

## Chapter 2

# Introduction

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

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

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

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

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

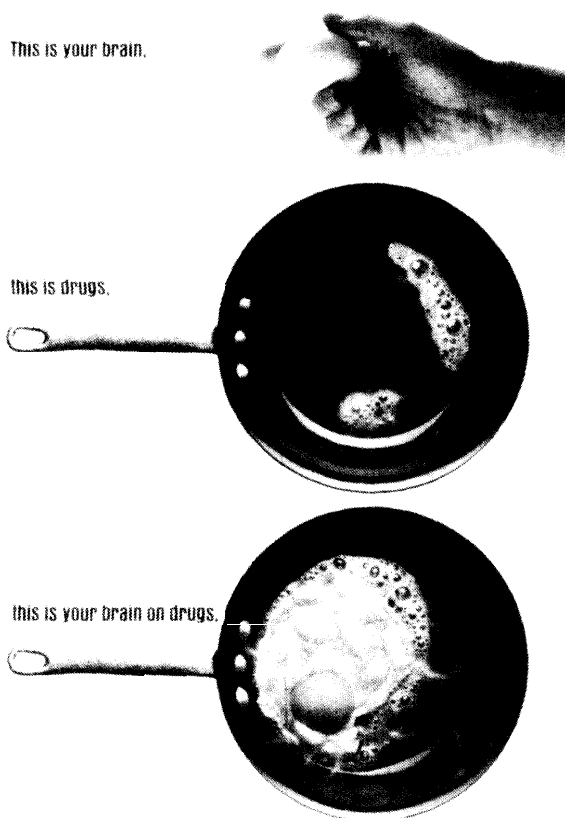
More than 65,000 chemicals are in the Environmental Protection Agency's (EPA's) inventory of toxic chemicals, and each year the Agency receives approximately 1,500 notices of intent to manufacture new substances (30). Since few of these chemicals have been tested to determine if they adversely affect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

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

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

### WHAT IS neurotoxicITY?

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



Partnership For A Drug-Free America

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

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

Care must be taken in labeling a substance neurotoxic because factors such as dose and intended effects must be taken into consideration. A substance may be safe and beneficial at one concentration but neurotoxic at another. For example, vitamins A and B<sub>6</sub> are required in the diet in trace amounts, yet both cause neurotoxic effects in large doses (50). In other cases, a substance that is known to be neurotoxic may confer benefits that are viewed as outweighing the adverse effects. For example, thousands of individuals suffering from schizophrenia have been able to live relatively normal lives because of the beneficial effects of the antipsychotic drugs. However, chronic use of prescribed doses of some of these drugs may give rise to tardive dyskinesia—involuntary movements of the face, tongue, and limbs—side-effects so severe that they may incapacitate the patient (50).

Another factor that complicates efforts to evaluate neurotoxicity is the potential additive effects of toxic substances. For example, independent exposure to two toxic substances may lead to no observable

adverse effects, but simultaneous exposure could result in damage to the nervous system. In addition, the body has an effective but limited capacity for detoxifying many chemical agents. Some chemicals thought to be relatively nontoxic may cause adverse effects if exposure occurs after the body's detoxifying systems have been saturated (17). Such situations might occur following chronic exposure to a complex mixture of chemicals in the workplace or to chemicals at hazardous waste sites.

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

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

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

## SCOPE OF THIS STUDY

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

## WHO IS AT RISK?

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

The elderly are more susceptible to certain neurotoxic substances because decline in structure and function of the nervous system with age limits

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

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

## EXAMPLES OF neurotoxic SUBSTANCES

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



Illustrated by: Ray Driver

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

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

**Table 2-1-Neurological and Behavioral Effects of Exposure to Toxic Substances**

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

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

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

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

Table 2-2-Selected Major neurotoxicity Incidents

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

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

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

Manganese is required in the diet in trace quantities but is highly toxic when relatively large amounts are inhaled. Hundreds, perhaps thousands, of miners in several countries have suffered from 'manganese madness,' a disorder characterized by hallucinations, unusual behavior, emotional instability, and

numerous neurological problems (43). Other metals, including aluminum, cadmium, and thallium, are neurotoxic in varying degrees. It is particularly challenging to limit public exposure to metals because they occur naturally in the environment.

### *Industrial Chemicals*

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



*Photo credit: W. Eugene Smith 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.



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

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

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

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

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

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

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

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

often unaware of the permanent damage that this type of substance abuse can cause (46).

### ***Pesticides***

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

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

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

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

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

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

### ***Therapeutic Drugs***

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

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

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

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

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

### **Abused Drugs**

In 1986, drug abuse in the United States led to more than 119,000 emergency room visits and 4,138 deaths (37). Many more cases go unreported. As users and their families and friends sometimes discover, substance abuse can permanently damage the nervous system. In some cases, damage is so severe as to cause personality changes, neurological disease, mental illness, or death. Persons who abuse

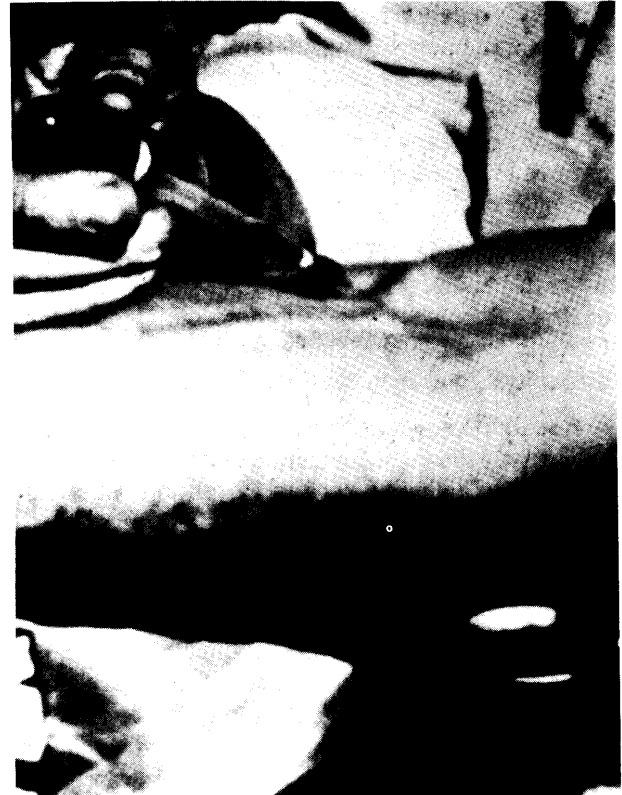


Photo credit: John Boyle, Drug Enforcement Agency

drugs are often not aware of, or do not take seriously, the threat these substances pose to their health.

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

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

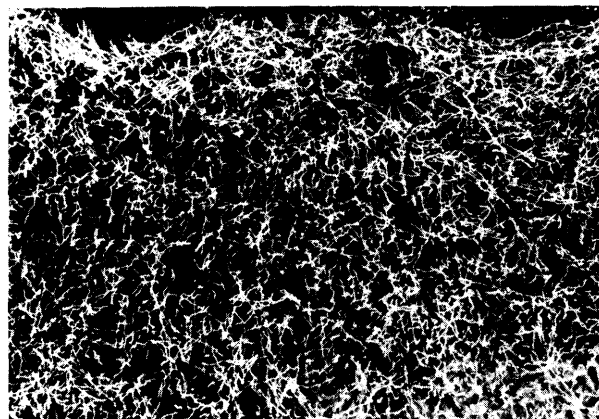
Phencyclidine (PCP) is another major abused drug. In 1984, it was responsible for 11,000 hospital emergency room visits and more than 225 deaths. Chronic use of PCP leads to depression, speech difficulties, and memory loss (32,36).

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

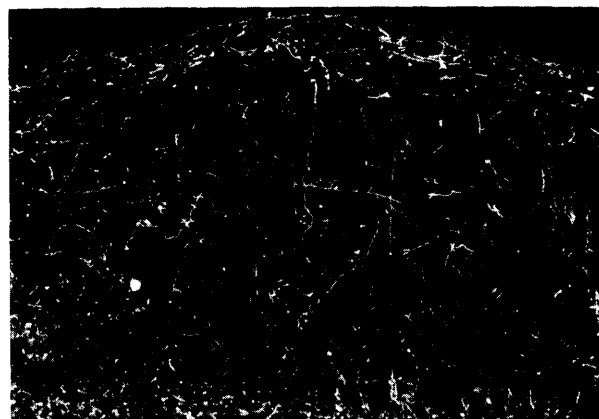
### ***Food Additives***

Food additives serve a variety of purposes, such as to prolong shelf-life or to improve flavor, and hundreds of them are used during the preparation, manufacture, and marketing of foods. The use of these substances is regulated by FDA, which maintains a list of additives that are generally recognized as safe and may be used without specific approval. All other food additives must be approved prior to use. However, few additives have undergone neurotoxicity testing. In 1984, the NAS reported that 73 percent of the food additives it examined had not been tested for neurobehavioral toxicity (30). Although animal testing of food additives is required under the Federal Food, Drug, and Cosmetic Act to evaluate their safety, studies in humans are not

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



A. Control



B. MDMA

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

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

required. Approval of drugs, however, does require human testing. Many observers believe that food additives should come under the same scrutiny as drugs, particularly because many of them are regularly ingested by millions of people. The food additive approval process is examined in a case study in appendix A.

### ***Cosmetics***

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

### ***Box 2-B-Cocaine and the Developing Fetus***

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

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

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

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



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

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

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

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

## **TOXIC SUBSTANCES AND NEUROLOGICAL AND PSYCHIATRIC DISORDERS**

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

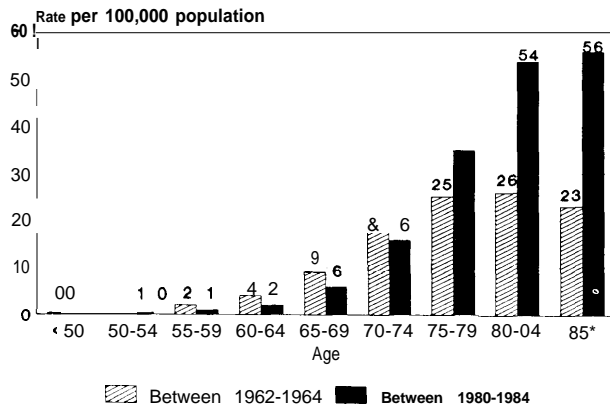
Because of this finding, the possibility that toxic chemicals might be causative agents in some cases of Parkinson's disease is being actively considered by researchers. Some recent findings support this hypothesis. For example, it has been reported that in cases in which Parkinson's disease afflicts several members of a family, the onset of the disease tends to cluster in time (5,21). Normally, if a disorder has a purely genetic basis, onset of symptoms occurs at similar ages, not at similar times. Evidence that Parkinson's disease does not occur more frequently

in identical than fraternal twins also argues against a hereditary determinant of the disorder (18). A recent epidemiological study revealed that between 1962 and 1984, U.S. mortality rates for Parkinson's disease substantially increased in individuals over the age of 75 (figure 2-2). Environmental factors appear to have played a significant role in the increase (23). The relative roles of hereditary and environmental factors in triggering Parkinson's disease remain to be determined.

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

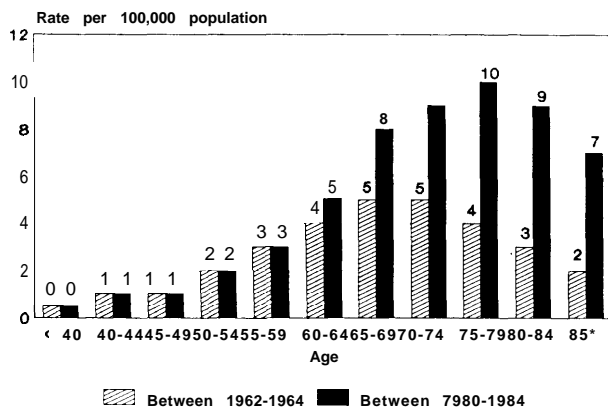
Naturally occurring toxic substances can also affect the nervous system. An unusual combination of the neurodegenerative disorders ALS, Parkinson's disease, and Alzheimer's disease endemic to Guam (known as Guam ALS-Parkinson's dementia) puzzled investigators for many years because of the correlation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

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



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

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



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

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

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

Several other foods contain known neurotoxic substances and can be responsible for severe neurological disorders. The drought-resistant grass pea causes lathyrism, a disease characterized by weak-

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

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

## IDENTIFYING neurotoxic SUBSTANCES

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

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

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

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

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

## **REGULATING neurotoxic SUBSTANCES**

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

New and existing industrial chemicals are regulated under the Toxic Substances Control Act. Pesticides are controlled by the Federal Insecticide, Fungicide, and Rodenticide Act, and exposure to toxic substances in the workplace is regulated by the Occupational Safety and Health Act. In addition, the

Federal Food, Drug, and Cosmetic Act regulates food additives, drugs, and cosmetics. Although these laws address most toxic substances, more than a dozen other acts focus on less prevalent but equally important substances. While neurotoxicity is often not explicitly mentioned in laws regulating toxic substances, it is implicit in general toxicity concerns.

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

## **ECONOMIC CONSIDERATIONS**

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

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

## **INTERNATIONAL CONCERNS**

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



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

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

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