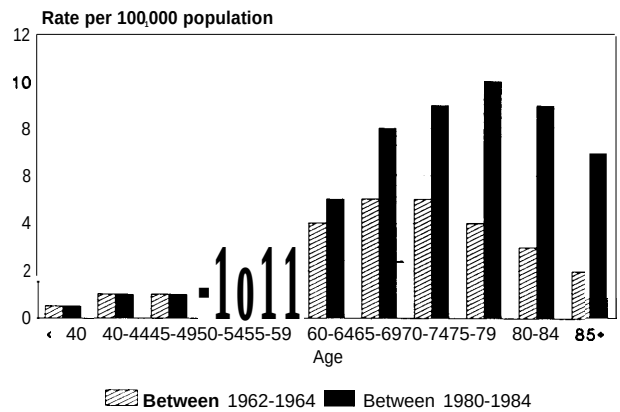
Chemicals are an integral part of our daily lives and are responsible for substantially improving them. Chemicals can also endanger our health, even our survival. This assessment focuses on neurotoxic substances, those chemicals that adversely affect the nervous system. Included among such substances 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

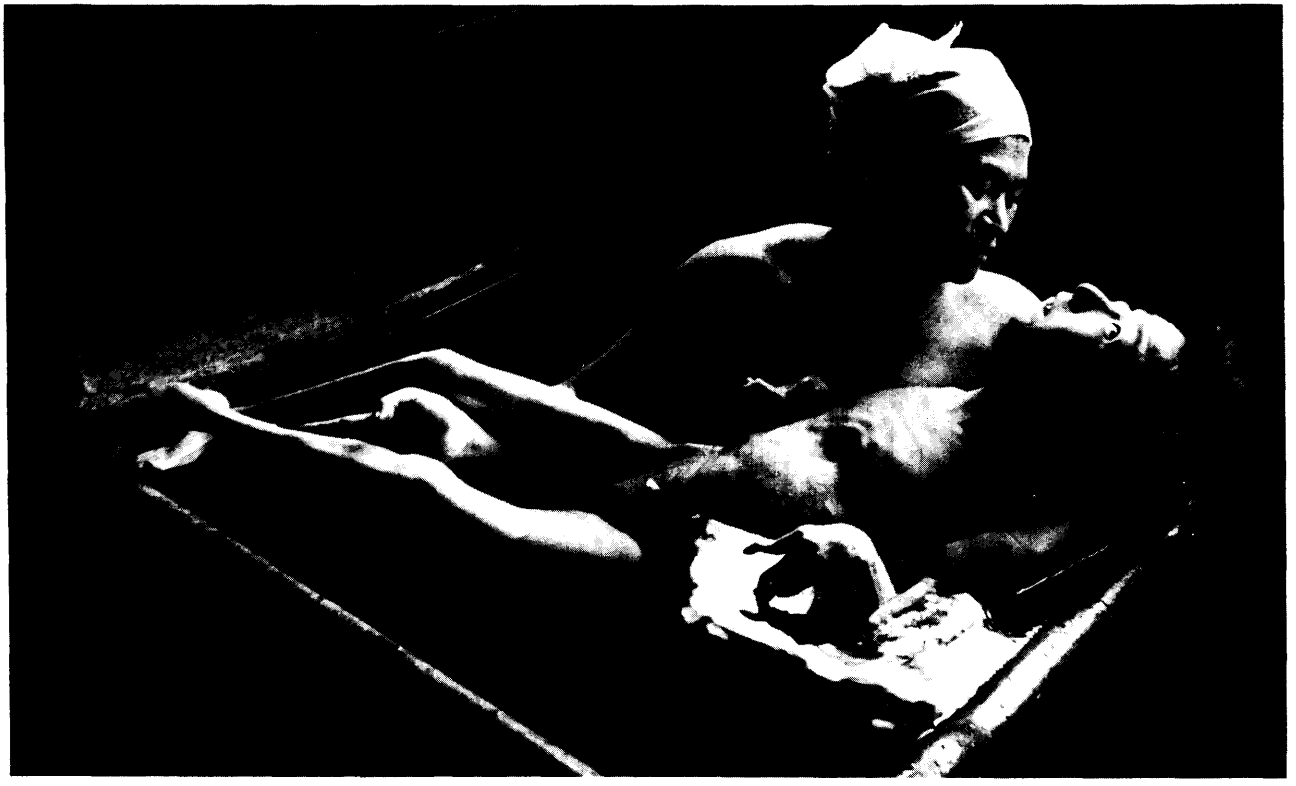
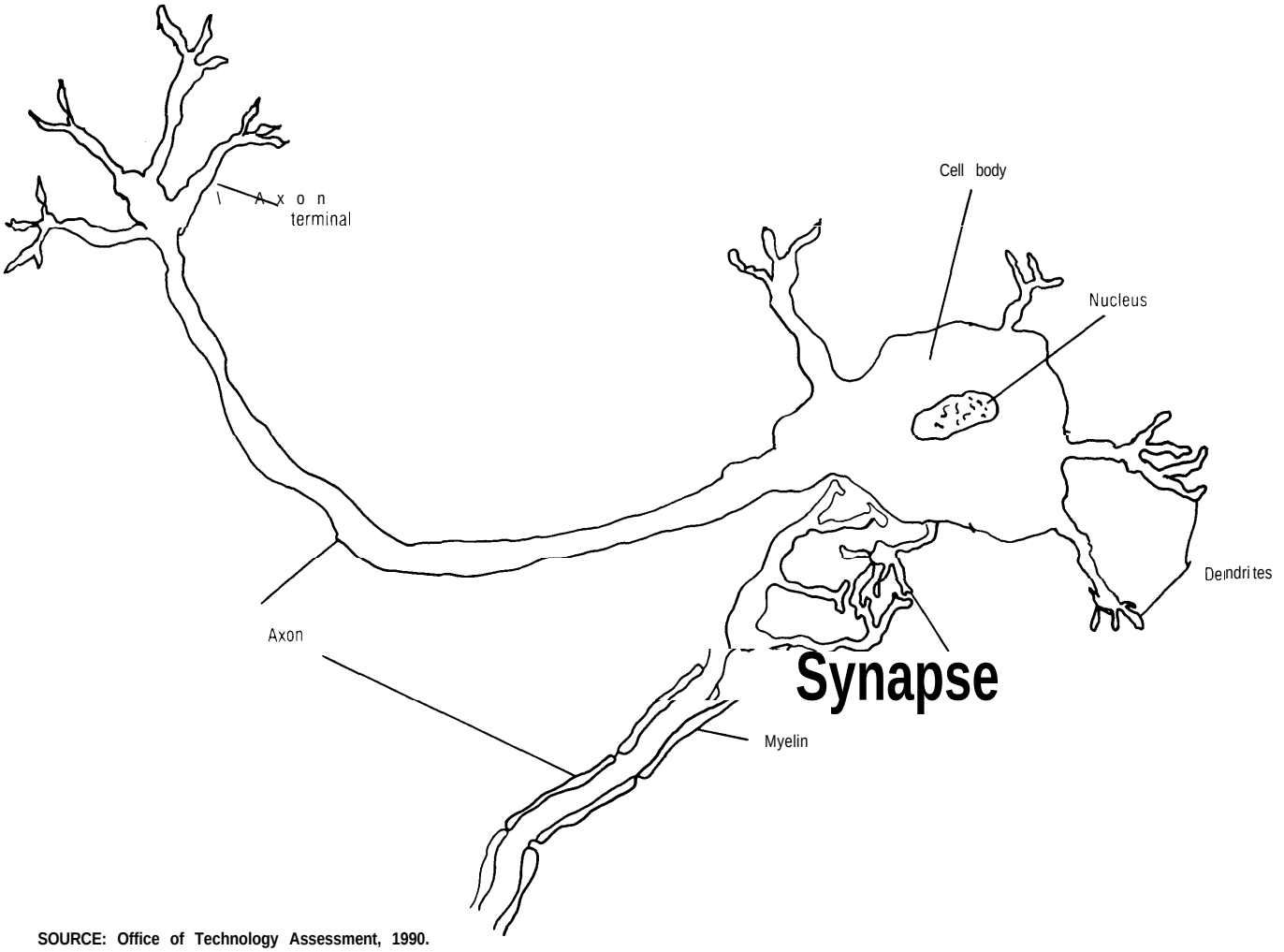


Photo credit: W Eugene Smith and Aileen Smith

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.

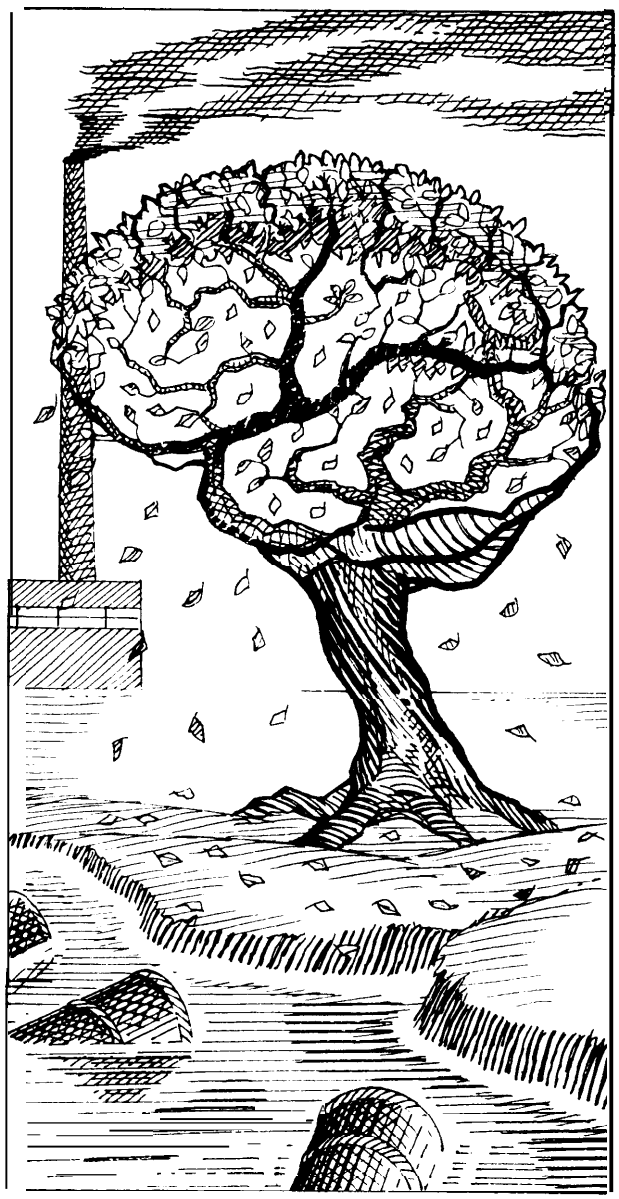
The discovery of the link between MPTP and Parkinson's disease has dramatically changed the nature of research on this disease. Much work has focused on MPP^+, a metabolize of MPTP that is responsible for the adverse effects on the brain. Recently, researchers discovered that a monoamine oxidase inhibitor, 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.

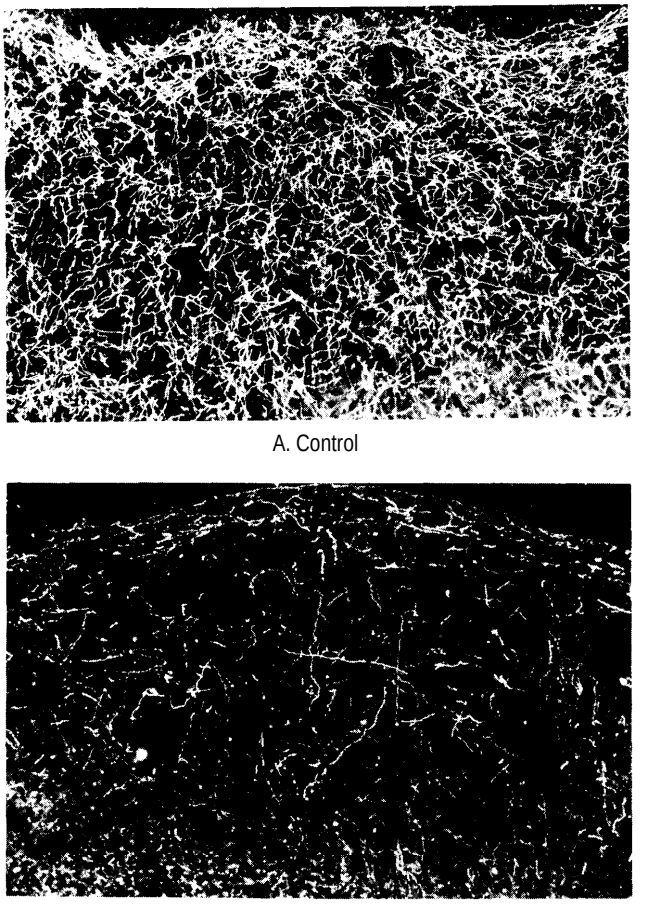
SOURCES: H.L. Needleman, A. Schell, D. Bellinger, et al., "The Long Term Effects of Exposure to Low Doses of Lead in Childhood," New *England Journal of Medicine* 322:83-88, 1990. K.L. Florini, G.D. Krumbhaar, Jr., and E.K. Silbergeld, "Legacy of Lead: America's Continuing Epidemic of Childhood Lead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

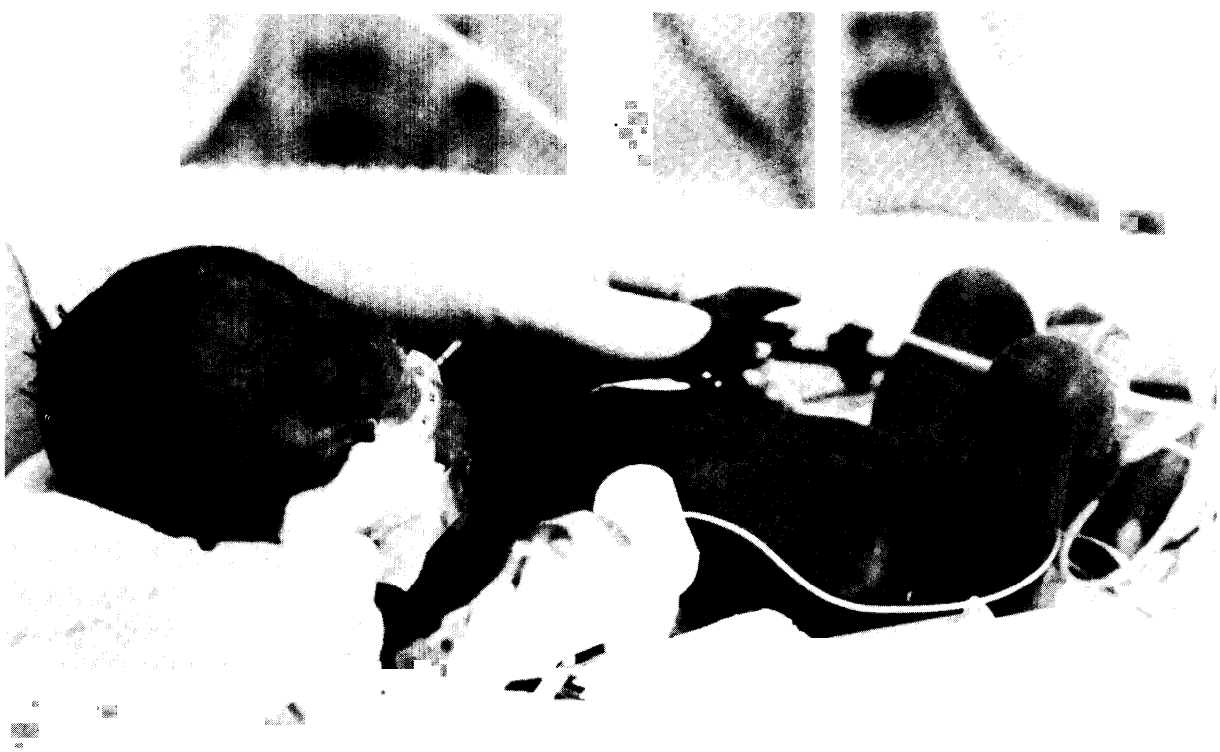


Photo credit: Courtesy of Dr. Emmaiee S. Bandstra, M. D., Division of Neonatology, University of Miami/Jackson Memorial Medical Canter

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.

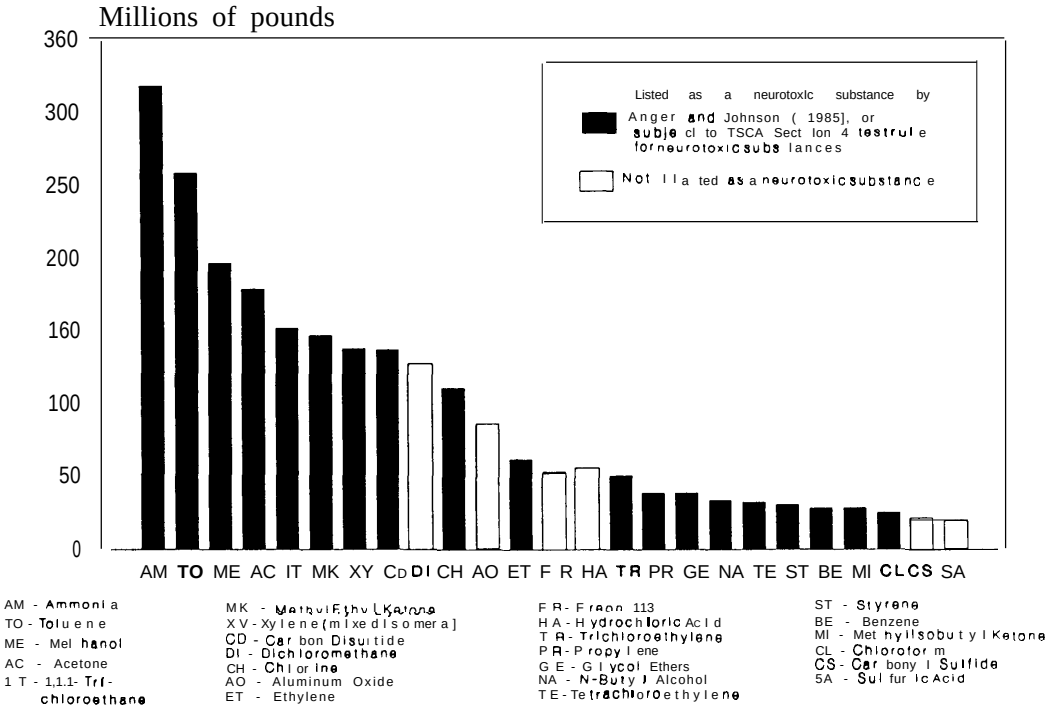
Monitoring exposure to neurotoxic substances is a critical component of public health and environmental protection efforts. Monitoring may be conducted by regularly surveying contaminants in the food supply, banking animal specimens, and collecting biological data on humans. Biological specimens can 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

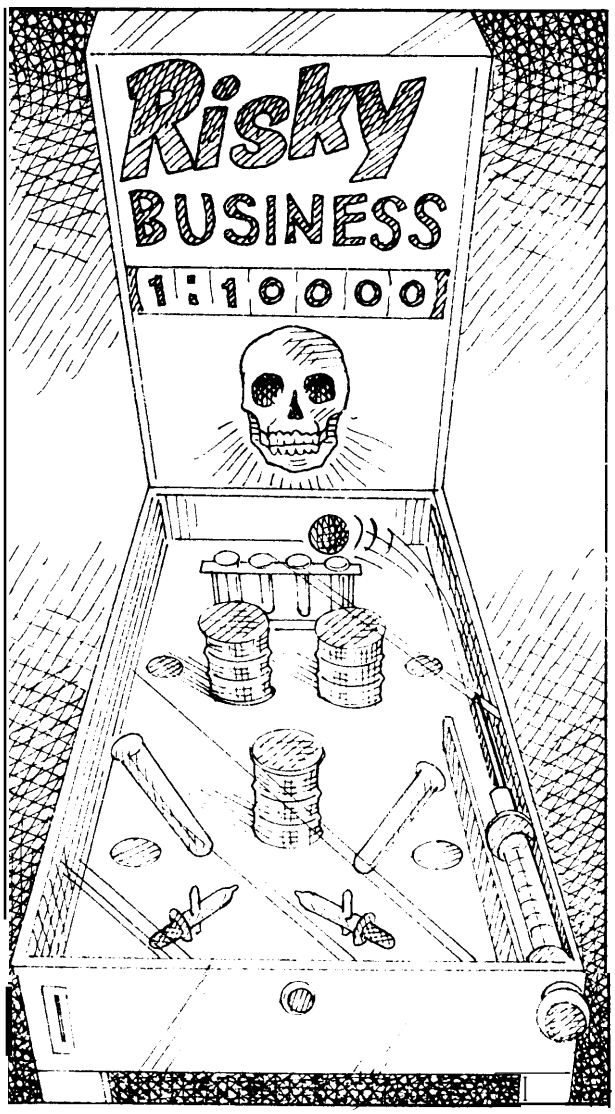


SOURCES: Data obtained from W.K. Anger and B.L. Johnson, "Chemicals Affecting Behavior," *neurotoxicity of Industrial* and Commercial Chemicals, vol. 1, J.L. O'Donoghue (cd.) (Boca Raton, FL: CRC Press, 1965), tables 1 and 2, pp. 70-141; TSCAsec. 4,52 FR 31445; TSCAsec. 4,53 FR 5932; 54 FR 13470; 54 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

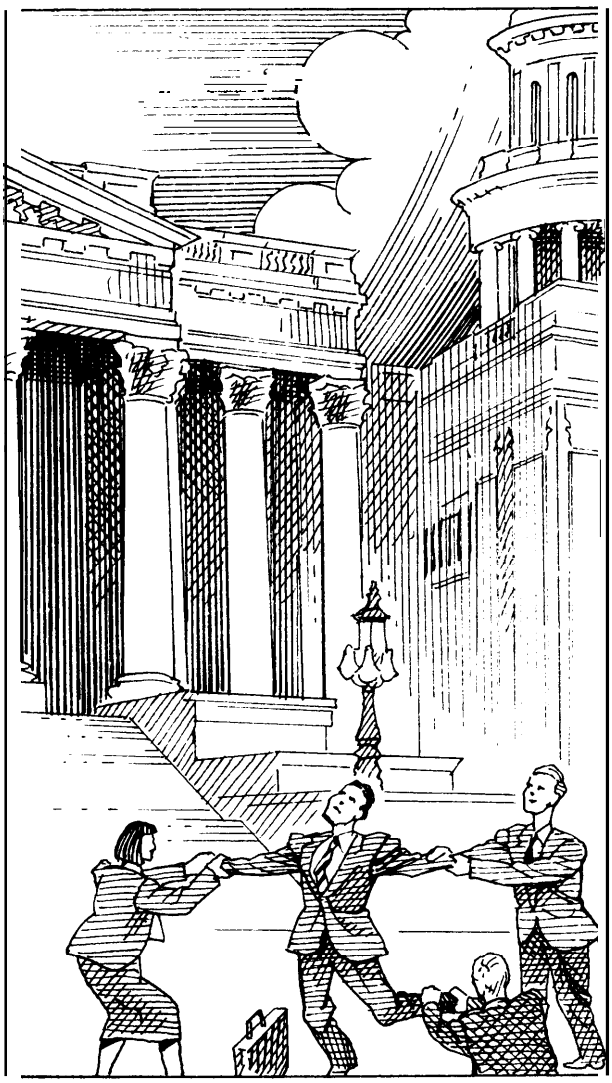
Six broad policy issues related to the identification and regulation of neurotoxic substances were identified during the course of this assessment:

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.

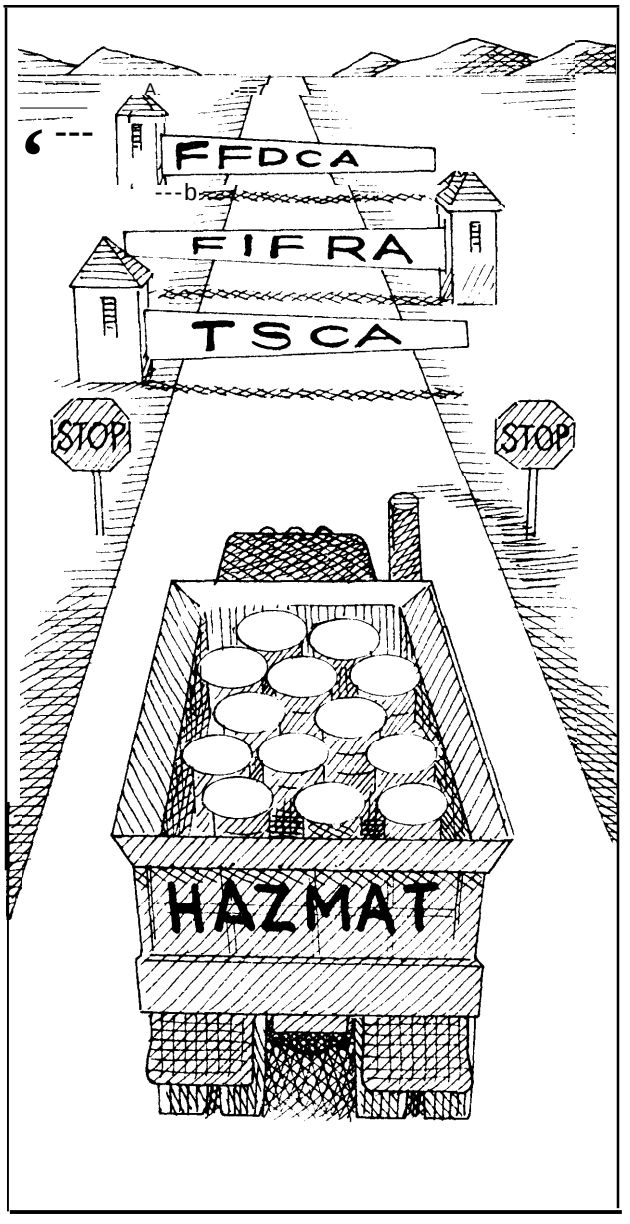
Option 1: Take no action.

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.

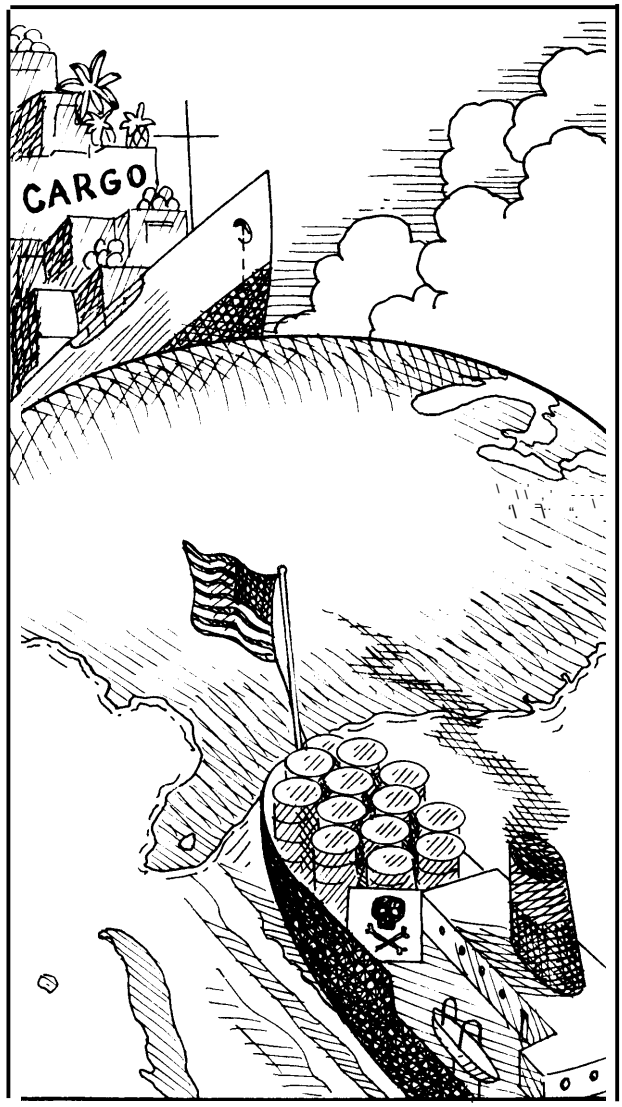
Choosing this option will result in enhanced communication of neurotoxic health risks to the public. Congress could require that information provided to workers under the Hazardous Communication Standards of the Occupational Safety and Health Act include a description of significant hazards posed by 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.