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Acute Exposure Research with Organic Solvents: The NIOSH Experience

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Des travaux sur les effets aigus chez l'être humain de l'exposition aux solvants ont été menés par l'Institut National de la Santé et de la Sécurité au Travail depuis sa fondation (1970). Les recherches ont porté sur les milieux confinés ou non et de gros efforts ont été faits pour diffuser nos connaissances sous forme de conférences, d'ateliers, de bulletins d'information, de documents normatifs et de publications des recherches expérimentales.

Les recherches en milieu confiné se sont d'abord focalisées sur les effets neurocomportementaux subcliniques qui peuvent apparaître chez les travailleurs suite à une exposition professionnelle. On a étudié la combinaison des solvants entre eux et l'association avec des drogues, la caféine et l'alcool.

Il faudrait à l'avenir s'intéresser non seulement aux caractéristiques physiologiques, neurocomportementales et biochimiques de base des effets de l'exposition aux solvants, mais aussi à d'autres variables qui peuvent être importantes dans l'évaluation des risques sur le lieu de travail. Ces variables regroupent la charge de travail physique, l'exposition à plusieurs solvants associés, l'exposition conjointe à des agents physiques et chimiques, l'intéraction entre de médicaments absorbés pour traiter des troubles chroniques et l'exposition à un milieu chimiquement pollué.

Research on the acute effects of solvent exposures in humans has been supported by the National Institute for Occupational Safety and Health since the establishment of the Institute in 1970. Both extramural and intramural laboratory and field research has been undertaken, and there have also been extensive efforts to disseminate resultant information about the acute effects of solvent exposures. Information dissemination has included conference and workshop proceedings, current intelligence bulletins, criteria documents, and journal publications of research experiments.

NIOSH intramural research has concentrated primarily on the subclinical neurobehavioural effects that may occur in workers in response to workplace exposures. The experiments have studied solvent combinations, and solvents combined with drugs, caffeine, and alcohol.

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Future research on the acute effects of solvent exposures should concentrate not only on basic pharmacokinetic, physiological, and neurobehavioural characterisations of effects, but on other variables that may be of consequence in assessing workplace risks. These variables include: physical workload, exposures to combinations of solvents, combined exposures to chemical and physical agents, and interactions between chemical exposures and medications used to treat chronic medical problems.

INTRODUCTION

Since its inception in 1970 under the Occupational Safety and Health (OSH) Act, the National Institute for Occupational Safety and Health (NIOSH) has supported research on the acute effects of solvent exposures. Giving sanction to this work were two provisions of the OSH Act which directed NIOSH to:

1. Include psychological, behavioral and motivational factors in researching problems of worker safety and health, and to consider these factors in developing new methods, techniques or approaches in handling such problems (*sections 20(a)(1), 20(a)(4)*).
2. Describe exposure levels for toxic materials and harmful physical agents at the workplace which are not only safe for health, but which pose no threat to one's functional capacity (*section 20(a)(3)*).

NIOSH efforts addressing the acute effects of solvent exposures have taken various forms. There have been methods development studies, research directed at assessing the effects of exposures to solvents, and hazard evaluations of workplaces containing solvent exposures. Equally important have been NIOSH activities aimed at dissemination information about documented effects and risks from solvent exposures. This programme consists of the official publications of NIOSH, including: criteria documents, current intelligence bulletins, industry-wide study reports, technical reports, Health Hazard Evaluation and Technical Assistance reports (HETAs), journal publications, and proceedings of NIOSH-sponsored conferences and workshops (which included numerous references to issues of solvent toxicity). The HETAs probably are the best indicator of actual workplace hazards. Since 1971, over 2200 HETAs have been conducted and one-third of these reports cite solvents in the workplace environment. All of the aforementioned reports are cited in the NIOSH Document Information Directory System (DIDS) and in the NIOSH online bibliographic database of literature in the field of occupational safety and health (referred to as the NIOSH Technical Information Center (NIOSHTIC)).

The rest of this article will concentrate on NIOSH-sponsored research efforts documenting the acute effects of solvent exposures in humans, and

the workshops supported by NIOSH which addressed acute solvent effects. This discussion will conclude with recommendations for future human laboratory experimental research on this topic.

ACUTE EFFECTS RESEARCH

Acute solvent effects research at NIOSH has emphasised experimental investigations involving human volunteer subjects. The Institute's initial solvent research efforts began as a series of contract studies performed in the laboratory of Dr. Richard D. Stewart at the Medical College of Wisconsin. Perchloroethylene, trichloroethylene, acetone, toluene, methyl chloride, methylene chloride, methyl chloroform, styrene and xylene were among the solvents evaluated for their acute effects, with an added purpose being to develop biologic tests to monitor the magnitude of repeated daily exposures. The acute effects measured included both physiological and behavioural indicators. The behavioural performance measures used in these studies were a combination of sensory and motor tasks (e.g. Romberg, Heel-to-toe, Flanagan coordination); cognitive tasks (e.g. alertness test, inspection test, time-estimation tests); and physiological tests (e.g. EEG, evoked potentials). Dr. Stewart's work along with early experimental studies by Kylin et al. (1967) with trichloroethylene, and by Fodor and Winneke (1971) with methylene chloride, helped establish the controlled laboratory experiment as an appropriate model for conducting acute solvent effects research. In addition, the results of Dr. Stewart's studies appeared in several journal articles and were used to support NIOSH Criteria Documents for recommending safe workplace exposure standards to specific solvents.

In 1972, NIOSH established a human exposure laboratory for conducting human neurotoxicity studies. The first laboratory study was designed to resolve conflicting findings regarding the effects of carbon monoxide at low concentrations (Cohen & Margolis, 1973). This effort yielded two important findings. The first was that performance decrements could be detected at airborne concentrations of either carbon monoxide or methylene chloride equal to or below the levels considered safe for human exposures (i.e. sufficient to produce a 5% carboxyhaemoglobin (COHb) concentration in the subjects). The second was that certain performance test characteristics were indicated as key factors in detecting subclinical effects (Putz, 1979). These characteristics were: task demand (e.g. single versus dual tasks), difficulty, length, and interest level (boring versus interesting tests). These test characteristics were to become major considerations in the design of future experiments to detect subclinical effects.

Additional human exposure studies performed in the NIOSH laboratories during this early period evaluated the behavioural perform-

ance effects of multiple chemical agents having implications for worker health and safety. These studies included acute exposures to the following chemical combinations: Carbon monoxide and methylene chloride; alcohol, caffeine and methyl chloride; and methyl chloride and diazepam. The combined carbon monoxide and methylene chloride study (Putz, Johnson, & Setzer, 1979), demonstrated that both substances, in exposure concentrations sufficient to produce 5% COHb, significantly impaired human performance under difficult or demanding task conditions. The tests in this study were a dual task (i.e. an eye–hand coordination tracking task with two levels of tracking difficulty, paired with a peripheral brightness monitoring test), and an auditory vigilance test. The methyl chloride and diazepam study (Putz-Anderson et al., 1981a), involved the following exposures: Single exposures of methyl chloride at 100 and 200ppm; therapeutic doses of diazepam (10mg); and a combination of diazepam and methyl chloride. Single exposures to 100 and 200ppm of methyl chloride for three hours had little or no effect on the performance tests, whereas the diazepam-only treatment significantly impaired performance; the combination exposure showed no evidence of an interaction. The last study (Putz-Anderson, Setzer, & Croxton, 1981b), in this series compared methyl chloride with alcohol and caffeine; each chemical was tested singly, and then in combination with methyl chloride. Significant decrements on the performance tests were detected with alcohol (0.08% Blood Alcohol Concentration), and caffeine (200mg), but the acute exposure to methyl chloride only at 200ppm for 3.5 hours produced no significant performance effects. The combination of methyl chloride with ethanol produced some additive effects, but no evidence of an interaction was found.

During the 1980s, NIOSH's acute solvent effects research consisted primarily of inhouse laboratory efforts, as well as extramural research grants. During this period, published articles emerged which implicated chronic solvent exposures to neurobehavioural impairments among workers in several industries (Johnson & Anger, 1983). For example, NIOSH-supported research, and the research of other groups, confirmed that a ketone, methyl n-butyl ketone (MnBK), was the cause of an outbreak of peripheral neuropathy in workers at a plant manufacturing coated fabrics (Billmaier et al., 1974). Additionally, a review of several research articles showed that animals exposed to another ketone, methyl ethyl ketone (MEK), did not develop peripheral neuropathy, but exposure to MnBK in combination with MEK potentiated the peripheral neuropathy caused by MnBK (Spencer et al., 1980). A survey of HETA reports showed that MEK was a common solvent frequently occurring in combination with other industrial solvents at the worksite. This survey prompted NIOSH's attention toward evaluating other solvent-MEK combinations to determine possible interaction effects. In designing this research, individual agent

exposures were set at concentrations approximating either the Federal Occupational Safety and Health Administration (OSHA), Permissible Exposure Limits (PELs), or NIOSH-recommended limits (RELs), and the chemical combinations were set in accordance with the American Conference of Governmental Industrial Hygienists (ACGIH)-OSHA additive formula for mixtures (29 CFR 1910).

The first project was a series of experiments involving exposures to toluene and MEK—singly and in combination. Only the single exposure to toluene at 100ppm for four hours produced any significant performance decrements, and then only for one performance measure (% correct responses), in the visual-vigilance task (Dick et al., 1984). The next experiment involved exposures to acetone and MEK. A four-hour exposure to 250ppm acetone produced small but statistically significant performance impairments on two measures of the auditory tone discrimination task, but neither the MEK alone nor the combined acetone-MEK exposures, produced any significant performance effects (Dick et al., 1989). The last study in this series consisted of exposure to methyl isobutyl ketone (MIBK), and MEK, singly and in combination. Neither the MEK nor the MIBK single exposures, or the MEK-MIBK combined exposures, resulted in significant performance impairments (Dick et al., 1992). In summary, combined exposures to MEK and toluene, MEK and acetone, and MEK and MIBK, produced no neurobehavioural evidence of interactive effects at the concentrations tested.

Whereas NIOSH has made significant contributions to scientific knowledge regarding the acute effects of solvent exposures, other laboratories have made substantial contributions to the scientific literature which have greatly influenced the design of NIOSH experiments. This work includes the data described in the many publications of Francesco Gamberale of Sweden, Gerhard Winneke of Germany, and Kai Savolainen of Finland. Review articles by Francesco Gamberale (1985; 1989), and Gerhard Winneke (1982), have documented extensively the neurobehavioural effects of human solvent exposures.

CONFERENCES/WORKSHOPS

Two conferences and workshops, which occurred about 10 years apart, focused international attention on human research involving the subclinical effects of solvent exposures. The conferences were important because they helped consolidate and organise research efforts in this area. The first meeting, held in Cincinnati in 1973, was entitled: "Behavioral Toxicology: Early Detection of Occupational Hazards". The meeting was sponsored by NIOSH, the University of Cincinnati, the National Academy of Sciences, the International Brain Research Organisation, and the Inter-

national Association for Occupational Health. The meeting attracted an international audience and addressed the questions of whether repeated workplace exposures at current exposure limits could evoke behavioural and nervous system effects which were early indicators of subsequent disease process, and whether the behavioural changes were of a type that could increase accident risk (Cohen, 1974). A session entitled "Worker Exposure to Solvents", chaired by Dr. Stewart, noted the trends in such research, with efforts made to define dose-effect relationships for chemical substances used in the workplace that would be more protective. Dr. Stewart stated that during the 1940s, control of industrial exposures was directed toward preventing overt and permanent organic injury. In the 1950s, efforts were redirected toward preventing aversive subjective responses (e.g. irritant effects). During the 1970s, research was directed toward determining the effects of solvents on the physiological and behavioural functions of humans to establish reliable Biologic Threshold Limit values. Important questions regarding reliable exposure limits emphasised the relationship of solvent concentrations and durations of exposure to physiological effects, cognitive task performance, and behavioural impairments (Stewart, 1974). Consistent with Dr. Stewart's predictions, the long-range research goals of neurotoxicology remain to establish the most sensitive indicators for depicting the full range of neurotoxic effects of chemical agents to which workers may be exposed.

In addition to the session on organic solvents, the 1973 meeting included several presentations that emphasised the importance and feasibility of neurobehavioural testing in defining solvent toxicity. The workshop featured actual demonstrations of neurobehavioural, physiological, and neurological tests for use in conducting field studies and laboratory experiments to assess the neurobehavioural effects of chemical exposures. An official text of this meeting was published the following year (NIOSH, 1974). Coupled with the two-volume series entitled: *Adverse Effects of Environmental Chemicals and Psychotropic Drugs*, edited by Milan Horvath in collaboration with Emil Frantik (Horvath, 1973; 1976), these publications remain key source documents for researchers investigating the neurobehavioural effects of chemical exposures on humans.

The second conference: "Prevention of Neurotoxic Illness in Working Populations", was held in Cincinnati in 1983, and was co-sponsored by NIOSH and the World Health Organization. This conference addressed the entire spectrum of neurotoxicity testing, including laboratory and field studies. The purposes of this meeting were to provide research summaries of neurotoxic effects of chemical exposures and to recommend a battery of tests suitable for neurotoxicity screening. One outgrowth of the meeting was the development of the WHO-Neurobehavioral Core Test Battery (WHO-NCTB) and the computerised Neurobehavioral Evaluation System

test battery (NES) which are today used extensively in field research. Research on the acute effects of human chemical exposures is discussed in chap. 3 of the published monograph of the proceedings (Johnson, 1987). This chapter, entitled: *Review of Experimental Studies*, emphasised the principal contributions made by human experimental research in determining the acute effects of neurotoxic chemicals. Ethical issues, exposure conditions, experimental methods and designs, experimental procedures, and experimental results were discussed. The review noted that more controlled human exposure studies have been done using organic solvents than any other chemical group. Dick (1988) published a subsequent review article which included only the experiments using organic solvents. In this article the neurobehavioural test results from acute exposure experiments were compared with other indicators of acute effects (i.e. irritant effects and narcotic effects), for the purpose of providing objective benchmarks to aid in the development of recommended workplace exposure concentrations.

FUTURE RESEARCH

As we enter the 1990s, much important research remains to be conducted on the acute effects of organic solvents. The Institute lists neurotoxic disorders as one of the 10 leading work-related health problems, and has proposed a strategy aimed at prevention of neurotoxic disorders (Proposed National Strategies, 1988). The strategy includes a research agenda which serves as a guide for the immediate future. Those areas of research interest relevant to acute research effects are summarised as follows:

1. Establishing a complete profile of the effects of solvent exposures on humans in order to improve the scientific documentation necessary for recommending safe workplace exposure concentrations. Such research should include pharmacokinetic parameters, physiological effects, and neurobehavioural effects. While some experimental work (i.e. in Finland and Sweden), has been done in these areas, the existing scientific documentation for establishing safe workplace exposure standards to protect against acute effects is weak or unavailable (Castleman & Ziem, 1988). Initially, development of separate pharmacokinetic studies on each exposure condition prior to, or in concert with, the neurobehavioural assessments could be conducted. The test sessions should simulate an 8-hour workday, and both males and females should be included in the exposure groups. The inclusion of both sexes is important because demographic projections indicate that an increasing number of females will be employed in the American workforce during the 1990s.
2. Investigating the implications of different exposure patterns on the

development of neurotoxic health effects, especially the relationship of acute episodes of toxicity to the development of chronic or delayed effects. This research is essential to establish safe exposure concentrations involving repeated, acute exposures during the total working career. A need also exists to validate standardised neurobehavioural test batteries using on-the-job performance measures, including accidents. Laboratory test batteries should include the same or similar tests used in the WHO Neurobehavioral Core Test Battery and the Neurobehavioral Evaluation System for assessing neurotoxicity in field studies. The tests in these batteries can be revised to include test characteristics (e.g. difficulty, length), which appear to be essential in detecting subtle subclinical effects; such an effort would integrate laboratory and field research. The use of these tests would help standardise test protocols so that results obtained by different laboratories conducting human exposure research could be readily compared.

3. Establishing interactions between solvent exposures and select workplace, job demand, worker (host) factors that may be of consequence to occupational health and safety. These factors could include physical workload, chemical combinations, simultaneous exposure to both chemical and physical agents (e.g. noise, thermal stress), prescribed medications (consumed while exposed to chemicals), and health status (i.e. presence of chronic medical problems). The two latter variables (i.e. use of prescribed medications and medical status), may be especially important in future years because the proportion of older workers is expected to increase.

Other recommendations for future research using human experimental protocols have been published previously (Dick & Johnson, 1986). One of these recommendations was to improve the exchange of research findings and methods across national laboratories. The 1990 Dortmund meeting: "Acute effects of exposure to organic solvents: Experimental approaches and methods", contributed substantially to this recommendation by encouraging the exchange of research findings.

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