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The Neurotoxicity of Industrial Solvents: A Review of the Literature

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Organic solvents, particularly stryrene, are used widely in boatbuilding. They may be absorbed by workers either through the respiratory tract or the skin. Uptake is influenced by level and duration of exposure, work load, and specific physicochemical features of each solvent, as well as by work practices and use of protective equipment. Kinetics of metabolism and excretion kinetics are highly variable among compounds. Metabolites can be measured in blood, urine, or exhaled breath and may serve as indirect indices of absorption.

Acute high-dose exposure to organic solvents can produce a transient narcotic effect on the central nervous system. This effect occurs in proportion to brain dose, which in turn is determined by intensity and duration of exposure. Additionally, chronic exposures to organic solvents have been reported to produce an increased frequency of neurologic signs and symptoms. These findings include peripheral neuropathies and toxic encephalopathies. The latter are characterized by alterations in affect, memory loss, and impaired cognition. Concern exists that prolonged excessive exposure to organic solvents may lead to premature and persistent dementia in certain workers.

Key words: organic solvents, styrene, boatbuilding, neurotoxicity, occupational disease

INTRODUCTION

The construction and repair of modern boats involves the use of large volumes of organic solvents, particularly styrene. As is detailed in the work of Crandall and Hartle [1985], presented elsewhere in this issue of the journal, workers engaged in the manufacture of fiberglass-reinforced plastic (FRP) boats may be heavily exposed to styrene vapors, as the result of inadequate ventilation coupled with the frequent necessity to work in confined spaces.

The acute neurotoxic effects of heavy exposure to the vapors of organic solvents have been recognized since the 19th century and are described in detail by Browning

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[1965]. Axelson et al [1980] have noted that by virtue of their acute narcotic effects, several of the solvents, including trichloroethylene, vinyl chloride, and even gasoline, found at least brief use as general anesthetics.

The concept that chronic exposure to organic solvent vapors might have deleterious effects on the central nervous system, even in the absence of acute narcosis, has arisen more recently. Although there had been scattered early references to impaired neurologic function in relation to chronic solvent exposure [Browning, 1965], the modern recognition of this association appears to have resulted from the clinical observation in the early 1970s by a Swedish psychologist of memory loss in two workers who had heavy styrene exposure in the manufacture of sport boats and swimming pools (L. Sundell, personal communication, 1984). These observations led to a cross-sectional study in Sweden among house painters exposed to solvents [Sundell, 1975]. That investigation found decreases in reasoning capacity and in psychometric test results among exposed painters as compared witih unexposed controls. That seminal observation led to a series of further studies, conducted first in Scandinavia [Hane et al, 1977; Seppalainen et al, 1980; Struwe et al, 1980] and then elsewhere [Baker and Smith, 1984]. These reports confirmed and extended the notion that chronic solvent exposure causes both subjective and objective impairment of central neurological function in chronically exposed workers. A major unanswered question in this work is to determine the level of exposure at which this impairment first becomes evident.

In this report, we shall present a detailed summary of the literature relating to acute and chronic neurologic effects of solvent exposure, including that described by other investigators as the psychoorganic syndrome [Flodin et al, 1984].

UPTAKE

Uptake of solvent into the peripheral blood occurs within minutes of the onset of exposure by either the inhalation route or through percutaneous absorption [Engstrom et al, 1978, Riihimaki et al, 1979; Lauwerys et al, 1978]. Alveolar ventilation rate is an important determinant of solvent uptake through inhalation, and increased levels of physical exercise (associated with increased pulmonary capillary blood flow) have been associated with increasing uptake by a factor of two to three times the baseline level [Monster et al, 1979; Riihimaki et al, 1979]. Respiratory uptake varies between individual solvents in relation to their specific air/blood partition coefficients, which are determined by alveolocapillary membrane permeability and blood solubility. A general review of the factors affecting solvent uptake from inhalation exposure is contained within the report of Astrand [1975]. Although skin absorption is recognized as a possible major route of entry for some solvents, it has been studied for only a few. Engstrom and Bjurstrom [1977] found that brief (10–15 minute) immersion of a subject's hands in xylene produced blood concentrations of xylene comparable to those following an 8-hour inhalation exposure at 100 ppm (the threshold limit value [TLV]). The rate of solvent uptake through the skin varies substantially among workers owing to variations in skin thickness, skin perfusion, and the presence of cuts or abrasions of the skin [Riihimaki and Pfaffli, 1978; Bird, 1981]. Occlusion of skin surfaces such that solvent is trapped between clothing and the skin may also enhance solvent absorption. A review of percutaneous absorption kinetics for five

important organic solvents (xylene, styrene, toluene, 1,1,1 trichloroethane, and tetrachloroethylene) is contained within the report of Riihimaki and Pfaffli [1978]).

METABOLISM

A detailed description of the biotransformation reactions that influence the fate of absorbed solvents is beyond the scope of this discussion but is contained in the recent review of Toftgard and Gustafsson [1980]. Modification of metabolism rates by other exogenous substances will be briefly reviewed. Waldron et al [1983] have shown that blood toluene levels increased acutely in individuals who received ethanol concomitantly, presumably secondary to reduced metabolism because of competition for alcohol dehydrogenase. In contrast, workers chronically ingesting ethanol had lower blood toluene levels than nondrinking fellow workers, an effect attributed to induction of hepatic microsomal enzymes responsible for toluene metabolism. In a similar study, increased blood xylene concentrations were noted following concomitant ethanol exposure [Savolainen et al, 1980]. A reduced rate of metabolism of one solvent in the presence of other solvents has been reported in two studies [VanRees, 1972; Ikeda et al, 1972] involving trichloroethylene, styrene, benzene, and toluene. In a recent study [Riihimaki et al, 1982], ethanol ingestion appeared to decrease the metabolic clearance rate of xylene by about one half. Since xylene metabolism depends upon reactions catalyzed by alcohol and aldehyde dehydrogenase, metabolic interaction with ethanol is to be expected. Several volunteers experience nausea during the simultaneous exposure condition. In one individual, nausea was associated with an elevated blood acetaldehyde concentration consistent with a form of ethanol intolerance. In addition to causing higher levels of solvent in blood, the ethanol-induced metabolic inhibition may also be associated with adverse reactions caused by the accumulation of ethanol metabolites such as acetaldehyde.

In summary, acute ethanol ingestion raises blood solvent levels by competition for metabolism; chronic ethanol ingestion lowers blood solvent concentrations by inducing solvent-metabolizing enzymes. Simultaneous exposure to organic solvent mixtures may have similar synergistic effects.

EXCRETION

Solvents are eliminated primarily either through exhalation of unchanged solvent or through urinary excretion of unchanged solvent or solvent metabolites. The relative importance of each path of excretion and the excretion kinetics vary significantly between compounds and, therefore, influence the strategy for biological monitoring in which concentrations of these eliminated substances are measured as an index of solvent uptake. General discussions of the theoretical basis for alveolar air sampling have been recently presented [Fiserova-Bergerova et al, 1980; Kellman, 1982]. In general, rapid decreases are observed in concentrations of all organic solvents in expired air with increasing time from the end of exposure [Nomiyama and Nomiyama, 1974; Engstrom et al, 1978; Jakobson et al, 1982; Sedivec and Flek, 1976]. Thus, the timing of sample collection relative to the termination of exposure is critical for reliable estimates of uptake.

NERVOUS SYSTEM TOXICITY

General

In the evaluation of individuals exposed to organic solvents, assessment of nervous system function is central to any form of medical evaluation. Solvents exert both transient and persistent effects on the nervous system. Transient effects appear to be mediated directly by the pharmacologic action of solvents within the central nervous system and these transient changes in function are proportional to the measured concentrations of solvent within the brain. Persistent neurological effects have been associated with histopathological changes in neural tissue.

Experimental Human Studies

A variety of detailed experimental studies performed primarily by Gamberale and colleagues in Sweden and Savolainen and colleagues in Finland have elucidated the time course and nature of the changes in psychophysiological functions that occur following solvent exposure [Gamberale, 1976]. These reports show impairment in simple and choice reaction time and selected tests of psychomotor function as the level and duration of exposure to solvents increase over brief (usually 2–6 hours) exposure periods. In an evaluation of exposure to m-xylene at concentrations of 100–400 ppm [Riihimaki and Savolainen, 1980], acute central nervous system effects were correlated with blood xylene concentrations, and the occurrence of adverse effects also seemed to depend on a rapid rise of blood xylene concentration. Physical exercise was also noted in this study to increase the uptake rate and enhance the central nervous system effects of xylene absorption. The most pronounced effects noted in this report were a disruption of body balance and impairment of simple and choice reaction time. Some development of tolerance to the effects on reaction time were noted over extended exposures to xylene. In two other studies of short-term xylene exposure, exercise potentiated the effects on psychological function such as reaction time, manual coordination, and body balance [Savolainen et al, 1980; Gamberale et al, 1978]. Further studies have indicated that disruptions in equilibrium are a particularly sensitive neurologic effect of short-term exposure to xylene [Savolainen and Linnavuo, 1979]. Experimental exposure to toluene and methyl chloroform have shown similar patterns of dose-related performance decrement [Gamberale, 1976].

Clinical Case Reports

Several clinical case reports exist that relate neurological syndromes to prior exposure to organic solvents. Cerebellar syndromes have been reported following exposure to toluene by several authors [Boor and Hurtig, 1977; Grabski, 1961; Takeuchi et al, 1981]. Isolated reports of polyneuropathy among methyl ethyl ketone-exposed shoe factory workers has also appeared [Dyro, 1978].

Other neurological syndromes reported following solvent exposure include loss of smell [Emmat, 1976] and loss of visual acuity and other symptoms associated with toxic optic neuropathy (particularly recognized following exposure to methanol and ethanol, but also other organic solvents including trichloroethylene, carbon tetrachloride, and methylchloride) [Grant, 1974]. A loss of sensation and muscular function in the face as well as double vision has been described in several case reports following exposure to trichloroethylene and similar compounds [Feldman, 1979; Swedish Work Environment Fund, 1981]. One report indicated an increased rate of multiple sclerosis

among persons exposed to organic solvents in the shoe manufacturing industry [Amaducci et al, 1982]. Shoe manufacturing involves exposure to a variety of aliphatic hydrocarbons including pentane, hexane, and heptane derivatives.

Epidemiologic Investigations

Of greater significance than isolated cases reports are epidemiologic studies that evaluate acute and chronic effects of solvent exposure on the central and peripheral nervous systems. The principal neurologic syndrome affecting the peripheral nervous system is the occurrence of axonal degeneration with attendant symptoms and signs of peripheral neuropathy seen among workers exposed to hexane and methyl n-butyl ketone [Spencer and Schaumberg, 1980]. Chronic toxic encephalopathy following exposure to a variety of organic solvents constitutes the major concern with respect to solvent effects on the central nervous system (CNS) that persist after the immediate exposure period. Two epidemiologic studies, a case-referent investigation [Axelson et al, 1976] and a follow-up study [Mikkelsen, 1980], have demonstrated the association between employment in solvent-exposed jobs and the occurrence of excess rates of chronic neuropsychiatric conditions including dementia. In these studies, the risk of developing chronic CNS impairment in solvent-exposed groups was approximately twice that of the reference populations.

A much larger number of studies have been performed in which various solvent-exposed groups have been evaluated with a variety of neurophysiological and neurobehavioral tests. The two most important neurophysiological studies were performed by Seppalainen et al [1978] and by Elofsson et al [1980]. Both groups studied workers exposed as industrial painters, a group recognized to have heavy exposure to organic solvents. Standard motor and sensory nerve conduction velocities were measured in the nerves of the upper and lower extremities, and modest slowing of motor and sensory conduction was noted in exposed populations in both studies in comparison with unexposed groups. Seppalainen et al [1978] also performed electroencephalograms (EEGs) and found significant differences betwen exposed and unexposed populations with respect to EEG abnormalities. In the study of Elofsson et al [1980], although no significant differences were noted between exposed and unexposed populations with respect to the visual evaluation of EEGs, subtle abnormalities were described. In another similar investigation of workers exposed to jet fuel [Knave et al, 1978], a reduced amount of alpha activity was noted in exposed workers. In summary, the electrophysiologic evaluations of workers exposed to solvent mixtures using both standard techniques for evaluating peripheral nerve function as well as electroencephalography, have noted mild changes in neurophysiologic parameters.

A large number of evaluations of neurobehavioral function have been performed in solvent-exposed groups to assess both short-term and persistent effects of solvent exposure on behavior. To evaluate acute effects of styrene on workers employed in the manufacture of fiberglass boats, Cherry and colleagues [1980] performed reaction time testing, vigilance testing, and other measures of psychomotor function and mood before and after the work day. Mood changes and increased fatigability were noted to a greater extent in exposed workers than a reference group and, in subsequent analyses, individuals from the same population who cleared styrene slowly had slower reaction times than their co-workers with average rates of metabolism [Cherry et al, 1981]. A variety of behavioral studies that have evaluated solvent-exposed groups have noted an excess of subjective symptoms, abnormalities of psychomotor perfor-

mance, memory deficits, impairment in verbal concept formation, and disturbances of mood when compared with reference groups (Table I). The most extensive series of these investigations has been performed by Hanninen, Lindstrom, and colleagues at the Institute of Occupational Health in Helsinki. In addition to cross-sectional evaluations, Lindstrom [1980] evaluated a group of 56 male workers diagnosed between 1971 and 1973 as having an occupational illness caused by exposure to organic solvents. Follow-up testing performed five or more years after cessation of solvent exposure noted a decline in visual/motor performance and attentional deficits that correlated with the duration of solvent exposure that had occurred in these individuals prior to their time of diagnosis. A similar follow-up evaluation performed by Bruhn et al [1981] indicated that the neurological status, degree of neuropsychological impairment, and the degree of cortical atrophy, was unchanged two years after the initial diagnosis of chronic toxic encephalopathy among a group of 26 house painters. Neurological features of the toxic encephalopathy diagnosed primarily by neurobehavioral testing included cortical atrophy [Juntunen et al, 1980] and reduced cerebral blood flow [Arlien-Soborg et al, 1982]. Impaired vestibular function was also noted in one study of house and car painters who demonstrated reduced vestibular reactions following auditory canal irrigation with cold water [Arlien Soborg et al, 1981].

In a recent report [Maizlish et al, in press], 104 spray painters and 101 unexposed matched controls received a battery of behavioral and neurologial tests, a physical examination, and a medical questionnaire. Industrial hygiene sampling was performed to evaluate exposure levels. Despite the large number of tests performed, only two showed a dose-response relationship between exposure and performance: two-point discrimination on the dorsum of the foot and mean color-word time from the Stroop test. The authors conclude that the study did not show evidence that workers chronically exposed to hydrocarbon solvents at levels below the current TLV perform poorer on behavioral tests than unexposed individuals.

TABLE I. Summary of Epidemiologic Studies on Chronic Neurotoxic Effects of Solvents

Exposed group	Subjective symptoms	Visual/ motor performance	Memory	Verbal concept formation	Mood	Reference
Car painters	+[a]	+	+	+	+	Hanninen [1979]
Lacquerers	+				+	Struwe [1980]
Car painters	+					Husman [1980]
House painters	+	+	+	+	+	Arlien-Soborg [1979]
Spray painters	+	+	+	−[b]		Elofsson [1980]
House painters		+	−			Hane [1977]
Solvent-poisoned workers	−	+	+	−		Lindstrom [1980]
Laminators		+	−	−		Harkonen [1977]
Jet fuel-exposed workers	+	−				Knave [1978]
Printers		−	+	−		Hanninen [1979]
Steel workers		+			−	Anshelm Olson [1981]
Dry cleaners		−				Tuttle [1977]

[a] + = adverse effect was observed.
[b] − = effect was tested for but not observed.

Summary of Neurological Effects

In summary, existing studies indicate the occurrence of defined syndromes of peripheral neuropathy and toxic encephalopathy that occur in individuals heavily exposed to solvents over a period of months to years. An important recent study of individuals chronically exposed below the TLV failed to demonstrate significant nervous system impairment. Peripheral neuropathy occurs as a result of axonal degeneration caused by exposure primarily to the hexacarbon solvents n-hexane and methyl n-butyl ketone. Studies that indicate peripheral nervous system abnormalities on electrophysiologic testing in populations exposed to solvent mixtures deserve attention; further research is necessary to evaluate the potential for peripheral neurotoxicity in groups exposed to solvents other than n-hexane or methyl n-butyl ketone. The accumulated evidence supports the occurrence of a syndrome of toxic encephalopathy caused by excessive exposure to organic solvents in trades such as painting and boatbuilding. This syndrome is characterized by memory disturbances, impaired psychomotor function, impaired verbal abilities, and disturbances of mood. The onset of such behavioral complaints occurs during periods of excessive exposure to solvents and persists after exposure has ceased. A nonspecific manifestation of early solvent toxicity has been referred to as "the neurasthenic syndrome," which manifests primarily as fatigability, irritability, depression, and episodes of anxiety. Although obviously caused by many other etiologies, this constellation of symptoms occurs frequently in individuals with excessive exposure to solvents in the absence of more pronounced disruptions of neurobehavioral function [Swedish Work Environment Fund, 1981]. Follow-up studies of patients with solvent-induced toxic encephalopathy have shown persistence of functional impairment years after removal from solvent exposure.

PREVENTION OF DISEASE

Reduction of airborne exposure levels through the use of proper ventilation systems and process design is essential to prevent excessive exposure to organic solvents used in boatbuilding. Reduction of skin uptake and periodic medical monitoring of exposed workers can be used along with measurement of airborne solvent concentrations to provide additional steps to prevent significant illness.

Control of Skin Uptake

In addition to the previously known problem of penetration of solvents through glove materials, there are also significant questions about the efficacy of barrier creams. Two recent reports of the evaluation of barrier creams in humans [Lauwerys et al, 1978] and in animals [Boman et al, 1982] indicate little evidence of their efficacy in preventing percutaneous absorption of xylene, toluene, or benzene. In the animal study, blood solvent concentrations two to three hours after exposure onset were comparable between animals with unprotected skin and those where barrier creams or even glove materials were used to protect the animals' skin surface. A study of styrene-exposed workers showed a similar lack of barrier-cream efficacy [Brooks et al, 1980]. Previous studies have demonstrated that styrene is absorbed percutaneously [Dutkiewicz and Tyras, 1968]. Therefore, although skin protection to reduce the risk of percutaneous solvent absorption seems appropriate, a clear demonstration of its efficacy is lacking in the recent literature.

Biological Monitoring of Exposed Populations

In recent years, a variety of assays have been developed for monitoring the concentration of solvents and their metabolites in blood, urine, and exhaled air. These tests are useful because they measure uptake resulting from both inhalation and percutaneous absorption and, therefore, serve as an integrated index of the dose to the individual. An excellent recent publication summarizes the available information on biological monitoring for specific agents and should be referred to for a more detailed treatment of these issues [Lauwerys, 1983].

In general, urinary determinations reflect cumulative exposure to a greater extent than do blood or exhaled air analyses. The value of a specific urine determination varies with the pharmacokinetics of metabolism and the excretion route of the specific solvent. In most instances, blood concentrations and exhaled air concentrations show a similar concentration profile over time and the choice of test usually is determined by the availability of sampling procedures and analytical techniques. Blood and air determinations are usually only of value during the immediate exposure period in view of the short half-life of these compounds in the blood.

In some situations, such as the measurement of hippuric acid concentrations as an index of toluene uptake, dietary constituents interfere with test analyses owing to the presence of substances (eg, benzoic acid) that are metabolized to a common pathway. Drugs may also interfere in a similar fashion (eg, chloral hydrate, a common sedative, is converted to trichloroethanol and trichloroacetic acid). Therefore, a detailed dietary and drug history should be taken of individuals participating in biological monitoring programs. Interpretation of test results is further limited by the large variability in uptake occurring even at fixed exposure levels as a result of changing workload and variations in individual metabolic responses. Increasing physical exertion can increase the metabolite concentration by 3–5 times the level seen in sedentary individuals. Finally, the absence of normal population reference values, standard collection and analysis techniques, and a system of laboratory quality control for these assays limits their usefulness. Nevertheless, biological testing is of value in assessing individuals and groups exposed to solvents and as a means of quantifying total solvent uptake.

Comparison of pre- and post-shift urinary solvent metabolite concentration is a useful way of assessing time-weighted exposure over the eight-hour work period. If the concerns mentioned above are adequately addressed, such testing can prove useful in assessing individual exposures. Reliance on an experienced laboratory with careful quality control procedures cannot be overemphasized in the analysis of solvent metabolites in biological materials.

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