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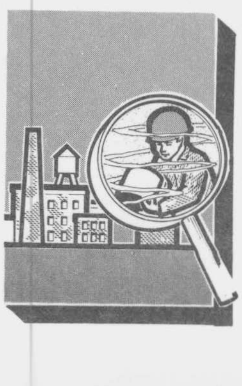
ORGANIC SOLVENT NEUROTOXICITY



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOREWORD

Current Intelligence Bulletins (CIB's) are issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, for the purpose of disseminating new scientific information about occupational hazards. A CIB may draw attention to a previously unrecognized hazard, or it may report new data suggesting that a known hazard is either more or less dangerous than was previously thought.

CIB's are prepared by the staff of the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226). They are distributed to representatives of academia, industry, organized labor, public health agencies, and public interest groups as well as to those Federal agencies that have responsibilities for protecting the health of workers. Our intention is to provide anyone who needs it with ready access to the information in these documents; we welcome suggestions concerning their content, style, and distribution.

Many organic solvents are recognized by NIOSH as carcinogens or reproductive hazards in the workplace. Examples of carcinogens recognized by NIOSH are benzene, carbon tetrachloride, trichloroethylene, and 1,1,2,2-tetrachloroethane. Reproductive hazards recognized by NIOSH include 2-methoxyethanol, 2-ethoxyethanol, and methyl chloride. This CIB describes other research results indicating the potential for organic solvents and various mixtures of organic solvents to cause neurotoxic effects in workers exposed to these substances. Neurotoxic disorders are listed by NIOSH among the ten leading work-related diseases and injuries. Because of expected increases in the manufacture of organic solvents, many of which may be neurotoxic, the population of exposed workers is likely to increase. NIOSH estimates that 9.8 million workers are potentially exposed to organic solvents used in such products as paints, adhesives, glues, coatings, and degreasing/cleaning agents, and in the production of dyes, polymers, plastics, textiles, printing inks, agricultural products, and pharmaceuticals.

No precise determination has been made of the excess risk of neurotoxic effects in workers exposed to specific concentrations of organic solvents, but the probability of developing such effects would be decreased by reducing exposure. NIOSH therefore recommends (1) that producers and users of organic solvents disseminate this information to their workers and customers, (2) that professional and trade associations and unions inform their members of the potential neurotoxic effects of working with organic solvents, and (3) that appropriate engineering controls, personal protective equipment, and worker education programs be used to reduce worker exposures--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.

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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, alcohols, 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 LIMITS

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*

Severity of condition	Category of CNS disorder: Identified by WHO/Nordic Council of Ministers Working Group, Copenhagen, June 1985†	International Solvent Workshop, Raleigh, N.C. 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 followup 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 (Knave 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 ($p\leq0.05$) in unspecified emotional changes. The exposed workers also showed a statistically significant decrease ($p\leq0.05$) 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 ($0.01<p\leq0.55$) 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 27% 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 (Engstrom 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 dehydrogenase 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 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 preexposure 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.

GUIDELINES FOR MINIMIZING WORKER EXPOSURE TO ORGANIC SOLVENTS

The guidelines below are general in nature and should be adapted to specific work situations as required. The area in which organic solvents are used should be restricted to those workers essential to the process or operation.

Exposure Monitoring

Qualified industrial hygiene personnel should make initial and periodic surveys of worker exposure. These surveys are necessary to determine the extent of worker exposure and to ensure that controls already in place are operational and effective. The NIOSH Occupational Exposure Sampling Strategy Manual (Leidel et al. 1977) may be helpful in developing efficient programs to monitor worker exposure to organic solvents. The manual discusses how to determine the need for exposure measurements and how to select sampling times.

Worker exposures to airborne contaminants should be estimated by 8-hr (or other full-shift) time-weighted averages (TWA's) and short-term (15-min) exposures calculated from personal (breathing zone) samples. Short-term samples should be taken during periods of maximum expected exposure by using all available knowledge of the work areas, procedures, and processes. Area and personal measurements may be useful in identifying sources of exposure at processes and operations.

Detailed analytical methods for individual organic solvents are in the NIOSH Manual of Analytical Methods, second and third editions (NIOSH 1978c, 1984b).

Controlling Worker Exposure

Proper maintenance procedures and worker education are all vital aspects of a good control program. An education program should be used to inform workers about the materials to which they are exposed, the nature of the hazards they pose, the methods for control, and appropriate personal hygiene procedures (29 CFR 1910.1200). Workers should also be given access to relevant exposure and medical records (29 CFR 1910.20). Three basic methods exist for limiting worker exposures to organic solvents: the use of contaminant controls, worker isolation, and personal protective equipment. Careful planning and thought should precede implementation of these methods.

Contaminant Controls

Engineering controls should be used as the primary method to eliminate the potential for organic solvent exposure in the workplace and to prevent fires and explosions. Achieving and maintaining reduced concentrations of organic solvents in the workplace depend on the implementation of engineering control measures such as properly constructed and maintained closed-system operations and exhaust ventilation with appropriate safety designs.

Closed-system operations provide the most effective means for minimizing worker exposures to organic solvents. Closed-system equipment should be used for manufacturing, storing, and processing organic solvents. Where closed systems cannot be used, local exhaust ventilation should be provided to direct vapors away from workers and to prevent the recirculation of contaminated exhaust air. Exhaust ventilation systems for quality control laboratories or laboratories where samples are prepared for analyses should be designed for adequate capture and containment of organic solvent vapors. Special consideration should be given to exposures that may occur during the release of these compounds from pressurized sampling containers. Guidance for designing local exhaust ventilation systems can be found in Recommended Industrial Ventilation Guidelines (Hagopian and Bastress 1976), Industrial Ventilation--A Manual of Recommended Practice (ACGIH 1984), and Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1979 (ANSI 1979).

Ventilation equipment should be checked at intervals that will ensure adequate performance. System effectiveness should also be checked when there are any changes in production, process, or control that might result in increased exposure to airborne organic solvents.

Worker Isolation

If feasible, workers should be isolated from direct contact with the work environment by the use of automated equipment operated from a closed control booth or room. The control room should be maintained at a greater air pressure than that surrounding the process equipment so that air flows out of the room rather than into it. Note, however, that this type of control will not protect workers who must perform process checks, adjustments, maintenance, and related operations. Thus special precautions are often necessary to prevent or limit worker exposure in these situations, and they frequently involve the use of personal protective equipment.

Personal Protective Equipment

Direct skin contact with organic solvents should be prevented through the proper use of solvent-resistant gloves, aprons, boots, or entire work suits, depending on the nature and extent of the hazard. Face shields or chemical safety goggles should be used wherever the potential for splashing exists. Any clothing that becomes contaminated with organic solvents should be removed and discarded or cleaned before reuse. Areas of the body that come in contact with organic solvents should be thoroughly washed with soap and water. As a general hygienic measure, facilities (e.g., change rooms, showers, etc.) should be provided for personal cleanliness.

The use of respiratory protection is the least preferred method of controlling exposures to airborne contaminants and should not be used as the only means of preventing or minimizing airborne exposures during routine operations. However, NIOSH recognizes that respirators may be required for protection in certain situations such as implementation of engineering controls, some short-duration maintenance procedures, and emergencies.

The use of respiratory protection requires employers to institute a respiratory protection program that, at a minimum, meets the requirements of 29 CFR 1910.134. A complete respiratory protection program should include (1) selection of respirators approved by the Mine Safety and Health Administration (MSHA) and NIOSH, (2) regular training of personnel, (3) fit testing, (4) periodic environmental monitoring, and (5) maintenance, inspection, and cleaning of equipment. The program should be evaluated regularly.

Selection of the proper respirator depends on the contaminant concentration, fit testing results, and specific conditions of use. Types of respirators recommended for protection against organic solvents are presented in Tables 2 through 4. Table 2 lists the types of respirators recommended for protection against solvents identified by NIOSH as potential occupational carcinogens. Table 3 lists types of respirators recommended for protection against organic solvents with poor warning characteristics or organic solvents for which effective adsorption-filtering media are unavailable.

Table 4 lists both air-purifying and atmosphere-supplying respirators recommended for chemicals with good warning properties.

Selection of a specific respirator should be based on the required reduction in solvent concentration, special use conditions, and the worker's proven ability (through fit testing) to wear the respirator. Note that air-purifying cartridge respirators cannot be used for solvent concentrations exceeding 1,000 ppm and that full facepieces, helmets, or hoods are recommended when eye irritation occurs.

Table 2.--Respirator selection table for solvents identified by NIOSH as potential carcinogens

Condition of use	Type of respirator recommended
Any detectable concentration	Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode
	Any supplied-air respirator that has a full facepiece and is operated in pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode
Escape only	Any full-facepiece respirator (gas mask) with a suitable organic vapor canister, or any appropriate self-contained breathing apparatus of the escape-type

Table 3.--Respirator selection table for noncarcinogenic solvents with poor warning properties or without suitable adsorption filtering media

Condition of use	Type of respirator recommended
Contaminant reduction multiple (protection factor) of:	
10x	Any self-contained breathing apparatus*
	Any supplied-air respirator*
25x	Any supplied-air respirator operated in a continuous-flow mode*
50x	Any supplied-air respirator with a full facepiece
	Any self-contained breathing apparatus with a full facepiece
	Any supplied-air respirator that has a tight-fitting facepiece and is operated in a continuous-flow mode
1,000x	Any supplied-air respirator that has a half facepiece and is operated in pressure-demand or other positive-pressure mode*
2,000x	Any supplied-air respirator that has a full facepiece and is operated in pressure-demand or other positive-pressure mode
A contaminant concentration that is IDLH† or unknown, or a contaminant reduction multiple greater than 2,000x	Any self-contained breathing apparatus that has a full facepiece and is operated in pressure-demand or other positive-pressure mode
	Any supplied-air respirator that has a full facepiece and is operated in pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode
Escape only	Any full-facepiece respirator (gas mask) with an appropriate organic vapor canister or appropriate self-contained breathing apparatus of the escape-type

* If eye irritation occurs, use full facepiece or other eye protection.

† Immediately dangerous to life or health. This level represents a maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects.

Table 4.--Respirator selection table for noncarcinogenic solvents with good odor warning properties and suitable adsorption filtering media

Condition of use	Type of respirator recommended
Contaminant reduction multiple (protection factor) of:	
10x	Any chemical cartridge, half-facepiece respirator*,†
	Any self-contained breathing apparatus*
	Any supplied-air respirator*
25x	Any supplied-air respirator operated in a continuous-flow mode*
	Any powered air-purifying respirator with suitable organic vapor cartridge(s)†
50x	Any full-facepiece respirator with suitable organic vapor cartridge(s)†
	Any full-facepiece respirator (gas mask) with a suitable organic vapor canister†
	Any supplied-air respirator with a full facepiece
	Any self-contained breathing apparatus with a full facepiece
	Any powered air-purifying respirator with a tight-fitting facepiece and appropriate organic vapor cartridge(s)*,†
	Any supplied-air respirator with a tight-fitting facepiece and continuous-flow mode operation

See footnotes at end of table.

(Continued)

Table 4 (Continued).--Respirator selection table for noncarcinogenic solvents with good odor warning properties and suitable adsorption filtering media

Condition of use	Type of respirator recommended
1,000x	Any supplied-air respirator that has a half facepiece and is operated in pressure-demand or other positive-pressure mode*
2,000x	Any supplied-air respirator that has a full facepiece and is operated in pressure-demand or other positive-pressure mode
A contaminant concentration that is IDLH§ or unknown, or a contaminant reduction multiple greater than 2,000x	Any self-contained breathing apparatus with a full facepiece operated in a pressure-demand or other positive pressure mode
	Any supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode
Escape only	Any full-facepiece respirator (gas mask) with an appropriate organic vapor canister or appropriate self-contained breathing apparatus of the escape-type

* If eye irritation occurs, use a full-facepiece respirator or other eye protection.

† Air-purifying cartridge respirators cannot be used for concentrations exceeding 1,000 ppm.

§ Immediately dangerous to life or health. This level represents a maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects.

Worker Education

Employers are to establish a worker education program for all workers exposed to hazardous chemicals. Training is to be provided at the time of initial assignment and whenever a new chemical hazard is introduced into the work area. This training should be designed to inform the worker about the materials to which they are exposed, the potential health risks from exposure to these materials, the proper use of personal protective equipment and clothing and other methods for control, and proper work practice procedures (29 CFR 1910.1200).

Medical Surveillance

Employers should establish a medical surveillance program to evaluate both the acute and chronic effects of exposure to organic solvents. The physician should be given information concerning the adverse effects of exposure to organic solvents and an estimate of the worker's potential exposure to them. This information should include any available results from workplace sampling and a description of any protective devices or equipment the worker may be required to use. A medical and work history should be taken initially and updated periodically. Workers who are currently exposed or who may be exposed to organic solvents should have preplacement and periodic evaluations focusing on their histories of previous exposure to organic solvents and other agents, particularly those associated with neurotoxic effects. The examining physician should direct particular attention to the nervous, respiratory, reproductive, and cardiovascular systems, and to the skin, eyes, liver, blood, kidneys, and gastrointestinal tract, as these are the most likely targets for the adverse effects of organic solvents.

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APPENDIX A

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING
OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
Alkanes (C5–C8)	TWA values in ppm (mg/m^3): Pentane: 120 (350); Hexane: 100 (350); Heptane: 85 (350); Octane: 75 (350); Mixtures not to exceed 350 mg/m^3 TWA; Ceiling values (15-min) singly or mixtures in ppm (mg/m^3): Pentane: 610 (1,800); Hexane: 510 (1,800); Heptane: 440 (1,800); Octane: 385 (1,800)	8-hr TWA values in ppm (mg/m^3): Pentane: 1,000 (2,950); n-Hexane: 500 (1,800); n-Heptane: 500 (2,000); Octane: 500 (2,350)	TWA values in ppm (mg/m^3): Pentane: 600 (1,800); n-Hexane: 50 (180); Other hexane isomers: 500 (1,800); n-Heptane: 400 (1,600); Octane: 300 (1,450) STEL values in ppm (mg/m^3): Pentane: 750 (2,250); Other hexane isomers: 1,000 (3,600); n-Heptane: 500 (2,000); Octane: 375 (1,800)
Allyl chloride	1 ppm (3.1 mg/m^3) TWA; 3 ppm (9.3 mg/m^3) ceiling (15-min)	1 ppm (3 mg/m^3), 8-hr TWA	1 ppm (3 mg/m^3) TWA; 2 ppm (6 mg/m^3) STEL
Benzene	Ca 0.1 ppm (0.32 mg/m^3) 8-hr TWA; 1 ppm (3.2 mg/m^3) ceiling (15-min)	10 ppm, 8-hr TWA; 25 ppm acceptable ceiling; 50 ppm maximum ceiling (10-min)	10 ppm (30 mg/m^3) A2 TWA; 25 ppm (75 mg/m^3) A2 STEL (15-min)
Benzyl chloride	5 mg/m^3 ceiling (15-min)	5 mg/m^3 (1 ppm), 8-hr TWA	1 ppm (5 mg/m^3) TWA

See footnotes at end of table.

(Continued)

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING
OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
Carbon disulfide	1 ppm (3 mg/m^3) TWA; 10 ppm (30 mg/m^3) ceiling (15-min)	20 ppm, 8-hr TWA; 30 ppm acceptable ceiling; 100 ppm maximum ceiling (30-min)	10 ppm (30 mg/m^3) TWA (skin)
Carbon tetra-chloride	Ca 2 ppm (12.6 mg/m^3) ceiling 45-liter sample (60-min)	10 ppm, 8-hr TWA; 25 ppm acceptable ceiling; 200 ppm maximum ceiling (5 min in 4 hr)	5 ppm (30 mg/m^3) A2 TWA (skin)
Chloro-ethane	To be handled in the workplace with caution	1,000 ppm (2,600 mg/m^3), 8-hr TWA	1,000 ppm (2,600 mg/m^3) TWA
Chloroform	Ca 2 ppm (9.78 mg/m^3) ceiling 45-liter sample (60-min)	50 ppm (240 mg/m^3) ceiling	10 ppm (50 mg/m^3) A2 TWA
Chloroprene	Ca 1 ppm (3.6 mg/m^3) ceiling (15-min)	25 ppm (90 mg/m^3), 8-hr TWA	10 ppm (35 mg/m^3) TWA (skin)
Cresol	2.3 ppm (10 mg/m^3) TWA	5 ppm (22 mg/m^3), 8-hr TWA (skin)	5 ppm (22 mg/m^3) TWA (skin)
Di-2-ethyl-hexyl-phthalate	Ca Reduce exposure to lowest feasible level	5 mg/m^3, 8-hr TWA	5 mg/m^3 TWA; 10 mg/m^3 STEL

See footnotes at end of table.

(Continued)

APPENDIX A (Continued)

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
Dioxane	Ca 1 ppm (3.6 mg/m^3) ceiling (30-min)	100 ppm (360 mg/m^3), 8-hr TWA (skin)	25 ppm (90 mg/m^3) TWA (skin)
Epichloro-hydrin	Ca Minimize occupational exposure	5 ppm (19 mg/m^3), 8-hr TWA	2 ppm (10 mg/m^3) TWA (skin)
Ethylene dibromide	Ca 0.045 ppm (0.38 mg/m^3), 8-hr TWA; 0.13 ppm (1 mg/m^3) ceiling (15-min)	20 ppm, 8-hr TWA; 30 ppm acceptable ceiling; 50 ppm maximum peak (5-min)	A2 (skin)
Ethylene dichloride	Ca 1 ppm (4 mg/m^3) TWA; 2 ppm (8 mg/m^3) ceiling (15-min)	50 ppm, 8-hr TWA; 100 ppm acceptable ceiling; 200 ppm maximum ceiling (5 min in 3 hr)	10 ppm (40 mg/m^3) TWA
Furfuryl alcohol	50 ppm (200 mg/m^3) TWA	50 ppm (200 mg/m^3), 8-hr TWA	10 ppm (40 mg/m^3) TWA (skin); 15 ppm (60 mg/m^3) STEL
Glycol ethers	Reduce exposure to lowest feasible level	2-Methoxyethanol: 25 ppm (80 mg/m^3), 8-hr TWA (skin); 2-Ethoxyethanol: 200 ppm (740 mg/m^3), 8-hr TWA (skin)	2-Methoxyethanol: 5 ppm (16 mg/m^3) TWA (skin) 2-Ethoxyethanol: 5 ppm (19 mg/m^3) TWA (skin)
Isopropyl alcohol	400 ppm (984 mg/m^3) TWA; 800 ppm (1,968 mg/m^3) ceiling (15-min)	400 ppm (980 mg/m^3), 8-hr TWA	400 ppm (980 mg/m^3) TWA; 500 ppm (1225 mg/m^3) STEL

See footnotes at end of table.

(Continued)

Compound	NIOSH REL*
Ketones	TWA values in ppm (mg/m^3): Acetone: 250 (590); Methyl ethyl ketone: 200 (590); Methyl n-propyl ketone: 150 (530); Methyl n-butyl ketone: 1 (4); Methyl n-amyl ketone: 100 (465); Methyl isobutyl ketone: 50 (200); Methyl isoamyl ketone: 50 (230); Diisobutyl ketone: 25 (140); Cyclohexanone: 25 (100); Mesityl oxide: 10 (40); Diacetone alcohol: 50 (240); Isophorone: 4 (23)
Methyl alcohol	200 ppm (262 mg/m^3), TWA; 800 ppm (1,048 mg/m^3) ceiling (15-min)

See footnotes at end of table.

APPENDIX A (Continued)

REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING OSHA PEL'S AND ACGIH TLVs®

OSHA PEL	ACGIH TLV†
8-hr TWA values in ppm (mg/m^3): Acetone: 1,000 (2,400); Methyl ethyl ketone: 200 (590); Methyl n-propyl ketone: 200 (700); Methyl n-butyl ketone: 100 (410); Methyl n-amyl ketone: 100 (465); Methyl isobutyl ketone: 100 (410); Methyl isoamyl ketone: none; Diisobutyl ketone: 50 (290); Cyclohexanone: 50 (200); Mesityl oxide: 25 (100); Diacetone alcohol: 50 (240); Isophorone: 25 (140)	TWA values in ppm (mg/m^3): Acetone: 750 (1,780) Methyl ethyl ketone: 200 (590); Methyl propyl ketone: 200 (700); Methyl n-butyl ketone: 5 (20); Methyl n-amyl ketone: 50 (235); Methyl isobutyl ketone: 50 (235); Methyl isoamyl ketone: 50 (240); Diisobutyl ketone: 25 (150) Cyclohexanone: 25 (100) (skin); Mesityl oxide: 15 (60); Diacetone alcohol: 50 (240); Isophorone: C5 (C25); STEL values in ppm (mg/m^3): Acetone: 1,000 (2,375); Methyl ethyl ketone: 300 (885); Methyl propyl ketone: 250 (875); Methyl n-amyl ketone: 100 (445); Methyl isobutyl ketone: 75 (300); Cyclohexanone: 100 (400); Mesityl oxide: 25 (100); Diacetone alcohol: 75 (360)
200 ppm (260 mg/m^3), 8-hr TWA	200 ppm (260 mg/m^3) TWA (skin); 250 ppm (310 mg/m^3) STEL

(Continued)

APPENDIX A (Continued)

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING
OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
Methyl bromide	Ca Reduce exposure to lowest feasible level	20 ppm (80 mg/m^3), ceiling concentration (skin)	5 ppm (20 mg/m^3) TWA (skin)
Methyl chloride	Ca Reduce exposure to lowest feasible level	100 ppm, 8-hr TWA; 200 ppm ceiling; 300 ppm acceptable maximum peak for 5 min in any 3-hr period above the acceptable ceiling for an 8-hr shift	50 ppm (105 mg/m^3) TWA; 100 ppm (205 mg/m^3) STEL
Methylene chloride	Ca Reduce exposure to lowest feasible limit	500 ppm, 8-hr TWA; 1,000 ppm acceptable ceiling; 2,000 ppm acceptable maximum peak for 5 min in any 2-hr period above the acceptable ceiling for an 8-hr shift	100 ppm (350 mg/m^3) TWA
Methyl iodide	Ca Reduce exposure to lowest feasible level	5 ppm (28 mg/m^3), 8-hr TWA (skin)	2 ppm (10 mg/m^3) A2 TWA (skin)
Nitriles	All are TWA values in ppm (mg/m^3): Acetonitrile: 20 (34); n-Butyronitrile: 8 (22); Isobutyronitrile: 8 (22); Propionitrile: 6 (14);	Acetonitrile: 40 ppm (70 mg/m^3), 8-hr TWA; Tetramethyl succinonitrile: 0.5 ppm (3 mg/m^3), 8-hr TWA (skin)	Acetonitrile: 40 ppm (70 mg/m^3) TWA (skin); 60 ppm (105 mg/m^3) STEL; Tetramethyl succinonitrile: 0.5 ppm (3 mg/m^3) TWA (skin)

See footnotes at end of table.

(Continued)

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
	Malononitrile: 3 (8); Adiponitrile: 4 (18); Succinonitrile: 6 (20). All ceiling values (15-min) in ppm (mg/m^3): Acetone cyanohydrin: 1 (4); Glycolonitrile: 2 (5); Tetramethyl succinonitrile: 1 (6). When present as mixtures or with other sources of cyanide, exposure to be considered additive and environmental limit to be calculated		
2-Nitro-propane	Ca Reduce exposure to lowest feasible level	25 ppm (90 mg/m^3), 8-hr TWA	C25 ppm (C90 mg/m^3) A2
Paint and allied coating products, manufacture of	Various recommendations for the handling of raw materials and finished products; dispersion of pigment or resin particles; thinning, tinting, and shading; filling; and laboratory functions	Many aspects covered under the numerous OSHA regulations for general industry (29 CFR 1910)	Many solvents for which TWA's and STEL's have been adopted
Pentachloro-ethane	To be handled in the workplace with caution	None	None

See footnotes at end of table.

(Continued)

APPENDIX A (Continued)

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
Refined petroleum solvents	Kerosene 100 mg/m^3 TWA; all other solvents (petroleum ether, rubber solvent, VM & P naphtha, mineral spirits, and Stoddard solvent): 350 mg/m^3 TWA; 1,800 mg/m^3 ceiling (15-min)	2,900 mg/m^3 (500 ppm), 8-hr TWA (Stoddard solvent)	VM & P Naphtha: 300 ppm (1,350 mg/m^3) TWA; 400 ppm (1,800 mg/m^3) STEL Stoddard solvent: 100 ppm (525 mg/m^3) TWA; 200 ppm (1,050 mg/m^3) STEL Rubber solvent: 400 ppm (1,600 mg/m^3)
Styrene	50 ppm (213 mg/m^3) TWA; 100 ppm (426 mg/m^3) ceiling	100 ppm, 8-hr TWA; 200 ppm acceptable ceiling; 600 maximum ceiling (5 min in 3 hr)	50 ppm (215 mg/m^3) TWA; 100 ppm (425 mg/m^3) STEL
1,1,1,2-Tetrachloroethane	To be handled in the workplace with caution	None	None
1,1,2,2-Tetrachloroethane	Ca Reduce exposure to lowest feasible level	5 ppm (35 mg/m^3), 8-hr TWA (skin)	1 ppm (7 mg/m^3) TWA (skin)
Tetrachloroethylene	Ca Minimize workplace exposure levels; limit number of workers exposed	100 ppm, 8-hr TWA; 200 ppm acceptable maximum ceiling; 300 ppm maximum ceiling (5 min in 3 hr)	50 ppm (335 mg/m^3) TWA; 200 ppm (1,340 mg/m^3) STEL

See footnotes at end of table.

(Continued)

APPENDIX A (Continued)

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
Thiols: n-alkane mono thiols, cyclohexanethiol, and benzenethiol	Ceiling values (15-min) in ppm (mg/m^3): 1-Ethanethiol: 0.5 (1.3); 1-Propanethiol: 0.5 (1.6); 1-Butanethiol: 0.5 (1.8); 1-Pentanethiol: 0.5 (2.1); 1-Hexanethiol: 0.5 (2.4); 1-Heptanethiol: 0.5 (2.7); 1-Octanethiol: 0.5 (3.0); 1-Nonanethiol: 0.5 (3.3); 1-Decanethiol: 0.5 (3.6); 1-Undecanethiol: 0.5 (3.9); 1-Dodecanethiol: 0.5 (4.1); 1-Hexadecanethiol: 0.5 (5.3); 1-Octadecanethiol: 0.5 (5.9); Cyclohexanethiol: 0.5 (2.4); Benzenethiol: 0.1 (0.5); Mixtures of thiols to be controlled by calculation of equivalent concentrations	Butyl mercaptan (butanethiol): 10 ppm (35 mg/m^3), 8-hr TWA; Ethyl mercaptan (ethanethiol): 10 ppm (25 mg/m^3) ceiling	Butyl mercaptan (butanethiol): 0.5 ppm (1.5 mg/m^3) TWA; Ethyl mercaptan (ethanethiol): 0.5 ppm (1 mg/m^3) TWA
Toluene	100 ppm (375 mg/m^3), 8-hr TWA; 200 ppm (750 mg/m^3) ceiling (10-min)	200 ppm, 8-hr TWA; 300 ppm acceptable ceiling; 500 ppm maximum ceiling (10-min)	100 ppm (375 mg/m^3) TWA; 150 ppm (560 mg/m^3) STEL
1,1,1-Trichloroethane	350 ppm (1,910 mg/m^3) ceiling (15-min)	350 ppm (1,900 mg/m^3), 8-hr TWA	350 ppm (1,900 mg/m^3) TWA; 450 ppm (2,450 mg/m^3) STEL

See footnotes at end of table.

(Continued)

APPENDIX A (Continued)

SUMMARY OF NIOSH REL'S FOR ORGANIC SOLVENTS WITH CORRESPONDING OSHA PEL'S AND ACGIH TLVs®

Compound	NIOSH REL*	OSHA PEL	ACGIH TLV†
1,1,2-Trichloroethane	Ca Reduce exposure to lowest feasible level	10 ppm (45 mg/m^3), 8-hr TWA (skin)	10 ppm (45 mg/m^3) TWA (skin)
Trichloroethylene	Ca 25 ppm TWA	100 ppm, 8-hr TWA; 200 ppm acceptable ceiling; 300 ppm maximum ceiling (5 min in 2 hr)	50 ppm (270 mg/m^3) TWA; 200 ppm (1,080 mg/m^3) STEL
Vinyl acetate	4 ppm (15-mg/m^3) ceiling (15-min)	None	10 ppm (30 mg/m^3) TWA; 20 ppm (60 mg/m^3) STEL
Vinylidene chloride	To be controlled as specified for vinyl chloride in 29 CFR 1910.1017 with eventual goal of zero exposure	None	5 ppm (20 mg/m^3) TWA; 20 ppm (80 mg/m^3) STEL
Xylene	100 ppm (434 mg/m^3) TWA; 200 ppm (868 mg/m^3) ceiling (10 min)	100 ppm (435 mg/m^3), 8-hr TWA	100 ppm (435 mg/m^3) TWA; 150 ppm (655 mg/m^3) STEL

* NIOSH recommendations for time-weighted averages (TWA's) are based on exposures of up to 10 hr per workday unless otherwise noted. "Ca" indicates that NIOSH recommends that the substance be treated as a potential human carcinogen.

† ACGIH TWA recommendations are based on exposures of up to 8 hr per workday or 40 hr per workweek. ACGIH recommendations for short-term exposure limits (STEL's) are based on a 15-min TWA exposure that should not be exceeded at any time during a workday. Exposures at the STEL should not be longer than 15 min and should not be repeated more than four times per day. The ACGIH designation "C" indicates the concentration that should not be exceeded during any part of the working exposure. The ACGIH designation "A2" indicates an industrial substance suspected of having carcinogenic potential for humans. The ACGIH designation "skin" refers to the potential contribution of a substance to the overall exposure by the cutaneous route, including mucous membranes and eyes.

APPENDIX B

EXAMPLES OF HUMAN NEUROTOXIC SOLVENTS

CARBON DISULFIDE (CS_2)

Carbon disulfide is used as a solvent for a variety of fats, oils, waxes, and resins (NIOSH 1977b), and it has been known since the 19th century to cause psychosis and peripheral neuropathy in exposed workers (Seppalainen et al. 1972; Seppalainen and Haltia 1980). Chronic exposure to CS_2 at workplace concentrations of approximately 20 to 40 ppm produced psychomotor deficits and impaired intellectual function in viscose rayon workers compared with unexposed workers (Seppalainen and Haltia 1980; Hanninen 1971; Hanninen et al. 1978; Cassitto et al. 1978). Experimental animal studies have confirmed that CS_2 is a neurotoxicant (Spencer and Schaumburg 1985). Dogs exposed to approximately 400 ppm CS_2 by inhalation for 10 to 15 weeks developed behavioral disturbances, ataxia, and paralysis (Lewey et al. 1941). Male and female Sprague-Dawley rats and male New Zealand rabbits exposed to 750 ppm CS_2 by inhalation for 22 and 10 weeks, respectively, showed slowed nerve conduction velocities and weakness of hind limbs (Seppalainen and Linnoila 1975, 1976).

n-HEXANE

n-Hexane is used as a solvent in quick-drying rubber cements and glues, inks, varnishes, and seed oil extractions (NIOSH 1977a). n-Hexane is a human neurotoxicant that has produced sensorimotor or motor peripheral neuropathy in workers who chronically inhaled workplace concentrations of approximately 60 to 240 ppm (Herskowitz et al. 1971; Spencer et al. 1980a) and in individuals who abusively inhaled the compound (Altenkirch et al. 1977, 1982). 2,5-Hexanedione, a metabolic product of n-hexane (DiVincenzo et al. 1980) that possesses a greater neurotoxic potential than the parent compound, is believed to be responsible for producing peripheral neuropathy in humans (Krasavage et al. 1980). Sprague-Dawley rats were subchronically exposed to n-hexane either by repetitive subcutaneous injections of increasing doses up to 2 g/kg or by continuous inhalation of 400 to 600 ppm (Schaumburg and Spencer 1976). They developed pathophysiologic changes in the central and peripheral nervous systems (giant axonal swelling and fiber degeneration) similar to those seen in humans with n-hexane neuropathy. Inhalation exposure to 1,000 ppm methyl ethyl ketone (MEK) in combination with 9,000 ppm n-hexane for 15 weeks potentiated the neurotoxicity of n-hexane in male Wistar rats when compared with exposures to 10,000 ppm n-hexane alone for the same period (Altenkirch et al. 1978).

METHYL n-BUTYL KETONE (MBK)

Methyl n-butyl ketone is used commercially as a solvent for lacquers, nitrocellulose, resins, oils, fats, and waxes; it is also used in varnish and lacquer removers (NIOSH 1978a). Like n-hexane, MBK is also metabolized to 2,5-hexanedione (DiVincenzo et al. 1980), and chronic occupational exposure has produced a peripheral neuropathy in workers that is similar to that seen in n-hexane-exposed workers (Allen et al. 1975; Spencer et al. 1980b). Continuous MBK inhalation exposure of chickens (100 to 200 ppm) and of cats and Sprague-Dawley rats (400 to 600 ppm) for 12 weeks produced a pattern of neurologic damage (focal axonal swelling and myelin sheath degeneration) similar to that seen in workers (Mendell et al. 1974). In male Wistar rats, a 23-day continuous inhalation exposure to 750 ppm MEK and 225 ppm MBK potentiated the neurotoxicity of MBK, whereas a 2-month continuous exposure to 400 ppm MBK alone did not (Abdel-Rahman et al. 1976).

TRICHLOROETHYLENE

Trichloroethylene is used in vapor degreasing operations and solvent extraction (NIOSH 1973b). This solvent has caused a generally reversible cranial and peripheral neuropathy associated with sensory loss and motor weakness in the trigeminal nerve and, to a smaller extent, in the facial and optic cranial nerves (Feldman 1970; Politis et al. 1980). Volunteers exposed for two 4-hr periods at average concentrations of 110 ppm showed statistically significant decreases in performance ability on tests of perception, reaction time, memory, and manual dexterity compared with their performance ability before exposure (Salvini et al. 1971). Chronic occupational exposure at concentrations above 100 ppm (Politis et al. 1980) has been associated with neuropsychiatric (Type 1*) and neuropsychologic (Type 2*) effects (Bardodej and Vyskocil 1956; Grandjean et al. 1955; Lilis et al. 1969). No adequate epidemiologic studies or experimental animal studies have yet been conducted to corroborate these reports (Spencer and Schaumburg 1985).

In male and female Mongolian gerbils, 3 months of inhalation exposure to 60 ppm trichloroethylene followed by a 4-month recovery period produced increases in brain protein levels associated with brain damage (Haglid et al. 1981, 1985).

PERCHLOROETHYLENE (TETRACHLOROETHYLENE)

Perchloroethylene, widely used in the commercial dry cleaning of fabrics and the degreasing of metal parts (NIOSH 1976a), has produced neuropsychiatric (Type 1*) and neuropsychologic (Type 2*) effects similar to those associated with chronic trichloroethylene exposure, including changes in personality and memory (Gold 1969). In male and female Mongolian gerbils, 3 months of inhalation exposure to 60 ppm perchloroethylene followed by a 4-month recovery period produced increases in brain protein levels associated with brain damage (Haglid et al. 1981, 1985).

TOLUENE

Toluene is used in the manufacture of chemicals and in paints and coatings as a solvent (NIOSH 1973a). Toluene abuse (e.g., deliberately inhaling pure

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* See Table 1 in text.

toluene vapors or toluene-based paints or glues for their euphoric properties) has induced progressive damage to CNS structure and function that appears after 1 to 20 years of repeated exposure (Spencer and Schaumburg 1985). This damage begins with Type 1 neurobehavioral changes and progresses to Type 3 chronic toxic encephalopathy (see Table 1 of text), including impairment of intellect and memory and evidence of CNS atrophy (Lazar et al. 1983; King et al. 1981; Knox and Nelson 1966). When male Wistar rats inhaled 50 to 100 ppm thinner containing 60% toluene over a 10-or 20-day period for 15 min/day, they developed alterations of neuronal structures in the CNS (nucleolus, perichromatin fibrils, and ribosomes) (Vazquez-Nin et al. 1980).

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