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ORGANIC SOLVENT NEUROTOXICITY[1]

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Organic solvent neurotoxicity represents one of the most important emerging issues in the field of occupational health. Over the last three years, major international meetings have been devoted to this difficult and controversial subject. This discussion reviews the basis for concern regarding solvent neurotoxicity and summarizes existing experimental, clinical, and epidemiological studies that have formed the basis for our current understanding. Although significant uncertainty still exists with regard to this problem, recommendations can be made for prudent public health practice designed to prevent the excess occurrence of solvent-related illness.

Why has this problem received so much attention? First, exposure to organic solvents is extraordinarily common. Guillemin (9) indicates that an estimated four million tons of solvent were produced worldwide in 1978. Production is projected to increase at approximately 1.7% per year through the end of this decade. Surface coating constitutes the most important single use of organic solvents in Europe (Table 1) and probably throughout the world.

Concern for solvent neurotoxicity stems not only from the extent of exposure but also from the importance of the central and peripheral nervous systems to overall well-being and the ability to perform activities of normal daily and working life. Furthermore, since damage to the central nervous system is potentially irreversible, repeated, modest insults may result in significant cumulative impairment.

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TABLE 1 Solvent production by category[a,b]

Category	Total 1979 (%)	Expected demand 1988 (%)
Aliphatic hydrocarbons	28	30
Aromatic hydrocarbons	20	12
Halogenated hydrocarbons	18	17
Alcohols	14	17
Ketones	10	11
Esters	7	8
Others	3	5

[a]Total production in 1978: 4.3 million tons = $1.5 billion.
[b]From Ref. (4).

State of Current Knowledge

In certain areas, our understanding of issues related to the health effects of organic solvents is well developed and in others, quite rudimentary. Several recent international conferences have summarized the state of our understanding and have identified directions for future research. First, the International Conference of Organic Solvent Toxicity (ICOST) was held in Stockholm in October 1984 under the auspices of the Swedish National Board of Occupational Safety and Health. The proceedings of this important meeting were published in the *Scandinavian Journal of Work, Environment and Health* (12) in articles that summarize solvent toxicokinetics, occupational hygiene, biological effects, and current research activities.

In June 1985, the World Health Organization (WHO) and the Nordic Council of Ministers organized a workshop on the chronic effects of organic solvents on the central nervous system and diagnostic criteria for those effects. The working group summarized the experience of Nordic countries and dealt with the difficult issue of criteria for diagnosing solvent-induced CNS disorders. The summary of this meeting, published by the World Health Organization Regional Office for Europe, provides a very succinct and authoritative overview of the current state of knowledge of the effects of organic solvents on the central nervous system (17). Much of this discussion derives from the consensus reached at this international workshop.

Finally, in October 1985, a workshop on neurobehavioral effects of solvents was held in the United States under the sponsorship of the Chemical Industry Institute of Toxicology and a number of large petrochemical companies and trade associations. This workshop included many participants from the earlier WHO workshop and developed recommendations for occupational health practice in relationship to solvent neurotoxicity (5).

Toxicokinetics

Uptake of organic solvents occurs either via skin absorption or inhalation. Factors determining the rate and degree of skin absorption include the duration of solvent exposure, solvent concentration, status of the skin (e.g. abrasions, humidity, etc), and the solubility characteristics of the solvent itself. The rate of skin penetration has been shown to be directly related to the aqueous solubility of the particular solvent (4). In general, chlorinated hydrocarbons are better absorbed through the skin than nonchlorinated hydrocarbons. Aromatic hydrocarbons more easily penetrate the skin than aliphatic hydrocarbons.

Absorption through the lung is dependent on the concentration of inhaled solvent, solubility characteristics of the solvent, and the pulmonary ventilation rate (7). A worker engaged in strenuous activity, with resulting increase in pulmonary ventilation rate, would be expected to absorb a greater solvent dose of many common organic solvents.

Toxicokinetics have direct relevance to the manifestations of acute effects of solvent exposure on the central nervous system (i.e. acute intoxication). In this regard, concentration of the solvent of interest in the central nervous system is proportional to the degree of impairment of psychomotor function and other behavioral parameters. In fact, certain substances used in industry were once used as agents to induce general anesthesia. Much of our understanding of organic solvent kinetics derives from similar research in the field of anesthesiology.

The relationship of acute effects to chronic effects is unclear. In general, it can be said that repeated acute episodes of intoxication clearly reflect repeated excess exposure to organic solvents. Repeated episodes of excess exposure have been implicated in the etiology of chronic health effects. Thus, chronic adverse effects can be prevented by the improved recognition and prevention of acute uptake of organic solvents through the lung and skin.

Animal Studies

Experimental toxicology has used various methods to clarify the mechanisms of pathogenesis of certain neurotoxic chemicals. The literature is best developed for carbon disulfide and hexacarbon solvents (e.g. *n*-hexane and methyl *n*-butyl ketone). Experimental evidence suggests that during long-term exposure, organic solvents interact by modifying membranes, altering neurotransmitter balance, and interfering with cell respiration and protein metabolism (17). Long-term exposure to many different organic solvents has been shown to result in irreversible structural change of the central nervous system. The relationship of these changes to various brain functions is currently under active investigation.

The experimental neuropathology of damage of the peripheral nervous

system caused by substances such as *n*-hexane and methyl *n*-butyl ketone has been well described (14). Exposed animals (as well as humans) exhibit a distal axonopathy, which consists of symmetrical damage to sensory and motor fibers of the longest peripheral nerves. Symptoms of this disorder include symmetrical distal sensory loss and weakness. Solvent "sniffers" display a more significant pathology, which may extend to affect the cranial nerves and the autonomic nervous system. Typically, damage to the peripheral nervous system ceases to progress after exposure has ceased, and partial or complete recovery ensues.

Clinical Neuropsychology and Neurology

In contrast to what we clearly know about the toxicokinetics of organic solvents and our relatively well-developed understanding of the neuropathology caused by certain substances, a summary of the clinical view of solvent-induced conditions is considerably more difficult to develop. This difficulty derives, in part, from the relative lack of scientific scrutiny given to these disorders in many countries, with the notable exception of certain Scandinavian countries. More importantly, the effects of organic solvents, particularly those relating to the central nervous system, are rather nonspecific and easily confused with other conditions. Their onset is typically insidious, and various social factors mitigate against bringing these complaints to the attention of appropriate medical specialists.

In evaluating the state of clinical knowledge, it is useful to examine the role of neuropsychology as a central tool for evaluating exposed patients (16). By administering carefully standardized neurobehavioral tests and applying an understanding of the functions of the central-nervous-system, neuropsychologists are able to measure deficits in neurobehavioral function in patients suspected of having various neurological conditions. Individuals exposed to organic solvents have been shown to display characteristic deficits in certain areas of psychological function (Table 2). Typically, the severity of the deficit is proportional to the intensity and duration of exposure. Mild performance deficits tend to be reversible upon cessation of exposure; more severe ones may not be. The WHO workshop (17) provided a detailed discussion of the process of neuropsychological evaluation of the adverse effects of organic solvent exposure [see particularly Lindstrom (11); it is summarized briefly in Table 3. The neuropsychological approach for evaluating workers exposed to organic solvents is increasing throughout the world and holds promise for a more objective assessment of this difficult clinical syndrome.

Certain symptoms appear to be typical in a case of solvent neurotoxicity (17). Overt, clinical symptomatology of the peripheral nervous system is relatively uncommon except for individuals having heavy exposure to hexacarbon solvents or carbon disulfide (14). Therefore, this discussion is re-

Table 2 Typical changes of psychological function in mild chronic toxic encephalopathy

Function	Frequency of abnormal test performance
Verbal and nonverbal reasoning	Rare
Visuoconstructive functions	Possible
Short-term memory	Usual
Psychomotor function and perceptual speed	Nearly always
Mood	Nearly always, depending on premorbid personality

stricted to the treatment of more difficult issues regarding damage to the central nervous system. To help characterize patients for clinical and epidemiological study, a three-category classification scheme was developed at the World Health Organization Workshop (17) and modified subsequently at the workshop held in the United States later the same year (5). Although these two characterization schemes do not correspond exactly, some similarities are present (Table 4). A brief discussion of nomenclature is useful in understanding the previous literature on the effects of organic solvents on the central nervous system. Prior research has referred to a "psycho-organic" syndrome as well as a "neurasthenic" syndrome as conditions caused by chronic solvent exposure. Although these descriptions seemed useful when discussed at the WHO workshop, the meaning of these terms varies considerably among research groups. Therefore, a more general international characterization scheme was adopted to facilitate communication among investigators in different locations who perform similar research activities. The term "chronic toxic encephalopathy" was selected to describe a syndrome of dysfunction of the central nervous system characterized by neurobehavioral deficits in psychomotor, perceptual, and/or memory function with frequent associated disturbances in mood (17). Typically, workers exposed to organic solvents display a mild form of chronic toxic encephalopathy. Individuals who intentionally abuse solvents and are exposed to very extreme concentrations of solvent vapors may exhibit a severe form of toxic encephalopathy with features similar to clinical dementia. The more severe form is presumed to be minimally reversible, and profound deficits in behavioral function result in significant impairment.

Frequently, workers display symptoms of dysfunction of the central nervous system following exposure to organic solvents but do not exhibit documentable deficits on neurobehavioral test performance. The WHO working group adopted the term "organic affective syndrome" to describe a mild form of mood disturbance characterized by symptoms of depression, irritabil-

Table 3 Neuropsychological evaluation of adverse effects of solvent exposure

Process	Short-term exposure	Long-term exposure
1. Test specification and data collection	Psychomotor tests before and after workday(s)	Tests of multiple function compared with baseline/ reference
2. Formal evaluation of motivation of individual and data quality	Direct questioning and data examination	Direct questioning regarding effort and internal data examination
3. Calculation of changes or deficits in performance	P.M.–A.M. score difference	Determination of Z score-based deviation between observed and expected performance
4. Estimation or measurement of exposure intensity	Direct measurement through environmental or preferably biological monitoring of individual or multiple chemical exposure	Estimation of exposure intensity, duration, and, if possible, chemical characteristics by standardized work history questionnaire
5. Evaluation of potential confounding control through data analysis where possible	Diurnal variation, alcohol use, and workload during day of testing	Demographic, personal habits, other fluctuating characteristics and prior physical or emotional illness
6. Comparison of deficits seen with known characteristics of solvent toxicity	Acute intoxication criteria	Neuropsychological test-based criteria for mild chronic toxic encephalopathy
7. Relation of deficit pattern to exposure history, and other relevant neuropsychological factors	Performance decrement present or absent, based on neuropsychological testing	Mild chronic toxic encephalopathy—definite, probable, possible, absent

ity, and loss of interest in daily activities. This mild condition is similar to that described as Type 1 organic-solvent, central-nervous-system effect (5). The term "organic affective syndrome" derives from the categorization scheme developed by the American Psychiatric Association—*The Diagnostic and Statistical Manual of Mental Disorders,* Third Edition (1).

In the typical case presentation, onset of symptoms is characteristically insidious, and symptoms attributable to solvent exposure are difficult to distinguish from those occurring for many other reasons. Patients often complain of increased fatiguability, irritability, loss of interest in various social activities, and difficulty in performing tasks that require sustained attention. Often, symptoms are more apparent to relatives than to the individual worker. After exposure ceases, symptoms usually remit over a period of weeks. In more severe cases, neurobehavioral deficits persist. Thus, the syndrome is nonspecific but does have features that are consistent for individuals sharing common exposures to selected solvents.

Epidemiology

In comparison with other areas of research on solvent-induced health disorders, epidemiology presents some of the most difficult problems. First, characterizing the exposure of individual workers to organic solvents is a complex and challenging process. The chemical complexity of solvent mixtures makes the physical characterization of their presence in the work site analytically challenging. Furthermore, records for reconstructing past exposure profiles are typically inadequate to provide quantitative exposure estimates. The diversity of work practices engaged in by individuals currently exposed to solvents makes characterizing even current exposures impossible at times. Unfortunately, the use of biological monitoring does not usually help characterize chronic exposure. Although measuring solvents or their metabolites in blood or exhaled breath does provide a useful index of current exposure, concentrations fluctuate dramatically over a period of hours and any such determination represents only the most recent exposure period. In contrast to the study of other toxic substances, such as inorganic lead, no biological test for organic solvents exists that integrates exposure over a period that is meaningful for the pathogenesis of the health effects of interest (e.g. chronic toxic encephalopathy).

In addition to the complexity associated with characterizing exposure, specifying health effects is also quite different in epidemiological studies. Frequently, neuropsychological tests are administered by technicians to workers in an individual testing situation. Unfortunately, this method of collecting data is subject to intertester variability and is also expensive and time consuming. Recently, computerized versions of neurobehavioral tests have been developed to help evaluate CNS function in health surveys (2a, 10). This approach was used in recent field surveys of solvent-exposed workers (2b) and results were consistent with other epidemiologic studies using manual techniques.

In one of the earliest epidemiological studies, Elofsson et al (6) evaluated Swedish spray painters who had long-term exposure to organic solvents. These workers exhibited a statistically significant increase in the occurrence of subjective psychiatric complaints (e.g. memory problems, headache, and fatigue) when compared with unexposed matched reference populations. Psychological testing also revealed statistically significant decrements in the performance of exposed workers on tests of simple reaction time, manual dexterity, perceptual speed, and short-term memory. A subsequent study (15) evaluated 55 shipyard painters who had more than ten years of exposure to methyl isobutyl ketone, perchloroethylene, xylene, ethylene glycol, and mineral spirits. Test scores of exposed workers showed significantly diminished performance on selected performance measures when compared with unexposed workers. Gregersen et al (8) showed similar results in 65 workers involved in a variety of jobs where solvent exposure occurred

regularly. The deficits noted by Gregersen are consistent with the diagnosis of mild toxic encephalopathy as described above. In another study of 50 workers exposed to solvents in the paint industry (13a), psychiatric evaluations showed statistically significant increases in symptoms of mental disturbance. Various psychological test scores were lower (i.e. worse) in exposed than in unexposed workers, but only one test showed a significant difference—a test of focused attention.

The studies of Lindstrom and his colleagues in Helsinki are particularly important in addressing essential issues of neurobehavioral deficits among solvent-exposed workers and, most importantly, in studying the course of the disorder. Lindstrom (11a) reported a study involving 56 workers who were diagnosed as having occupational diseases resulting from exposure to organic solvents. These individuals had a mean duration of exposure of 9.1 years and concentrations reported to be generally below the Finnish threshold limit value. Tests performed five or more years after solvent exposure ceased revealed significant decrements in visuomotor performance and freedom from distractability compared to unexposed groups. Visuomotor performance scores declined with increasing duration of solvent exposure. In a recent study (2b), we found similar increasing rates of neurobehavioral symptoms in painters chronically exposed to organic solvents. The symptom rates were proportional to an index of solvent exposure derived from work histories and other job information. Decrements in neurobehavioral performance were also seen on tests involving speed and sustained attention. Other research, summarized elsewhere (3), is consistent with that described in detail here.

In summary, epidemiological studies to date confirm the occurrence of dose-related impairment in central-nervous-system dysfunction among individuals chronically exposed to a variety of organic solvents. These studies are limited by the inability to investigators to measure carefully exposure intensity. In some cases, deficits appear to persist for significant periods after exposure ceases.

Conclusions and Recommendations

Despite the uncertainty surrounding this complex area, certain steps can be taken to develop a prudent strategy for disease prevention in the workplace (5). Environmental monitoring is essential for documenting significant exposure levels and for designing and evaluating worksite control measures. Biological monitoring has a role but must be tailored to the needs of confidentiality and other worksite constraints. Medical monitoring of neurotoxic effects appears to be advisable at times, but no formal protocol can be recommended. Questionnaires have been used in several countries and have been useful in detecting early symptoms of solvent-related central system dysfunction. However, caution is advised because of the high rate of false positive and false negative results from such questionnaires.

The US National Institute for Occupational Safety and Health (NIOSH) has recently released a *Current Intelligence Bulletin* on organic solvent neurotoxicity (13), which provides additional guidelines for minimizing worker exposure to organic solvents. Importantly, engineering controls should be used as the primary method to eliminate potential exposures to organic solvents in the workplace and to prevent fires and explosions. Various closed-system designs exist that provide the most effective means for minimizing worker exposure in certain jobs. If feasible, workers should be isolated from direct contact with the work environment by the use of automated equipment. Personal protective equipment is essential in many jobs where direct skin contact with organic solvents is possible.

Respiratory protection is also important to consider; however, significant limitations exist regarding the efficacy of this approach. Furthermore, many persons involved in activities such as spray painting will find the use of respiratory protection extremely difficult in many job activities. Finally, workers should be educated and trained to understand the potential health risks of exposure to organic solvents, the proper use of personal protective equipment, and other methods for control.

In conclusion, our understanding of organic solvent toxicity has improved due to recent international workshops and increasing levels of research activity. Despite the level of uncertainty that persists, certain measures can be taken to minimize workers' exposure and, therefore, to prevent unnecessary disease and disability in the future.

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