PLAINTIFF'S EXHIBIT

UC-3594

Leading Work-Related Diseases and Injuries — United States

The National Institute for Occupational Safety and Health (NIOSH) has developed a list of 10 leading work-related diseases and injuries. The first six categories have been described previously (1-6); a discussion of the seventh category, Neurotoxic Disorders, appears below.

NEUROTOXIC DISORDERS

Background. Diseases of the nervous system resulting from toxic exposures in the workplace were known as early as the first century A.D., when Pliny identified palsy as a manifestation of lead poisoning among workers exposed to lead dust (*7*). In 1557, Jean Fernel linked gingival pigmentation, tremor, and behavioral changes to occupational mercury poisoning (*8*); in the nineteenth century, Delpech recognized rubber processing as the cause of the bizarre psychoses occurring among French workers who manufactured condoms and balloons in small cottage industries. Later, carbon disulfide was implicated as the specific neurotoxic agent (*9*).

Industrial hygiene practices have improved in the twentieth century, and some animal models of neurotoxic disease have been developed. In addition, workers who become ill often draw attention to outbreaks of neurotoxic diseases. Despite the prior identification of acrylamide as neurotoxic in animals, its neurotoxicity in humans was first recognized in the 1950s, when several Japanese workers involved in a pilot production project developed peripheral neuropathy (*10*). During the 1960s and early 1970s, dozens of cases of neuropathy occurred among Japanese and Italian workers exposed to solutions containing *n*-hexane during the manufacture of shoes (*11*). Subsequently, high doses of *n*-hexane were found to be neurotoxic in exposed animals. In the past 15 years alone, outbreaks of serious human neurotoxicity occurred among workers exposed to three substances not previously known to be neurotoxic: the chlorinated hydrocarbon, chlordecone, which caused opsoclonus, tremor, disturbances of gait, and changes in personality (*12*); and two hexacarbons, methyl-*n*-butyl ketone and 2-t-butylazo-2-hydroxy-5-methylhexane, both of which caused a predominantly peripheral neuropathy (*13,14*).

Nature of Neurotoxic Disorders. Neurotoxic disorders are on the NIOSH list of Ten Leading Work-Related Diseases and Injuries (*1*) because of their potential severity—as exemplified by the neurotoxicity of chlordecone—and because of the large number of workers potentially at risk. A conservative estimate of the workers exposed full time to one or more neurotoxic agents is 7.7 million (*15*). The number of potentially neurotoxic chemicals found in the workplace exceeds 850; an abbreviated list of the more commonly used of these chemicals is shown in Table 3 (*16*).

Clinically, symptoms and signs of neurotoxicity can be diverse. Depending on the intensity of exposure, the molecular configuration of the agent, and the mechanism of toxicity, either central or peripheral neurologic effects may predominate. Most neurotoxic chemicals, however, affect both the central and peripheral nervous systems. Because the symptoms of peripheral neuropathy are more specific and the nerves themselves more directly accessible to precise diagnostic examinations, the effects of neurotoxic agents on the peripheral nervous system are usually more easily identified than effects on the central nervous system (CNS). Early symptoms of peripheral neuropathy may include numbness, tingling, or pain in the feet or hands. As the disease progresses, clumsiness or incoordination due to both sensory and motor changes may develop. Production workers may find their ability to do usual work partially or fully impaired. Chemicals used extensively in industry, which cause peripheral neu-

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ropathy when present in sufficiently high and persistent concentrations, include: lead, *n*-hexane, acrylamide, carbon disulfide, mercury, and methyl bromide (*17,18*) (Table 4). Several chemicals are known to cause selective impairment of cranial-nerve function, including dysfunction of the fifth cranial nerve (trichloroethylene) (*18*).

The effects of neurotoxic agents on the CNS present a far wider range of disturbances (*16,18,19*) (Table 5). At times, the most striking effects are changes in mood and personality (*20*). High levels of exposure to manganese or carbon disulfide produce psychoses and suicidal tendencies. Delusions and hallucinations may result from exposure to high concentrations of solvents, such as methylene chloride. Manifestations of cognitive dysfunction, such as reduced attention span, lack of alertness, and memory loss, are prominent neurotoxic effects that may occur in addition to personality changes after exposure to many solvents and to asphyxiants, such as carbon monoxide. Other neurologic effects occur under certain restricted conditions of exposure to unique chemical substances (Table 6).

Although research into the neurobehavioral effects of industrial chemicals is relatively new, early results suggest that occupational neurotoxicity may be a larger problem than previously suspected. Sensitive methods for evaluating subtle losses in cognitive function have only recently been applied to the evaluation of exposed workers. Because of the complexity of the nervous system and the variety of potentially neurotoxic exposures, the true scope of this health hazard in the workplace is unknown.

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Editorial Note: Studies of the neurotoxicity of workplace chemicals demonstrate the problems encountered in recognizing occupational disease in general. Despite occasional large and dramatic outbreaks of neurotoxic disorders, such as those mentioned above, more often small numbers of workers in many workplaces are chronically exposed to neurotoxic agents

TABLE 3. Commonly used industrial chemicals recognized as neurotoxic

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

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that subtly and slowly alter nervous-system functions. Several neurotoxic syndromes mimic diseases of nonoccupational and "idiopathic" etiology, e.g., the toxic axonopathy associated with exposure to various metals and solvents, the parkinsonian syndrome of chronic intoxication with manganese, and the organic brain syndrome of chronic solvent intoxication. Because of these similarities to other nonoccupational diseases, such cases are frequently not identified as occupational in origin. In addition, many physicians are not trained to take an adequate occupational medical history (*21*). For these reasons, the prevalence of occupational neurologic disease is unknown, and important causal relationships between chemicals and disease remain obscure.

The prevention of neurotoxicity among workers will require strategies such as those suggested in the 1990 objectives for improving the nation's health (*22*), developed by the U.S. Public Health Service: (1) analyses of structural analogues of known neurotoxic agents in an effort to predict the neurotoxicity of untested chemicals; (2) continuing search for animal models of disease; (3) ongoing research in establishing an acceptable human exposure level for identified neurotoxic agents; (4) epidemiologic evaluations of suspected neurotoxicity; (5) development of simple screening tools for use on asymptomatic populations exposed to known neurotoxic agents; and (6) premanufacture and premarket testing of new chemicals as required by the Toxic Substances Control Act (*23*). As in the prevention of other work-related diseases, however, the most direct and effective method for preventing neurotoxic illness will continue to be the environmental control of exposures to neurologic chemicals. Such efforts as the substitution of less toxic substances where possible, engineering controls, teaching appropriate work practices, and educating workers about the potential neurotoxicity of chemicals will aid a comprehensive prevention effort.

References

1. CDC. Leading work-related diseases and injuries—United States. MMWR 1983;32:24-6, 32.
2. CDC. Leading work-related diseases and injuries—United States. MMWR 1983;32:189-91.

TABLE 4. Examples of peripheral neuropathies associated with occupational toxins

Type of neuropathy	Toxin	Comments
Motor	Lead	Wrist extensors primarily involved; wrist and ankle drop are rare.
Mixed sensorimotor	Acrylamide	Ataxia; desquamation of hands and soles; sweating of palms.
	Arsenic	Early distal paresthesias; pain in limbs, especially calves; hyperpathia of feet; weakness prominent in legs.
	Carbon disulfide	Peripheral neuropathy rather mild; CNS effects more important.
	Carbon monoxide	After severe intoxication.
	DDT	Only with ingestion.
	n-Hexane, methyl *n*-Butyl ketone	Distal paresthesias, motor weakness; weight loss, fatigue, and muscle cramps.
	Mercury	Predominantly distal sensory involvement; more common with alkyl mercury exposure.

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TABLE I. Summary—cases specified notifiable diseases, United States

Disease	8th Week Ending			Cumulative, 8th Week Ending		
	Feb. 22, 1986	Feb. 23 1985	Median 1981-1985	Feb. 22 1986	Feb 23 1985	Median 1981-1985
Acquired Immunodeficiency Syndrome (AIDS)	224	92	N	1,804	878	N
Aseptic meningitis	80	80	73	633	553	655
Encephalitis: Primary (arthropod-borne & unspec.)	18	19	19	119	120	123
Post-infectious	-	2	1	7	18	11
Gonorrhea: Civilian	13,299	15,233	16,561	117,512	119,548	141,048
Military	398	315	344	2,272	2,448	3,829
Hepatitis: Type A	397	461	527	3,333	3,075	3,427
Type B	388	518	479	3,290	3,533	3,341
Non A, Non B	53	87	N	409	572	N
Unspecified	75	57	167	747	618	1,046
Legionellosis	8	10	N	78	99	N
Leprosy	-	11	5	31	44	34
Malaria	13	19	19	90	102	102
Measles: Total*	249	27	28	399	112	112
Indigenous	246	27	N	390	79	N
Imported	3	-	N	9	33	N
Meningococcal infections: Total	83	86	86	444	447	489
Civilian	83	86	86	444	447	489
Military	-	-	-	-	-	1
Mumps	85	102	99	369	494	603
Pertussis	34	38	36	290	189	178
Rubella (German measles)	3	4	22	51	30	124
Syphilis (Primary & Secondary): Civilian	389	507	669	3,470	3,772	4,661
Military	6	-	7	28	26	64
Toxic Shock syndrome	4	14	N	35	82	N
Tuberculosis	377	347	416	2,501	2,425	2,999
Tularemia	1	3	2	12	19	13
Typhoid fever	7	6	9	31	39	60
Typhus fever, tick-borne (RMSF)	-	-	-	7	4	8
Rabies, animal	52	97	108	548	609	664

TABLE II. Notifiable diseases of low frequency, United States

	Cum 1986		Cum 1986
Anthrax	-	Leptospirosis (Iowa 1)	8
Botulism: Foodborne (Calif. 1)	3	Plague	-
Infant (Calif. 1)	7	Poliomyelitis, Paralytic	-
Other	-	Psittacosis	4
Brucellosis (Mo. 1)	6	Rabies, human	-
Cholera	-	Tetanus (S. Dak. 1)	5
Congenital rubella syndrome	1	Trichinosis	7
Congenital syphilis, ages < 1 year	-	Typhus fever, flea-borne (endemic, murine)	1
Diphtheria	-		

*Three of the 249 reported cases for this week were imported from a foreign country or can be directly traceable to a known internationally imported case within two generations.

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