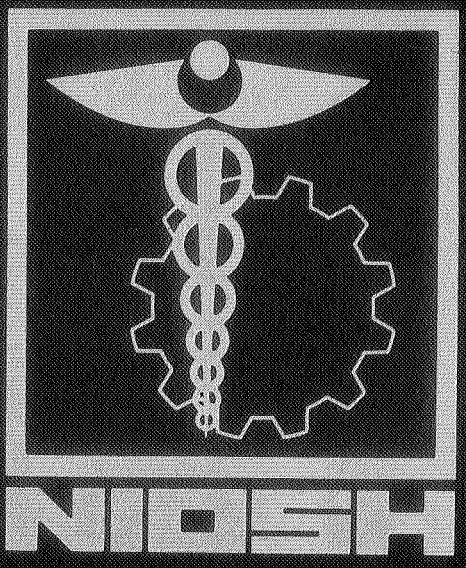

Proposed National Strategies for the Prevention of Leading Work – Related Diseases and Injuries

• Neurotoxic Disorders •

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Proposed National Strategy for the Prevention of Neurotoxic Disorders

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Introduction

This document, *A Proposed National Strategy for the Prevention of Neurotoxic Disorders*, summarizes what actions need to be taken to prevent occupational neurotoxic disorders. It was developed in 1985 at a conference sponsored by the National Institute for Occupational Safety and Health (NIOSH) and The Association of Schools of Public Health (ASPH), which brought together over 50 expert panelists and 450 other occupational safety and health professionals.

In addition to the strategy for neurotoxic disorders, NIOSH and ASPH have published strategies for the other nine leading occupational diseases and injuries: occupational lung diseases, musculoskeletal injuries, occupational cancers, severe occupational traumatic injuries, occupational cardiovascular diseases, disorders of reproduction, noise-induced hearing loss, dermatological conditions and psychological disorders.

The proposed strategies were originally published in a two volume set, *Proposed National Strategies for the Prevention of Leading Work-Related Diseases and Injuries, Part 1 and Part 2*. These proposed strategies are not to be considered as final statements of policy of NIOSH, The Association of Schools of Public Health, or of any agency or individual who was involved. Hopefully, they will be used in the quest to prevent disease and injury in the workplace.

To learn of the availability of the complete texts of Part 1 and Part 2, or to obtain additional copies of this or other Strategies, contact NIOSH Publications, 4676 Columbia Parkway, Cincinnati, Ohio 45226. Telephone (513) 533-8287.

A Proposed National Strategy For the Prevention of Neurotoxic Disorders

I. Introduction

A. Background

Disorders of the nervous system that result from toxic exposures encountered in the workplace have been noted throughout recorded history. In the first century A.D., Pliny discovered palsy in workers exposed to lead dust (*1*). Delpech observed bizarre psychoses among French workers who manufactured rubber products in small cottage industries during the 1800s and recognized that they were caused by carbon disulfide (*2*). During the 1960s and early 1970s, peripheral neuropathy was observed in Japanese workers exposed to acrylamide despite prior identification of its neurotoxicity in animals (*3*). Since 1970, at least three significant outbreaks of neurotoxicity have occurred as a result of exposure to chemicals: peripheral neuropathy from methyl-n-butyl ketone (MBK) and from 2-t-butylazo-2-hydroxy-5-methyl hexane (BHMH) in manufacturing operations (*4, 5*), and tremor, disturbances in vision and walking, and personality changes in workers using the pesticide, chlordecone (*6*). Despite improved industrial hygiene practices and the development of animal models for assessing some neurotoxic diseases, it is obvious that workers continue to serve as the "sentinel" indicator of neurotoxic disorders.

B. Definition of the Problem

Neurotoxic disorders were listed in 1983 by the National Institute for Occupational Safety and Health (NIOSH) among ten leading causes of work-related disease and injury (*7*). Neurotoxic disorders were included in this category because of:

- The large number of chemicals having demonstrable neurotoxic properties,
- The sensitivity of the nervous system to damage,
- The large number of workers exposed to neurotoxic chemicals,

- The importance of an intact nervous system for daily functions and thus the potential severity of neurotoxic illness.

More than 750 chemicals have been found to be potentially neurotoxic; a list of the most widely known toxic chemicals is found in Appendix 1 (*8*). The sensitivity of the nervous system to exogenous agents is the basis for limiting exposures to these chemicals. Of the 588 chemicals for which the American Conference of Governmental Industrial Hygienists (ACGIH) has adopted Threshold Limit Values (TLVs®), about one third (167) affect the nervous system (*9,10*). NIOSH has recommended standards for several chemicals, based in part on their neurotoxicity (*11*), including:

Acetone cyanohydrin	Malathion
Acetonitrile	Malonitrile
Acrylamide	Mercury (inorganic)
Adiponitrile	Methyl n-butyl ketone
Alkanes (C5-C8)	Methyl parathion
n-Butyronitrile	Methylene chloride
Carbaryl	Organotin compounds
Carbon disulfide	Parathion
Carbon monoxide	Phenol
Chloroform	Propionitrile
Chlordecone	Styrene
Dinitro-o-cresol	Succinonitrile
Ethylene dibromide	1,1,2,2-Tetrachloroethylene
Ethylene dichloride	Tetrachloroethylene
Glyconitrile	Tetramethylsuccinonitrile
Hydrogen sulfide	Toluene
Isobutyronitrile	1,1,1-Trichloroethane
Lead (inorganic)	Trichloroethylene
	Xylene

An estimated eight million workers may be exposed full time to neurotoxic agents (*12,13*). Although the extent of exposure to these compounds is not well documented, we estimate that millions of workers have exposures at levels known or suspected to cause neurotoxic effects. Many more workers may be exposed for short periods to high concentrations of substances that may lead to neurotoxic health effects. The projected trend for increased manufacture of organic chemicals, many of which are known or expected to be neurotoxic (due especially to their lipid solubility) foreshadows a growing population of exposed workers (*14*). Significant sources of exposure to major neurotoxic chemicals and the typical neurotoxic effects of those exposures are listed in Appendix 2. Neurotoxic effects can be diverse, and although either peripheral or central effects may predominate from exposure to any single neurotoxin, the involvement of both peripheral and central nervous systems is common (see Appendix 3).

One of the most serious neurotoxic effects encountered at the workplace is peripheral neuropathy. This disorder is characterized by numbness and tingling in the feet or hands, followed by clumsiness or incoordination due to both sensory and motor changes. Workers may find their capacity to do their usual work partially or fully impaired. Chemicals used extensively in industry that may, in sufficiently high and persistent concentrations, cause various manifestations of peripheral neuropathy include those listed in Appendix 3, top panel.

The effects of neurotoxic agents on the central nervous system (CNS) are less

readily recognized. They occur with a wider range of chemicals and present more varied forms of disturbances (Appendix 3, bottom panel) (*8,15*). Perhaps the most striking CNS disturbances noted in Appendix 3 are those related to personality and cognitive functions. Psychoses and suicidal tendencies, for example, have resulted from high exposures to manganese and carbon disulfide. High concentrations of methylene chloride produce delusions and hallucinations. Cognitive dysfunction manifested as shortened attention span, lack of alertness, or loss of memory have obvious implications for safety; these are prominent neurotoxic effects that occur following exposure to many chemicals, such as carbon monoxide and a wide range of solvents. The implications of these CNS effects for the quality of life of exposed workers is particularly important to consider, given the role that the affected functions play in everyday living. Appendix 4 summarizes a large number of chemicals reported to affect the central nervous system.

There is ample evidence for the use of neurotoxic chemicals throughout industry, and a broad range of serious neurotoxic effects has been seen in many case studies and significant sentinel health events (*8*). However, the actual extent of exposure to neurotoxic substances among U.S. workers is not known. Existing systems for health and safety surveillance do not measure the reversible or more subtle, insidious effects of neurotoxic chemicals in industry. Similarly, although the CNS changes noted above can either predispose workers to accidents or can cause accidents directly (*16*), the extent to which exposures to neurotoxic chemicals contribute to accidents also remains to be established.

In addition to neurotoxic exposures at work, workers may be exposed to neurotoxic chemicals elsewhere through hobbies, medication, and sources outside the job or in the lifestyle. Ethyl alcohol is one of the most common neurotoxicants, and other drugs, solvents, pesticides, and chemicals used at home or brought home with a worker's clothing may be neurotoxic. Some medications are used to treat patients who have nervous system disorders, and others produce changes in the nervous system as side effects. Outdoor or community exposures from waste dumps, accidental spills, power-plant emissions and the like can also contribute to the total neurotoxic insult. These off-the-job factors can confound, add to, or potentiate the effects of workplace exposure and cannot be ignored in evaluating neurotoxic effects in the workplace or in preventing neurotoxic disorders. As the average life span increases, the problem of lifetime exposures will become increasingly important. Thus, neurotoxic disorders as a cause of occupational disease and injury in the United States must command increased attention, including the formulation of an effective prevention strategy.

II. Components of a National Prevention Strategy

The prevention of neurotoxic disorders in the workplace requires a strategy based on the traditional public health approach for controlling disease problems. This approach has three main elements:

A. A sensitive *surveillance* system. Such a system must include both exposure and disease surveillance. Exposure surveillance identifies working populations exposed to neurotoxic substances, while disease surveillance identifies the occurrence of neurotoxic disorders among these workers. Both types of surveillance provide the basis for guiding the other components of this strategy: evaluation and control.

B. A strong *evaluation* program. This element relates the exposure factors identified in working populations by a surveillance system to the occurrence and extent of the neurotoxic manifestations observed. Essential parts of this element include

dose-response research on neurotoxic substances and on the illnesses that may result from exposure to them, and the identification of possible neurotoxic hazards by laboratory testing.

C. A broad-based *control* program. This program includes education to inform workers and employers of neurotoxic hazards; appropriate behavioral, personal-protective, and engineering control measures to maintain exposures within safe levels; and appropriate regulations to ensure that these control measures are implemented and maintained.

III. Current Status of Prevention Activities

A. Surveillance

Surveillance identifies both the exposure to neurotoxic substances among occupational or industrial groups and the development or prevalence of neurologic disorders. Such surveillance may also identify workers affected by known or previously unrecognized neurotoxic substances and provide information on the effectiveness of previously instituted control measures.

Information on the potential for exposure to neurotoxic substances is currently available from the National Occupational Hazard Survey (NOHS) of NIOSH, from records of inspections by the Occupational Safety and Health Administration (OSHA), and from consultative activities such as Health Hazard Evaluations (HHEs). Thus far, these data have been used mainly to identify general industrial groups where neurotoxic exposures may occur.

Established systems for surveillance of disease, such as the Bureau of Labor Statistics Surveys, Social Security Disability Award Files, Workers' Compensation Systems, death certificate monitoring, and National Center for Health Statistics studies, are not currently designed to provide exact information on the occurrence of neurologic diseases of occupational origin. Such diseases are not often appropriately recognized as work-related, and these surveillance systems are thus inadequate for accurately identifying occupational neurologic diseases.

Most reports on outbreaks of neurologic diseases have come from medical clinics, state health departments, industrial medical groups, or consultative programs such as the NIOSH Health Hazard Evaluation (HHE) Program. Outbreaks of cases (e.g., the chlordecone-induced disturbances of gait and eye movement, and personality changes) have usually served as sentinel events to identify the neurotoxicity of chemical substances. The HHE Program and similar activities by academic or state groups embody mechanisms for rapid evaluation of reported outbreaks and can confirm initial reports of possible neurotoxic problems. In addition, California has pioneered in developing a reporting system for outbreaks of pesticide poisoning so that collaborating health and agricultural departments can intervene. Similar systems for physician reporting of such diseases, however, are not well established elsewhere in this country.

Current surveillance systems do not meet the needs of the country for identifying neurotoxic exposures or disorders. Medical professionals in direct contact with patients who have these disorders either lack the necessary knowledge to recognize the problems (a cause of inadequate surveillance at the primary reporting level) and/or do not have a convenient surveillance system into which to feed their findings.

B. Evaluation

Research as a prevention component serves to identify and evaluate chemicals that may produce neurotoxic effects. The resulting information can be used to alert the occupational health community that particular chemicals in unprotected populations may lead to adverse health effects.

A large number of chemicals have been tested experimentally and identified as toxic to the nervous system. In earlier years, industry conducted most of this research to identify potential problem chemicals. Although industry-supported research continues to make a valuable contribution, a shift to the federal government has occurred in sources of funding for research. Over the past 10-15 years, the federal government has vastly increased the resources allocated to research on the nervous system, but such funding has been directed primarily at basic research on the nervous system and applied research on clinical diseases, chiefly Alzheimer's disease. According to an Office of Technology Assessment (OTA) review, an estimated $500 million in federal funds were applied to research in the neurosciences for Fiscal Year 1983 (*17*). Of this amount, the OTA document identified only about $1.7 million spent by major federal research agencies on research in neurotoxicology. The Department of Defense, the Federal Aviation Administration, and the National Aeronautics and Space Administration have also contributed to research in neurotoxicity, and extramural funding by the federal government and the states has fostered a network throughout the country of independent academic institutions that conduct research on chemical neurotoxicity.

Recommendations and requirements mandated by regulatory agencies for testing industrial chemicals have also stimulated research on the neurotoxicity of industrial chemicals. Under the Toxic Substances Control Act (TSCA), the Environmental Protection Agency (EPA) can require the testing of a chemical for neurotoxicity if it has widespread use or is thought to pose substantial risk of neurotoxicity. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), also administered by EPA, requires testing for acute delayed neurotoxicity and subchronic delayed neurotoxicity. The United States Food and Drug Administration may request specific testing for the neurotoxicity of chemicals as part of its regulatory functions under the Food, Drug, and Cosmetic Act. These various regulations all spur research on neurotoxicity, and as a result of these public and private activities, a large number of federal, academic, and private institutions currently conduct research on neurotoxicity. Several specialized scientific journals have evolved that publish the results of this research.

The international research community also provides information on neurotoxicity through research and testing activities. The Office of Occupational Health of the World Health Organization (WHO) has recommended a battery of tests for assessing neurotoxicity in humans (*18*), and WHO's International Programme for Chemical Safety has identified validated protocols for testing neurotoxicity in experimental animals. International efforts also exist among industrialized countries to coordinate testing for neurotoxicity. For example, the Organization of Economic Cooperation and Development (OECD) has established standard protocols for testing the delayed neurotoxicity of organophosphates and is developing an expanded battery of tests to determine the neurotoxicity of other chemical classes. Industries in OECD signatory nations often test the neurotoxicity of products as a premarketing requirement.

Although the base for neurotoxicologic research has been laid, current efforts are meager and reflect the inadequate resources allocated to assess neurotoxic effects in environmental agents. A recent report from the National Academy of Sciences on testing for chemical toxicity documented the inadequacy of available test data on the toxicity of most chemicals, including those commonly used in commerce (*19*). There is also a lack of direction or research priorities in the field of neurotoxicology, and a lack of interaction between persons doing research in the basic neurosciences and those conducting applied research on occupational problems. Follow-up of initial research findings that have detected neurotoxic effects is also limited and is needed to define the magnitude of neurotoxic effects and the fundamental dose-response relationships.

C. Control

Control activities cut across a spectrum of disciplines and specialties. The main activities are education, control technology, and regulation.

Education provides the information needed to assess chemicals and increase awareness of their hazards; for training and developing skills to avoid or reduce exposures; and as a basis for modifying existing work practices or controls. Control technology reduces occupational exposures to hazardous agents (including neurotoxic substances) through engineering controls, safe work practices, protective equipment, and administrative controls. Regulation helps ensure that the appropriate control and educational activities are implemented.

Public education and training programs have been established at the national, state, and local levels to increase awareness of occupational health problems, although none are specific for neurotoxicity. These include programs provided to farmers by the U.S. Department of Agriculture (USDA) and by county extension offices in many rural communities throughout the country.

In the past, few substances in the workplace have had labels with warnings about their safe use or adequate information about their potential hazards. In the late 1970s, EPA implemented a program to license the handlers of pesticides that had inadequate label warnings. Although training about the hazards of these pesticides was initially required as part of the program, it was later eliminated. More recently, regulations — such as state and local "right-to-know" laws and the Federal Hazard Communication Standard (29 CFR 1910.1200) — have increased the amount of information available on the health effects of chemical agents in the workplace. They have also required training of employees and employers about the risks of exposure.

Although the education of workers about workplace hazards has expanded rapidly over the past few years, much remains to be done to improve the prevention of work-related health problems and to assure that appropriate information about workplace exposures is effectively communicated to all workers.

Control of occupational exposures in specific workplace settings may involve a variety of approaches, including education (described above), engineering controls, personal protective equipment, and improved work practices. Often control technology for occupational exposures must be industry-specific because of differences in industrial settings and operations.

- Substitution of less hazardous substances has been actively pursued over the years to reduce hazardous exposures (e.g., the substitution of water-based for solvent-based paints).

- Equipment substitution is another major means of reducing exposures, e.g., airless atomization and electrostatic attraction were substituted for compressed airsprayers to reduce the dispersion of paint particles during spray painting. (The higher application rates possible with this process can, however, result in increased exposure.)

- Process substitution, exemplified by the unique stage charging and aspiration system adopted in the loading of coke ovens, eliminates the by-product emissions of tar and light oils that contain neurotoxic substances.

- Isolation is practiced in the pesticide industry by keeping filling operations separate from other plant processes through use of a physical barrier and distance.

- Ventilation is widely used to control neurotoxic substances, as illustrated by the use of local exhaust ventilation to control solvent exposures in tire manufacturing.

- Training in effective work practices has significantly lowered exposures to styrene in boat building (*20*).

Current efforts to control neurotoxic exposures require the implementation of appropriate control measures in each workplace setting. More information is needed on the relative effectiveness of these different control approaches and on methods to improve effectiveness. Control measures must be applied or developed for industries where exposures have been difficult to control, and industries with extensive neurotoxicity problems must be especially targeted for development of control technology.

Although current regulations are not specific for neurotoxic disorders, the Occupational Safety and Health Act (OSH Act) (Public Law 91-596), the Mine Safety and Health Act (MSH Act), and the Toxic Substances Control Act (TSCA) (Public Law 94-469 administered by the Environmental Protection Agency [EPA]), provide a legal basis for prevention activities. Standards for limiting exposures to neurotoxic chemicals have been promulgated and monitored by both the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA). These standards are the Permissible Exposure Limits (PELs), which were adopted from the 1968 TLVs of the ACGIH and the recommendations of the American National Standards Institute (ANSI). Only a small number of federal PELs have been revised since 1971 (when the 1968 TLV recommendations were adopted). Since the purpose of the OSH Act is to ensure that no employee will suffer diminished health, life expectancy, or functional impairment as a result of work, the relationship of neurotoxic exposures to functional capacity is especially pertinent. EPA screens organophosphate pesticides for the deficits they cause in functional capacity (e.g., delayed peripheral neurotoxicity), but premarket screening has not been implemented for most chemical agents currently being placed into commerce.

State and local laws also affect the prevention of neurotoxic disorders in the workplace. Notable among these are workers' compensation laws, "right-to-know" laws, and state occupational safety and health laws. Workers' compensation laws, in addition to providing aid to disabled workers, foster an awareness of problems and may identify the need to institute corrective action. "Right-to-know" laws,

if effectively implemented, should provide workers with the necessary information to protect themselves and others. The OSH Act requires that state occupational safety and health standards be at least as protective as federal standards.

Although an extensive network of laws and regulations is in place that could provide the necessary regulatory apparatus for prevention, these measures have not been sufficient to prevent outbreaks of neurotoxic illness. The laws must be reviewed to assess their relevancy in protecting against neurotoxicity, and workable and effective programs should be developed to extend the benefits derived from legislation to groups not now covered, such as small businesses and agriculture, and to more effectively serve groups that are now covered.

IV. What Needs to Be Done

Although prevention of occupational neurotoxic disorders is partially addressed by current conditions described above, effective reduction of the risks requires a more deliberate prevention plan.

A. Surveillance

Major changes, noted above, are needed to improve our surveillance of neurotoxic disorders, including increased efforts in the surveillance of exposure and the resulting health effects.

Initial efforts for the surveillance of exposure must focus on occupational groups exposed to known neurotoxicants. Information available from the National Occupational Hazard Survey or the more recent National Occupational Exposure Survey, OSHA compliance monitoring, health hazard evaluations, and similar programs should first be reviewed to identify the occupational and industrial groups with a potential for significant exposures to these substances. Efforts should also improve the availability and increase the use of exposure surveillance data, including extension of the OSHA inspection database (i.e., the Management Information System [MIS]) to cover more states; include other OSHA activities (such as consultation); and evaluate other types of exposure-reporting systems (e.g., state "right-to-know" laws). Adequate information is not available for many industries on the degree of exposure; such information must be collected and then used to target efforts for better control of these exposures through compliance monitoring, development of better control technology, etc. Exposure surveillance must be a continual effort to monitor both changes in exposure over time and new industries or new uses of well-known chemicals. Such information on exposure should be combined with improved disease monitoring to identify high-risk industries.

Our present surveillance systems make it very difficult to monitor the occurrence of occupational neurotoxic diseases. Because these disorders are often subtle and can easily be overlooked or misdiagnosed, several steps must be taken to improve surveillance of them.

1. The ability to diagnose these disorders and to attribute them to workplace exposures must be increased. This will require better diagnostic tests and criteria, the latter being particularly important for surveillance. Uniform clinical definitions of these diseases are also needed to provide a common basis for physician reporting.

2. Systems must be established through which physicians can report these disorders (or suspected diseases) to health officials. These health officials can then collect more information on the cases and provide appropriate follow-up and prevention in the workplace. State and local health departments, in collaboration with occupational clinic groups, probably provide the best basis for such reporting systems. Analysis of other data systems (workers' compensation, etc.) should supplement this direct reporting system to evaluate the occurrence of neurotoxic illnesses in occupational and industrial groups.

   To assure continued physician involvement in the surveillance program, the reporting systems must be interactive and provide a means for follow-up of reported cases. Improved disease reporting must then be supported by disseminating more information on neurotoxic illnesses to physicians and other health professionals.

These two critical priorities — developing improved disease definitions and developing a more usable, interactive reporting system — serve as a basis for the remaining prevention activities.

B. Evaluation

Although current and past research has identified many neurotoxic chemicals and neurotoxic effects, the magnitude of these effects or their impact on workers have not been adequately defined. Additional data are needed to permit dose/response evaluations of neurotoxic chemicals used in the United States. Increased research should seek to improve both our understanding of neurotoxic mechanisms and the test methods used to identify neurotoxic substances. Because the vast numbers of chemicals that could be neurotoxic cannot possibly be assessed individually, the most important goal of neurotoxicology research is to improve knowledge of the basic mechanisms of neurotoxicants. This will ultimately lead to a better understanding of structure/activity relationships and, in turn, could be used to predict the effects of untested chemicals. Even more fundamental is a greater understanding of nervous-system function, which we can gain only through continued and increased emphasis on basic research in the neurosciences.

1. To move toward these goals, we must increase interactions between the neuroscience community and investigators conducting studies of neurotoxic diseases in the workplace. The neuroscience community must begin to integrate research on toxic mechanisms into their ongoing efforts, most of which are now directed toward neurodegenerative diseases. Two targeted research programs that will lead toward this integration can now be identified: a) assessing the hypothesis that major neurodegenerative diseases (e.g., Parkinsonism) may be caused by exposure to toxicants. This effort will involve testing worker populations exposed to selected neurotoxicants combined with research into the mechanisms of these diseases; and, b) investigating the implications of different exposure patterns on the development of neurotoxic health effects, especially the relationship of acute episodes of toxicity to the development of chronic or delayed effects. First, laboratory research should assess the neurotoxic properties of these chemicals during acute exposure, and then workers who are acutely or intermittently exposed to these neurotoxic substances should be evaluated.

2. A major priority is the implementation of valid and reliable neurotoxicologic test methods. The most immediate needs are methods for screening or monitor-

ing working populations exposed to possible neurotoxic substances and test methods for premarket screening of newly developed substances in animals. Human screening tests, such as the WHO battery for assessing neurobehavioral effects in exposed workers (*18*), will be especially important in responding to neurotoxic illnesses reported through the surveillance system described above. An understanding of basic mechanisms will lead to the development of better in vitro and in vivo tests to screen new chemicals for neurotoxicity.

Better methods are also needed to identify subtle deficits in neurobehavioral function in both humans and animals. Workplace studies of neurotoxic substances also require improved methods of monitoring exposure, especially for short-term exposures. Specific needs to which research emphasis should now be directed are: a) dose-effect determinations involving multiple exposure concentrations; b) relationships of neurotoxic disorders to workplace accidents; c) interactions between exposures to occupational neurotoxicants and the use of drugs, alcohol, and medications; d) assessment of multiple chemicals and complex mixtures, especially as they relate to acute exposure effects; and, e) pharmacokinetics, especially in susceptible populations, in ongoing neurotoxicology research. These ideas would form part of an agenda for the larger field of environmental neurotoxicology. Scientists involved in this broad field should be convened to recommend a more focused agenda for the field as a whole.

3. To have practical, usable payoffs, this research program must also be tied to surveillance and control efforts. Surveillance for exposure and disease can identify populations at risk of exposure to neurotoxic chemicals. Public health responsibilities must then be established to ensure that these groups are evaluated and that appropriate control steps are taken as needed.

Neurotoxic research must be improved, in terms of both quantity and focus, as outlined above. Better coordination must be developed between the involved federal agencies (especially an augmented NTP program), industry research groups, and academic institutions. Only through a better understanding of neurotoxic disorders and their relationship to exposure will we be able to adequately prevent the occurrence of such problems.

C. Control

Because our current surveillance system is inadequate and our knowledge of the effects of exposure to neurotoxic substances is imprecise, we do not know the full extent of the improvements needed to control neurotoxic exposures in the workplace. Several general areas, however, can be identified where improvements are needed if an effective prevention strategy is to be realized.

1. An extensive education program should be implemented to raise general awareness of the danger of neurotoxicity and its related effects on safety, the extent to which neurotoxic chemicals pervade our lives, and the fact that suitable methods are available to assess the effects before irreversible changes occur. Schools at all levels need to teach more occupational safety and health to their students. Information must be provided at three levels — professional, public, and workplace — using appropriate levels of instruction.

2. Members of the industrial hygiene profession must receive advanced instruction in neurotoxicity recognition and testing methods. Integration of such

information into licensing examinations would provide a stimulus for such efforts.

Information on control programs for specific industries must be disseminated to managers and the other industrial officials responsible for implementation. To improve the medical monitoring of workers exposed to neurotoxic substances, health professionals need a better knowledge of the effects of these substances.

3. Public instruction in high school and vocational schools can provide the necessary information base on which worker education will be built. Workplace education must be built through on-the-job instruction involving competency demonstrations (not just tests). Such education must be ongoing, and exemplary programs funded by NIOSH and OSHA could serve as models. Material safety data sheets and labeling need special attention, but are only useful supplements to ongoing training efforts. Research is needed to develop effective education and training programs, and the field should be surveyed to identify present educational resources (e.g., voluntary organizations, insurance companies) and to capitalize on those programs. Finally, the underserved worker/workplace must be targeted. Workers in small businesses, service industries, and agriculture especially have difficulty obtaining needed information and training.

4. Neurotoxic disorders continue to occur, indicating that the regulatory apparatus currently in place has not been sufficiently effective in preventing such disorders. Pre-market testing for neurotoxic endpoints is almost non-existent, and NIOSH-recommended standards, many of which are based on neurotoxicity, have not resulted in revised PELs. Several steps should be taken to reverse these failures. Successful programs, such as voluntary compliance with ACGIH TLVs and independently checked exposure monitoring, should be promoted and extended to supplement ongoing regulatory activities. A single set of strategies or protocols for pre-market screening should be developed and implemented.

   Reasons for the shortcomings in current regulations should be investigated and remedied. For example, workers' compensation laws may reduce cleanup incentives by spreading the costs over all employers. Such potential problems should be investigated, and alternatives should be proposed. The use of quantitative risk assessment should be explored to determine its role as an appropriate procedure for establishing safe levels of exposure. Exposure standards for neurotoxic substances should be reviewed frequently and updated appropriately. Finally, all workers potentially exposed to neurotoxic substances must have the benefits of appropriate regulation and compliance monitoring to ensure that their exposures are properly controlled. In particular, exposures in small businesses and agriculture, which may not be adequately covered by current regulations, must be addressed. Industries that present high exposures, identified through an improved surveillance system, should be targeted for more frequent monitoring.

5. Efforts are needed to ensure that feasible and cost-effective methods are available to control neurotoxic exposures and that business owners and workers are aware of these methods for their specific industries. These control efforts must take into account multiple exposures to neurotoxicants in many workplaces and the time course of these exposures (e.g., intermittent peak exposures). Control activities should be targeted at industries that present

significant exposures to neurotoxic chemicals as identified through the surveillance and evaluation activities described above. In particular, simple inexpensive engineering controls for small industries should be developed and disseminated to owners of such businesses. Similarly, personal protective equipment and work practices for specific industries should be evaluated and appropriate improvements should be made. Industry can play a major role by helping their direct consumers or users identify proper control measures. Introduction of these topics into professional education curricula will also provide necessary dissemination of control information. Medical monitoring of exposed workers should also be improved. Efforts to develop uniform definitions of disease and improved methods for neurobehavioral testing will provide the basis for these improvements.

V. Conclusions

Preventing neurotoxic disorders by implementing the provisions of this strategy will depend on concerted efforts involving surveillance, evaluation, and control activities. A restructured and aggressive surveillance system for exposure and disease is needed to identify industries or occupational groups at high risk for neurotoxic hazards. These data can be used to direct appropriate control actions. The evaluation component will provide better knowledge of neurotoxic illnesses, particularly their relationship to specific levels of exposures. A better knowledge of the mechanisms of neurotoxicity will lead to improved tests for screening and characterizing neurotoxic chemicals. This knowledge is basic to monitoring and other measures aimed at keeping occupational exposures below levels that produce neurotoxicity. Controls to ensure that workers are adequately protected from undue exposures will require adequate premarket testing of new chemicals that enter the workplace and improved regulatory mechanisms that extend coverage to the total workforce. The surveillance system will track control measures once in place, providing necessary feedback to judge their success. Implementing this strategy will require the involvement of many different groups — government agencies, industry, labor, academic institutions, and others. Through their joint efforts, the major workplace problem of occupational neurotoxic illnesses can be averted.

VI. Appendices

Appendix 1. Chemicals Used in Industry That Have Been Historically Established as Neurotoxic

Acetyl ethyl tetramethyl tetralin
Acetyl pyridine
Acrylamide
Adiponitrile
Alkyl phosphates
Aluminum
Aniline
Arsenic, inorganic
Arsine
Aryl phosphates
Azide
Barium
Benzene
Boron
p-Bromophenyl acetylurea
Cadmium
Carbon disulfide
Carbon monoxide
Carbon tetrachloride
Chlordane
Chlordecone
Chloroprene
Cobalt
Cuprizone
Cyanide
2,4-Dichlorophenoxy acetic acid (2,4-D)
Dichlorodiphenyl trichloroethane (DDT)
Diethyl ether
Diisopropyl fluorophosphate (DFP)
Dimethyl sulphate
Ethylene dichloride
Hexachlorophene
n-Hexane
Hydroquinone
Lead
Lead, tetraethyl
Leptophos
Malonitrile
Manganese
Mercury
Methanol
Methyl bromide
Methyl chloride
Methyl n-butyl ketone
Nickel (carbonyl)
Nitrogen trichloride
Organochlorine insecticides
Organophosphate esters
Organotins (Triethyltin)
Paraquat
Phenol
Phenyl mercury
Phthalate esters
Polybrominated biphenyls (PBBs)
Selenium
Styrene
Sulfur dioxide
Tetrachlorobiphenyl
Thallium
Toluene
Trichloroethylene
Triorthocresylphosphate (TOCP)
Vanadium, inorganic salt
Zinc
Zinc pyridinethione

Appendix 2. Examples of Major Sources of Exposure to Neurotoxic Substances*

Neurotoxic Chemicals	Neurotoxic Effects	# Exp	Sources of Exposure	
Solvents				
Carbon disulfide	Psychosis Polyneuropathy Encephalopathy Vision deficits	1.1M†	Paints Textiles Varnishes Rubber cement	Viscose rayon Preservatives Electroplating
n-Hexane	Polyneuropathy Optic neuropathy Memory loss	2.1M	Lacquers Stains Glues	Rubber cement Printing inks Pharmaceuticals
Methyl n-butyl ketone	Polyneuropathy CNS pathology	Min	Paints Varnishes Lacquers	Metal cleaning Quick drying inks Paint removers
Toluene	Delerium Vertigo Vision deficits Paresthesias	4.8M	Benzene mfg. Glues Paints Gasoline Lacquers	Fuels (auto, plane) Rubber solvents Cleaning agents Paint thinners
Trichloro-ethylene	Confusion Vision deficits CNS pathology Trigeminal neuropathy	3.7M	Degreasing Painting Varnishes	Dry cleaning Rubber solvents Shoe adhesives Lacquers Caffeine extraction
Metals				
Arsenic	Polyneuropathy Paresthesias Fatigue	‡	Pesticides Smelters Seafood Well water	Semiconductors Antifouling paint Electroplating Pigments
Lead	Encephalopathy Depression Polyneuropathy Blindness CNS pathology Neurochemistry changes	1.4M	Solder Lead shot Pottery Smelters Insecticides Foundries Mining	Leaded paint Storage battery Lead stained glass Lead pipes Auto body shops Illicit whiskey
Manganese	Psychosis Emotional lability Tremor	‡	Fertilizers Mining Welding Iron, steel	Steel finishing Oxidation catalysts Fireworks, matches Dry cell batteries
Mercury	Personality changes Polyneuropathy Tremor Visual field loss Paresthesias	24K	Farming Amalgams Pigments Photography Taxidermy	Scientific instruments Electrical equipment Electroplating Felt making Textiles

Appendix 2, Cont.

Neurotoxic Chemicals	Neurotoxic Effects	# Exp	Sources of Exposure	
Nickel	Tremor Chorea	‡	Paints Inks Alloys Coinage	Electroplating Surgical instruments Ni-cad batteries Mining
Tellurium	Polyneuropathy Vision changes Lethargy	‡	Foundries Electronics Glazes, glass Semiconductors	Rubber vulcanization Thermoelectric devices
Thallium	Psychosis Delerium Polyneuropathy Tremor	‡	Rodenticides Fungicides Special lenses	Photoelectric cells Optical devises Mercury, silver alloys
Tin	Vision changes Weakness Convulsions Tremor	‡	Solder Silverware Fungicides Mining	Canning Electronics Polyvinyl plastics Coated wire
Monomers				
Acrylamide	Polyneuropathy Encephalopathy Hallucinations Tremor	10K	Grouting: basements tunnels dams	Photography Water, waste treatment Paper, pulp
Styrene	Memory changes Incoordination EEG changes	329K	Rubber Resins Tires Insulators	Polystyrene Polyester fibers Fibrous glass
Gases				
Carbon monoxide	Memory loss Lethargy CNS pathology Paralysis Blindness	‡	Poorly ventilated stoves, furnaces	Acetylene welding Internal combustion engine exhaust Enclosed areas (mines, tunnels)
Ethylene oxide	Paresthesias Neuropathy	144K	Sterilizers	
Anesthetic Gases				
Nitrous oxide Halothane		2.0M	Dental offices	Operating rooms
Pesticides				
Methyl bromide	Polyneuropathy	‡	Fumigants	
Organochlorines			Chemical production	Pest extermination

Appendix 2, Cont.

Neurotoxic Chemicals	Neurotoxic Effects	# Exp	Sources of Exposure	
Organophosphates	Polyneuropathy Psychosis	‡	Pest control	Agriculture

* Modified from World Health Organization (*18*), Anger and Johnson (*8*); NIOSH (*13*).

† M = Million;
Min = Minimal;
K = Thousand

‡ Exposure estimates based substantially on "generic" formulas in NIOSH (*13*) are not included in the Table.

Appendix 3. Effects of Occupational Chemicals on the Nervous System*

Peripheral Nervous System

Effect	Agent	Comments
Motor neuropathy	Lead	Wrist extensors (drop rare)
Mixed sensorimotor neuropathy	Acrylamide	Ataxia, hand and sole desquamation, palm sweating
	Arsenic	Distal paresthesias, painful limbs, calves, foot hyperpathia, leg weakness
	Carbon disulfide	Mild (CNS effects more important)
	Carbon monoxide	Only after severe intoxication
	DDT	Only seen with ingestion
	N-hexane, methyl n-butyl ketone	Distal paresthesias, motor weakness, weight loss, fatigue, cramps
	Mercury (esp. alkyl)	Distal sensory involvement

Central Nervous System

Effect	Agent
Cranial neuropathy	Carbon disulfide, Trichloroethylene
Bladder neuropathy	Dimethylaminopropionitrile (DMAPN)
Constricted visual fields	Mercury
Impaired visual acuity	n-Hexane, Mercury, Methanol
Myoclonus	Benzene hexachloride, Mercury
Nystagmus	Mercury
Opsoclonus	Chlordecone
Paraplegia	Organotin compounds
Parkinsonism	Carbon disulfide, Carbon monoxide, Manganese
Seizures	Lead, Organic mercurials, Organotin compounds, Organochlorine insecticides
Tremor	Carbon disulfide, Chlordecone, DDT, Manganese, Mercury
Ataxic gait	Acrylamide, Chlordane, Chlordecone (Kepone) DDT, n-Hexane, Manganese, Methylmercury, Methyl n-butyl ketone (MBK), Methyl chloride
Impaired psychomotor function	Organophosphate insecticides, Mercury, Carbon disulfide, Lead, Styrene, Perchloroethylene
Memory impairment	Arsenic, Carbon disulfide, Lead, Manganese
Neurasthenia, irritability, mild systemic symptoms	Acrylamide, Arsenic, Lead, Manganese, Mercury, Methyl n-butyl ketone (MBK), Organotin compounds, Styrene
Emotional instability/psychosis (acute)	Carbon disulfide, Manganese, Toluene (rare)

* Adapted from Baker (*15*)

Appendix 4. Number of Chemicals for Which Various Neurobehavioral Effects Have Been Reported*

Motor	Number of chemicals
Activity changes	32
Ataxia	89
Convulsions	183
Incoordination/ unsteadiness/clumsiness	62
Paralysis	75
Pupil size changes	31
Reflex abnormalities	54
Tremor/twitching	177
Weakness	179
Sensory	
Auditory disorders	37
Equilibrium changes	135
Olfaction disorders	37
Pain disorders	64
Pain, feelings of	47
Tactile disorders	77
Vision disorders	121
Cognitive	
Confusion	34
Memory problems	33
Speech impairment	28

General	Number of chemicals
Anorexia	158
Autonomic dysfunction	26
Cholinesterase inhibition	64
CNS depression	131
Fatigue	87
Narcosis/stupor	125
Peripheral neuropathy	67
Affect/Personality	
Apathy/languor/ lassitude/lethargy/ listlessness	30
Delirium	26
Depression	40
Excitability	58
Hallucinations	25
Irritability	39
Nervousness/tension	29
Restlessness	31
Sleep disturbances	119

* Adapted from Anger (*12*)

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