

The acute neurotoxic effects of organic solvent exposure in workers and laboratory animals are narcosis, anesthesia, central nervous system (CNS)depression, respiratory arrest, unconsciousness, and death.

ORGANIC SOLVENT NEUROTOXICITY

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ABSTRACT

The acute neurotoxic effects of organic solvent exposure in workers and laboratory animals are narcosis, anesthesia, central nervous system (CNS)depression, respiratory arrest, unconsciousness, and death.

Acute experimental exposures of human volunteers to one or several organic solvents have impaired psychomotor function as measured by reaction time, manual dexterity, coordination, or body balance.

Chronic animal studies with a limited number of organic solvents support the evidence for peripheral neuropathy and mild toxic encephalopathy in solvent-exposed workers.

Epidemiologic studies of various groups of solvent-exposed workers have demonstrated statistically significant chronic changes in peripheral nerve function (sensory and motor nerve conduction velocities and electromyographic abnormalities) that persisted for months to years following cessation of exposure. Epidemiologic studies have also shown statistically significant increases in neurobehavioral effects in workers chronically exposed to organic solvents. These effects include disorders characterized by reversible subjective symptoms (fatigability, irritability, and memory impairment), sustained changes in personality or mood (emotional instability and diminished impulse control and motivation), and impaired intellectual function (decreased concentration ability, memory, and learning ability). Among organic solvent abusers, the most severe disorders reported are characterized by irreversible deterioration in intellect and memory (dementia) accompanied by structural CNS damage.

On the basis of the identified adverse health effects of solvent exposure, the National Institute for Occupational Safety and Health (NIOSH) recommends that employers use engineering controls, personal protective equipment and clothing, and worker education programs to reduce exposure to organic solvents--at least to the concentrations specified in existing Occupational Safety and Health Administration (OSHA) permissible exposure limits (PEL's), or to NIOSH recommended exposure limits (REL's) or the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) if they provide a greater degree of protection.

BACKGROUND

Physical and Chemical Properties

The term "organic solvents" refers to a group of volatile compounds or mixtures that are relatively stable chemically and that exist in the liquid state at temperatures of approximately 0° to 250°C (32° to 482°F). Common organic solvents are classified as aliphatic hydrocarbons, cyclic hydrocarbons, aromatic

hydrocarbons, halogenated hydrocarbons, ketones, amines, esters, alcohol's, aldehydes, and ethers. Many common solvents often exist as mixtures or blends of chemical compounds (e.g., Stoddard solvent and thinners) (WHO 1985; Parrish 1983).

Production, Use, and Potential for Occupational Exposure

Organic solvents are used for extracting, dissolving, or suspending materials such as fats, waxes, and resins that are not soluble in water. The removal of the solvent from a solution permits the recovery of the solute intact with its original properties (Considine 1976). Solvents are used in paints, adhesives, glues, coatings, and degreasing/cleaning agents, and in the production of dyes, polymers, plastics, textiles, printing inks, agricultural products, and pharmaceuticals (WHO 1985; Parrish 1983). In 1984, approximately 49 million tons of industrial solvents were produced in the United States (USITC 1985).

Approximately 9.8 million workers are potentially exposed to organic solvents. This estimate is based on data collected during the National Occupational Hazard Survey conducted by the National Institute for Occupational Safety and Health (NIOSH) during 1972-1974 (NIOSH 1977d).

EXPOSURE L I M I T S

The Occupational Safety and Health Administration (OSHA) has promulgated permissible exposure limits (PEL's) for occupational exposure to some of the chemicals and mixtures that are used as organic solvents (29 CFR* 1910.1000). Each PEL is determined as an 8-hr time-weighted average (TWA) concentration, and it is based on the 1968 threshold limit value TLV(of the American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH 1968) for a specific organic solvent.

NIOSH has established recommended exposure limits (REL's) for 92 chemicals and mixtures that can be defined as organic solvents. Appendix A lists those chemicals and mixtures with NIOSH REL's, OSHA PEL's, and ACGIH TLVs (ACGIH 1986). Additional organic solvent PEL's and TLVs are listed in 29 CFR 1910.1000 and in TLVs(Threshold Limit Values and Biological Exposure Indices for 1986-1987 (ACGIH 1986), respectively.

* Code of Federal Regulations. See CFR in references.

TOXICITY

Results of Animal Studies

Acute Toxicity

To date, most experimental animal studies with organic solvents have been conducted to determine their acute neurotoxic effects on the central nervous system (CNS) rather than the potential chronic neurotoxic effects from long-term exposure. The acute toxic effects of solvent inhalation noted in animals reflect those seen in humans--that is, narcosis, anesthesia, CNS depression, respiratory arrest, unconsciousness, and death (Browning 1965).

Chronic Toxicity

Experimental and neuropathologic animal studies support the evidence associating a limited number of organic solvents (Appendix B) with the peripheral neuropathy and mild toxic encephalopathy observed in exposed humans. However, the majority of solvents in daily use have yet to be tested for chronic

neurotoxic effects in animals, and therefore an adequate animal model for the induction of these effects is not yet available. An animal model of the mechanism of pathogenesis would lead to more accurate methods for predicting the NEUROTOXICITY of organic solvents. In research studies to develop animal models for NEUROTOXICITY (Haglid et al. 1981, 1985), Mongolian gerbils were exposed to one of four organic solvents (trichloroethylene, perchloroethylene, methylene chloride, or ethanol) for 3 months, followed by an exposure-free rehabilitation period of 4 months, to determine whether any irreversible cellular changes had occurred in the brain. Increases in brain protein levels, which are known to indicate cell proliferation characteristic of irreversible brain damage (Persson et al. 1976; Bignami and Dahl 1974), were shown following inhalation of 60 parts per million (ppm) of trichloroethylene, 60 ppm of perchloroethylene, or 350 ppm of methylene chloride, or following daily ethanol ingestion of 11.7 grams per kilogram (g/kg) of body weight. The investigators concluded that these changes may indicate irreversible brain reactions to organic solvent exposure.

Human Health Effects

Acute Toxicity

The acute, transient neurotoxic effects of organic solvent exposure in humans result from the pharmacologic action of the solvent within the CNS. These effects include CNS depression, psychomotor impairment, and narcosis. Solvent inhalation by workers may cause effects ranging from an alcohol-like intoxication to narcosis and death from respiratory failure, with a spectrum of intermediate symptoms that include drowsiness, headache, dizziness, dyspepsia, and nausea (Browning 1965).

In several Swedish and Finnish investigations, acute experimental exposure of human subjects to methyl chloroform (1,1,1-trichloroethane), styrene, or toluene impaired psychomotor functions of the CNS as measured by performance of a task. Inhalation exposure to these organic solvents for up to 2 hr at or above the NIOSH REL's of 350 ppm (ceiling) (NIOSH 1976b), 50 ppm (TWA) (NIOSH 1983a), or 100 ppm (TWA) (NIOSH 1973a), respectively, impaired simple or choice reaction time, perceptual and sensory motor speed, or manual dexterity and coordination in a statistically significant manner ($p < 0.05$) (Gamberale and Hultengren 1972, 1973, 1974; Gamberale 1976). Exposure of 8 volunteers to xylene for 6 hr/day over a period of 6 days at varying concentrations of 90 or 200 ppm (NIOSH REL, 100 ppm [NIOSH 1975]) caused a statistically significant impairment of body balance, manual coordination, and simple and choice reaction times ($p < 0.05$) when compared with baseline data established for these volunteers before and after exposure (Savolainen et al. 1980). Most of the observed neurologic effects of xylene disappeared after a few days of exposure, suggesting the development of tolerance. The investigators noted that concomitant physical exercise increased the xylene uptake and may have potentiated the above-mentioned CNS effects.

The effects of exposure on mood change were measured using visual analogue scales in 108 factory workers exposed to solvents (styrene, 6 to 191 ppm; methylene chloride, 28 to 173 ppm; or trichloroethane, toluene, and xylene combined, 3 to 67 ppm) during the production of fibrous glass panels and boats, acetate film, or paint (Cherry et al. 1983). The workers' subjective ratings of mood indicated a statistically significant deterioration ($p < 0.05$) by the end of a workshift. This result was measured by ratings of sleepiness, physical and mental tiredness, and general good health for exposed workers compared with unexposed control workers or controls exposed to low levels of styrene. When workers exposed to styrene or methylene chloride were evaluated for blood solvent levels, a statistically significant correlation ($p < 0.05$) existed between the elevation of solvent level in the blood at the end of the workshift and deterioration in mood during the Workshift.

Chronic Toxicity

Two international workshops have categorized solvent-induced CNS disorders according to their severity (Table 1) (WHO 1985; Baker et al. 1986). Correspondence between the two systems of nomenclature is not exact, but the categories produced by these two workshops do help clarify the chronic effects of solvents on the CNS. The further development of a standardized approach to describing the effects of chronic solvent exposure on the CNS will aid in the interpretation of studies in different parts of the world (Waldron 1986).

Each workshop identified three categories of effect, varying from minimal and reversible to pronounced and irreversible. Using the nomenclature from either workshop will be useful in classifying effects in future epidemiologic and clinical studies.

The mildest type of disorder is the organic affective syndrome (WHO Workshop), or the Type 1 disorder (International Solvent Workshop). This disorder is characterized by fatigue, memory impairment, irritability, difficulty in concentrating, and mild mood disturbance. Table 1.--Categories of solvent-induced CNS disorders

Category of CNS disorder

Category of CNS disorder		
Severity of Condition	Identified by WHO/Nordic Council of ministers Working Group Copenhagen, June 1985+	International Solvent Workshop, Raleigh, NC October 1985++
Minimal	Organic Affective Syndrome	Type 1
Moderate	Mild chronic toxic encephalopathy	Types 2A or 2B
Pronounced	severe chronic toxic encephalopathy	Type 3

* In view of the difficulty of categorizing these disorders, correspondence between the two systems of nomenclature is not exact.

+ WHO 1985.

++ Baker and Seppalainen 1986.

The second level of disorder is described as mild chronic toxic encephalopathy (WHO Workshop), or the Type 2 disorder (International Solvent Workshop). This level involves both symptoms of neurotoxicity and abnormalities of performance on formal neuropsychological testing. The Type 2 disorder has been divided into Type 2A (sustained personality or mood changes such as emotional instability and diminished impulse control and motivation) and Type 2B (impairment in intellectual function manifested by diminished concentration, memory, and learning capacity).

The third and most pronounced level of disorder is described as severe chronic toxic encephalopathy (WHO Workshop), or the Type 3 disorder (International Solvent Workshop). The condition is characterized by global deterioration in intellectual and memory functions (dementia) that may be irreversible, or at best, only poorly reversible.

Type 1 and 2 disorders are the most likely to be reported among solvent-exposed workers. Type 3

disorders to date have been seen only in individuals who have abused solvent-containing products (i.e., by deliberately inhaling organic solvent vapors for their euphoric properties). For example, persons who abusively inhaled toluene almost daily for 1 to 7 years showed evidence of severe, multifocal CNS damage with cortical, cerebellar, and brain stem atrophy, electrophysiologic abnormalities, and neuropsychologic deficits (Lazar et al. 1983).

Neurophysiologic Effects

Neurophysiologic methods are useful indicators of nervous system malfunction or damage (Seppalainen 1985). Studies of various groups of solvent-exposed workers have demonstrated changes in neurophysiologic parameters measured by electroencephalograms (EEG's) and tests of peripheral nerve function.

Neurophysiologic effects of chronic exposure to a mixture of organic solvents were studied in 102 Finnish automobile spray painters who had a mean employment time of 14.8 years in car repair garages (Seppalainen et al. 1978). These painters were exposed to mixtures of nine organic solvents, the main components of which were butyl acetate, toluene, white mineral spirits, and xylene. Mean breathing zone concentrations for these four solvents were below the Finnish threshold limit values (150, 200, 200, and 100 ppm, respectively) and below the NIOSH REL's (none, 100, 55, and 100 ppm, respectively) (NIOSH 1973a, 1975, 1977c)--or in the absence of a REL, below the OSHA PEL (butyl acetate, 150 ppm) (29 CFR 1910.1000). A statistically significant decrease ($p < 0.05$) in motor and sensory nerve conduction velocities was noted in the painters compared with an age-matched reference group of railroad engineers. Eighty Swedish automobile and industrial spray painters experienced chronic exposures to mixtures of 19 organic solvents at breathing zone concentrations below the Swedish occupational exposure limit values and most NIOSH REL's--or in the absence of a REL, below the OSHA PEL (Elofsson et al. 1980). The painters demonstrated statistically significant decreases ($p < 0.05$) in motor and sensory nerve conduction velocities when compared with matched reference groups of unexposed electronics plant workers.

Seventy-seven workers were diagnosed as having "solvent poisoning" caused by occupational exposure (mean of 9.6 years for males and 7.6 years for females) to organic solvents such as halogenated, aromatic, and aliphatic hydrocarbons, paint solvents, and alcohol. The potential exposure of each subject was graded as low, intermediate, or high, based on workplace measurements of the solvents and information provided by the subject or the employer (Seppalainen et al. 1980). The frequency of abnormally slow nerve conduction velocities increased in a statistically significant manner ($p < 0.05$) when the intermediate exposure group was compared with the high exposure group.

A follow-up study was conducted with 87 patients 3 to 9 years after they were diagnosed as having chronic solvent intoxication following occupational exposure (mean of 10.7 years) to trichloroethylene, perchloroethylene, or solvent mixtures. The frequency of slow nerve conduction velocities in these workers remained relatively similar, and electromyographic abnormalities (fibrillations and loss of motor units) increased. These results suggest that electrophysiologic abnormalities may be permanent even after workers are removed from organic solvent exposure (Seppalainen and Antti-Poika 1983).

Studies of groups of solvent-exposed workers have also shown statistically significant differences in EEG abnormalities when compared with unexposed populations. One study involved 30 workers who were exposed for a mean of 17 years to jet fuel composed of organic hydrocarbons. The workers showed statistically significant ($p < 0.05$) EEG differences (lower amplitude, less observable rhythmic activity, higher alpha peak frequencies) when compared with unexposed matched controls (Knaive et al. 1978). A study of automobile and industrial spray painters revealed no statistically significant differences between exposed and reference populations in the visual evaluation of EEG's, but it described subtle EEG

abnormalities (increased alpha activity) in the exposed group (Elofsson et al. 1980). A cross-sectional study of the effects of chronic exposure (mean of 18 years) to solvents in the paint industry showed statistically significant differences ($p < 0.05$) in the EEG activity of the exposed group when compared with unexposed workers (Orbaek et al. 1985). The EEG results suggest changes in neurologic function indicative of chronic organic solvent exposure. EEG abnormalities persisted for 3 to 9 years in 42% of a group of patients diagnosed as having chronic solvent intoxication after occupational exposure (Seppalainen and Antti-Poika 1983).

Neurobehavioral Effects

When compared with groups of unexposed workers, groups exposed to solvents showed increases in subjective symptoms (Type 1), personality and mood changes (Type 2A), and poor performance on tests of CNS function, which indicated intellectual impairment (Type 2B). Studies were conducted of automobile and industrial spray painters with long-term exposures to organic solvents at concentrations below the Swedish occupational exposure limit values and most NIOSH REL's--or in the absence of REL's, OSHA PEL's. These workers exhibited a statistically significant incidence ($p < 0.001$) of Type 1 subjective psychiatric complaints (e.g., memory problems, headache, fatigability) when compared with unexposed matched reference groups (Elofsson et al. 1980). Psychologic testing also revealed statistically significant differences ($p < 0.05$) between the exposed and reference groups in simple reaction time, manual dexterity, perceptual speed, and short-term memory.

Neurobehavioral performance tests of CNS function (i.e., Block Design and Embedded Figures) were administered to 55 shipyard painters, 95% of whom had more than 10 years of work experience that involved exposure to methyl isobutyl ketone, perchloroethylene, xylene, ethylene glycol, and mineral spirits. The test scores of the exposed workers were significantly lower ($p < 0.004$) than those of the unexposed control workers (Valciukas et al. 1985).

Neurologic and Psychologic tests were administered to 65 workers (housepainters, paint and varnish factory workers, printers, dry cleaners, and boat factory workers) exposed primarily to white mineral spirits, toluene, perchloroethylene, or styrene for a mean of 12.9 years (Gregersen et al. 1984). Compared with an unexposed reference population, the exposed workers exhibited more symptoms of personality and mood change (Type 2A) and a statistically significant increase ($p < 0.05$) in unspecified emotional changes. The exposed workers also showed a statistically significant decrease ($p < 0.05$) in performance on the neuropsychologic tests of concentration ability/attention and abstraction functions (Type 2B) and a statistically significant correlation ($p = 0.045$) between degree of exposure and neuropsychologic and neurologic test performance. In addition, the exposed workers had lower scores in all five tests for learning/memory and in the combined index for intellectual impairment, although none of these were statistically significant. Also noted was a statistically significant frequency ($0.01 < p < 0.55$) of cerebral asthenopia (tiring, pain, and weakness in the eyes) among the exposed workers. This condition has been reported in another study in connection with diffuse cerebral atrophy (Willanger and Klee 1966).

Fifty workers exposed to solvents in the paint industry for a mean of 18 years, and 50 unexposed matched controls received psychiatric and Psychologic examinations (Orbaek et al. 1985). Results of the psychiatric examinations showed that the exposed workers had a statistically significant increase ($p < 0.05$) in 15 symptoms of mental disturbance (e.g., fatigability, tension, hostile feelings, memory problems) compared with the unexposed workers. The sum of the scores that each exposed subject received for the 15 symptoms correlated with an index of exposure in a statistically significant manner ($p < 0.001$). This result suggests that the greater the exposure of workers to organic solvents, the more frequent the symptoms of mental disturbance. The Psychologic examination consisted of a battery of psychometric tests for examining workers with suspected toxic encephalopathy. Exposed subjects

exhibited lower performance scores than unexposed workers for 10 of the 14 psychometric variables analyzed, but only one variable--a measure of focused attention abilities--was significantly different ($p < 0.01$). The individual test profiles revealed that 14% of the exposed workers and none of the reference group workers had definite indications of brain dysfunction (toxic encephalopathy), as indicated by significant deviation (>1 standard deviation) from expected values in two or more of the psychometric variables tested. The exposed workers with indications of brain dysfunction were among the more heavily exposed subjects, indicating a possible relationship between exposure level and effect.

Evaluations of neurobehavioral functions in groups of workers exposed to solvents have also addressed the reversibility of CNS effects resulting from solvent exposure. Fifty-six workers were diagnosed as having occupational diseases caused by exposure to organic solvents (primarily halogenated and aromatic hydrocarbons and mixtures of paint solvents) for a mean duration of 9.1 years at concentrations reported to be generally below the Finnish threshold limit value (Lindstrom 1980). The workers were given a series of Psychologic tests 5 or more years after cessation of solvent exposure. Test results revealed a statistically significant decrement ($p < 0.05$) in visuomotor performance and freedom from distractibility when compared with those of unexposed and styrene-exposed control groups. Visuomotor performance declined with increasing duration of solvent exposure in a statistically significant manner ($p < 0.001$). Bruhn et al. (1981) found that neurologic status and degree of neuropsychologic impairment were unchanged in 26 former house painters who had been diagnosed 2 years previously as having chronic toxic encephalopathy (cerebral atrophy and/or intellectual impairment) following a mean solvent exposure of 28 years.

Metabolism

Absorption

Inhalation and percutaneous absorption are the primary routes of solvent uptake into the peripheral blood, which begins within minutes of the onset of exposure (WHO 1985; Engstrom et al. 1978). Uptake by inhalation is the principal route and depends on the following: solvent concentration in inhaled air, blood/air partition coefficient of the solvent (which is determined by alveolocapillary membrane permeability and blood solubility), alveolar ventilation rate, blood perfusion of the lungs, and duration of exposure (WHO 1985; Astrand 1975). Increased levels of physical exercise increase pulmonary ventilation and cardiac output and lead to increased pulmonary solvent uptake over baseline resting levels in volunteers. A 27X increase in solvent uptake was noted in an inhalation study using 1,1,1-trichloroethane (Monster et al. 1979), and a 28% increase was reported in a study using xylene (Riihimaki et al. 1979).

Percutaneous absorption is also a major route of entry for organic solvents that are readily soluble in both lipids and water. Immersion of both hands in xylene for 15 min produced blood concentrations of xylene roughly the same as those following inhalation of 100 ppm for an equal period of time (Angstrom et al. 1977). Solvent uptake through the skin depends on (1) duration of contact, (2) skin thickness, perfusion, and degree of hydration, and (3) the presence of cuts, abrasions, or skin diseases (Riihimaki and Pfaffli 1978; Bird 1981).

Distribution and Transformation

Following absorption, organic solvents undergo biotransformation (which occurs primarily in the liver), or they accumulate in lipid-rich tissues such as those of the nervous system (WHO 1985; Bergman 1983). Metabolism in the liver generally consists of oxidative reactions catalyzed by the cytochrome P-450 mixed-function oxidase system followed by conjugation with glucuronic acid, sulfuric acid,

glutathione, or glycine. Metabolism usually results in the detoxication of the organic solvent through formation of water-soluble compounds that are excreted through urine or bile (Toftgard and Gustafsson 1980). However, metabolism may also produce reactive intermediate metabolites that are more toxic than the parent compound.

These metabolites are capable of covalently- binding to essential macromolecules (e.g., proteins, RNA, and DNA) and producing toxic effects (Toftgard and Gustafsson 1980; WHO 1985). For example, n-hexane and methyl n-butyl ketone (solvents that produce peripheral neuropathies in exposed workers [Herskowitz et al. 1971; Spencer et al. 1980b]) are both metabolized to 2,5-hexanedione (DiVincenzo et al. 1980), which has been shown to have a greater neurotoxic potency than either parent compound (Krasavage et al. 1980). This type of metabolic activation of solvents is believed to be mediated by the cytochrome P-448 system, which is more predominant in extrahepatic tissues (WHO 1985).

Studies have been conducted on the modification of-solvent metabolism rates in exposed workers by other exogenous substances, principally ethanol. The combined inhalation of toluene and ingestion of ethanol by seven volunteers caused a statistically significant increase ($p < 0.05$) in blood toluene concentrations when compared with toluene exposure with no alcohol (Waldron et al. 1983). The authors concluded that this increase in blood toluene concentration is possibly a result of competition for alcohol dehydrogenate necessary for the metabolism of both toluene and ethanol. In contrast, 33 toluene-exposed workers who chronically ingested alcohol had significantly lower blood toluene concentrations ($p < 0.05$) than did 13 workers from the same factory same factory who seldom drank. This result suggests an increase in toluene metabolism as a result of the alcohol-mediated induction of hepatic solvent-metabolizing microsomal enzymes (Waldron et al. 1983). In a study of the metabolic interaction of ethanol and xylene, 14 volunteers were exposed to m-xylene in an inhalation chamber, with and without prior ethanol ingestion (Riihimaki et al. 1982). The pre-exposure ingestion of ethanol caused statistically significant increases ($p < 0.05$) in blood xylene concentrations compared with those produced by corresponding xylene exposures without ethanol. This result suggests an ethanol-mediated inhibition of microsomal xylene metabolism. Thus it appears that acute ethanol ingestion raises blood toluene and xylene concentrations through competition for metabolism, whereas chronic ethanol ingestion induces solvent-metabolizing enzymes and thereby lowers blood solvent concentrations. Workplace exposures to several solvents simultaneously or to solvent mixtures may result in similar metabolic interactions.

..... **Excretion**

Solvent elimination occurs through exhalation of the parent compound in expired air or through urinary or biliary excretion of water-soluble metabolites or of unchanged solvent. Because excretion kinetics vary among compounds, kinetics must be considered in planning biologic monitoring in which elimination of these compounds is measured as an estimate of solvent uptake (Baker et al. 1985).

CONCLUSIONS

The research data presented in this CIB have focused on the neurotoxic effects produced in humans and animals exposed to organic solvents on an acute or chronic basis. The acute effects of solvent inhalation in both humans and animals include narcosis, anesthesia, CNS depression, respiratory arrest, unconsciousness, and death. The majority of organic solvents have yet to be tested for chronic neurotoxic effects in animals; thus experimental animal data supporting the evidence for chronic effects confirm only a limited number of organic solvents as neurotoxicants (see Appendix B). Research indicates that chronic exposure of animals to some organic solvents may cause irreversible CNS changes that are characteristic of brain damage.

In man, the acute reversible effects of exposure to organic solvents appear to result from properties of the parent compound. However, the chronic effects may be caused by metabolic activation of the parent compound, which results in more reactive intermediate metabolites (e.g., 2,5-hexanedione, a metabolite of n-hexane and methyl n-butyl ketone) that may alter nervous tissue structure. Chronic effects are often correlated with changes in nervous tissue structure and function that may be irreversible.

Chronic neurotoxicity in workers exposed to organic solvents over a period of months to years includes (1) peripheral neuropathies such as axonal degeneration seen in workers exposed to hexacarbon solvents (e.g., n-hexane, methyl n-butyl ketone), (2) Type 1 CNS symptoms such as fatigability, irritability, and memory impairment, and (3) Type 2 mild toxic encephalopathy, including sustained personality or mood changes such as emotional instability, diminished impulse control and motivation, and impairment in intellectual function manifested by diminished concentration, memory, and learning capacity. Epidemiologic studies have demonstrated correlations of workplace solvent exposures with the types of solvent-related CNS dysfunctions noted above and changes in neurophysiologic parameters such as nerve conduction velocities. Studies have demonstrated that these effects can persist for months to years after removal of workers from solvent exposure. The extent to which chronic neurotoxicity is reversible remains to be established peripheral nerves have the capacity to regenerate, but damage to the CNS is more often permanent.

The nervous system effects of exposure to organic solvents can lead to significant morbidity and increased risk of accidental injury, both on the job and away from work. The precise extent to which worker exposure to organic solvents increases the likelihood of accidents or illnesses remains to be determined, however.

The studies that indicate the potential for organic solvents to induce toxic effects on the human nervous system are not without shortcomings. Some evidence of CNS impairment is based on subjective data gathered from questionnaires. Neurophysiologic and neuropsychologic methods of detecting nervous system damage or deviations from normal CNS function can be questioned in epidemiologic studies because of the variability of response in normal individuals. In addition, workers using solvents are often exposed to complex mixtures of organic chemicals and other workplace chemical hazards; such exposures can confound the interpretation of epidemiologic data. However, NIOSH believes that the collective toxicologic and epidemiologic data on organic solvent neurotoxicity provide sufficient evidence to warrant concern about adverse health effects from occupational exposure to these chemicals.

RESEARCH NEEDS

The following research needs have been identified:

- Testing of chemical classes and structural analogues to provide the ability to predict neurotoxicity,
- Establishment of an adequate animal model to predict chronic neurobehavioral toxicity,
- Determination of the pathways and metabolic rates of specific solvents by brain and nerve tissues and the ability of these solvents to bind and accumulate in the CNS,
- Correlation of reported neurotoxic effects with exposure data,
- Epidemiologic research to establish the prevalence and incidence of neurologic disorders and to identify and validate quantitative tests for screening workers,

- Determination of the reversibility of neurotoxic effects of solvent exposure,
- Identification of the interactions or synergistic effects of solvent mixtures found in the workplace and the role of alcohol and other drugs in these interactions,
- Determination of the extent to which solvent exposure may increase accidental injuries on the job and away from work,
- Evaluation of the role of medical monitoring in the protection of workers exposed to neurotoxic solvents,

Development of improved methods for primary prevention of worker exposure (i.e., engineering controls, personal protective equipment, and work practices), and

- Development of new methods for biologic or process monitoring of skin exposures to organic solvents.

RECOMMENDATIONS

Occupational exposure to organic solvents can cause adverse health effects, and the potential for these solvent-induced effects may increase the risk of accidental injuries. NIOSH therefore recommends that engineering controls and personal protective equipment and clothing be used to reduce solvent exposures--at least to concentrations specified in existing OSHA PEL's, or to NIOSH REL's or ACGIH TLVs if they provide greater protection. NIOSH considers the PEL's, REL's, and TLVs for the specific organic solvents found in the workplace to be upper boundaries of exposure. Employers should therefore make every effort to keep exposure concentrations below these levels. Worker education programs should be instituted to inform workers about the hazards of exposure to organic solvents and to provide information on safe handling practices.

Many organic solvents are recognized by NIOSH as carcinogens or as reproductive hazards in the workplace. Examples of carcinogens recognized by NIOSH are benzene (NIOSH 1976c), carbon tetrachloride (NIOSH 1976d), trichloroethylene (NIOSH 1978d), and 1,1,2,2-tetrachloroethane (NIOSH 1978b). Reproductive hazards recognized by NIOSH include 2-methoxyethanol and 2-ethoxyethanol (NIOSH 1983a), and methyl chloride (NIOSH 1984a). NIOSH is also concerned about those organic solvents for which only neurotoxic effects have been reported. No precise determination has been made about the excess risk (i.e., risk beyond that expected-in an unexposed population) of neurotoxic effects in workers exposed to organic solvents, but the probability that a worker will exhibit such effects would be decreased by reducing exposure. Prudent public health policy requires that employers voluntarily assess the conditions under which workers may be exposed to organic solvents and take all reasonable precautions to reduce exposure.

[NC Chemical Injury Network](http://www.ncchem.com/niosh.htm)