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NEUROBEHAVIORAL EFFECTS OF OCCUPATIONAL SOLVENT EXPOSURE:

FINAL REPORT: REVIEW OF RECENT LITERATURE

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CONTENTS

I. Summary 1

II. Introduction 2

III. Methods Utilized In Studies of Solvent-Exposed Workers . . 3

IV. Findings in Solvent-Exposed Workers

A. Painters 6

B. Exposure to Jet Fuel 10

C. Styrene Exposure 11

D. "Solvent Poisoning" 12

V. General Conclusions 14

VI. Recommendations 17

VII. References 18

I. SUMMARY

Concern has recently developed over potential Central Nervous System (CNS) effects arising from long-term exposure to solvents at concentrations near currently accepted Threshold Limit Values (TLVs). The source of this concern is a growing number of Scandinavian studies which describe adverse CNS changes in workers occupationally exposed to various organic solvents. The purpose of the present review is to summarize and evaluate the significance of these studies.

The methods which have been used to collect data in the Scandinavian projects include questionnaires, psychometric/psychiatric evaluations, neurological examinations and neurophysiological tests. The results obtained collectively suggest that solvent-exposed workers more frequently experience "neurasthenic symptoms" (fatigue, worry, and memory and concentration difficulties) than do comparable nonexposed workers. In addition, differences between exposed and nonexposed subjects on various psychometric and psychological tests are frequently reported.

It is the opinion of REHD that the body of literature currently available does not adequately demonstrate an association between chronic exposure to low levels of solvents and significant CNS effects. In many of the reported studies the observed effects have been slight, and the long-term practical consequences are difficult to evaluate. Furthermore, the neurasthenic syndrome is a set of subjective and somewhat vague symptoms which do not readily lend themselves to objective analysis. A further serious deficiency in many of the published reports is that detailed records of solvent exposure are lacking, particularly in reference to exposure levels of the past.

Recommendations are made to continue following current scientific literature on this subject and to monitor developments in Europe, where pressures to give this "occupational disease" formal recognition are gaining momentum.

II. INTRODUCTION

Exposure to mixtures of organic solvents is a common occurrence in many occupational settings. The nature of these exposures varies from short-term, low level episodes to those involving large quantities of solvents for prolonged periods of time in industrial manufacturing and processing operations. The narcotic effect following acute exposure to high concentrations of solvent vapors is well established and is the basis for the abuse potential of certain volatile solvents. Inhalation of vapors characteristically produces central nervous system (CNS) depression with resultant dizziness, inebriation, ataxia, incoordination, collapse, anesthesia and eventual death due to respiratory depression. In addition, n-hexane and methyl-n-butyl ketone have been shown to be responsible for causing central-peripheral axonopathy in humans and experimental animals following subchronic exposure via a mechanism of action independent of generalized CNS depression.[17]

In the past, a major area of industrial concern with respect to solvent toxicity has been with acute effects, such as skin and eye irritation, and narcosis. However, more recently concern has developed over potential CNS effects arising from chronic exposure to solvents at concentrations near currently accepted Threshold Limit Values (TLVs). This concern arises from a growing number of studies conducted by researchers in Finland and Sweden which describe CNS changes in workers occupationally exposed to various organic solvents. The purpose of the present review is to summarize the findings of these studies and to evaluate their significance. The present critique is not meant to represent an exhaustive review of the literature on this subject, but rather attempts to examine the general situation by using selected, representative studies. It is important to emphasize that the primary topic under consideration is the CNS effect of long-term, low level solvent exposure in industrial workers. The voluminous literature on the acute effects of solvent exposure and the large body of clinical and experimental data on hexacarbon-induced axonopathy are outside the scope of this review.

III. METHODS UTILIZED IN STUDIES OF SOLVENT-EXPOSED WORKERS

It is worth briefly reviewing the methods and types of tests utilized in the studies under consideration. For purposes of categorization, these tests can be broadly classified as 1) questionnaires, 2) psychometric/psychiatric evaluations, 3) traditional neurological examinations, and 4) sophisticated neurophysiological tests. A description of each of these general approaches follows.

A self-administered questionnaire for monitoring neuropsychiatric symptoms has been developed by Hogstedt, et al.[5] based on common Scandinavian experiences with solvent exposed workers. This short questionnaire, or variations thereof, has been applied as a means of health evaluation in several different studies. Typically, the questions are formulated so as to cover psychological and neurological symptoms such as unusual tiredness, absentmindedness, concentration difficulties, disturbances in vigilance, affect liability and paresthesias. There are advantages and disadvantages to using the questionnaire approach as a screening tool. On the positive side, the method is obviously simple and inexpensive. Furthermore, the designers claim that the sensitivity of the questions and the reproducibility of responses are reasonably good. It might also be argued that subjective ill-being could hardly be registered by anything else but subjective symptoms and that, therefore, it may be a means of assessing early signs of CNS damage. However, quantitative analytical methods that could detect preclinical changes would be preferable. On the negative side, there are inherent difficulties in monitoring CNS dysfunction with a symptom questionnaire. Responses can be influenced by various cognitive factors such as awareness of symptoms and motivational incentives. Willingness of the respondent to report the information and the perceived consequences of reporting are issues which need to be considered. For example, exaggerated reporting of symptoms might be viewed as a way of protesting against a bad work environment or as a means of being removed from that environment. From the opposite point of view, underreporting of symptoms may be a result of unawareness of the symptoms or fear of being displaced from a job. A major problem with using questionnaires is their lack of specificity in regard to causative factors. That is, there is no valid reason for assuming that the symptoms reported are specifically caused by long-term solvent exposure. It is quite possible that differences in the incidence of reported symptoms could be due to differences in the total work environment or other stress factors, rather than to solvent expousre per se. In spite of these limitations, Hogstedt, et al.[5] have concluded that the questionnaire approach does seem to be a "crude but useful tool" in large-scale monitoring efforts.

The second broad category of test methods that have been utilized in studies of solvent-exposed workers is that of psychometric and psychiatric evaluations. Reported findings within this area have generated a great deal of interest and concern. These tests are normally performed in conjunction with medical examinations made by occupational health physicians, neurologists, neurophysiologists and psychiatrists. Although the specific test batteries used may vary from one study to another, they all generally cover a broad range of behavioral functions. The tests are typically designed to measure such functions as verbal comprehension, reasoning and spatial relations, perceptual speed, numerical ability, memory, manual dexterity, simple reaction time and motor speed.[1] The principal advantage offered by these evaluations of behavioral performance is that they are objective and quantifiable. Some studies of solvent-exposed workers have supplemented these tests with a psychiatric interview. By means of an interview, a psychiatrist can assess the prevalence of certain "neurasthenic symptoms" such as fatigue, worry, mood lability and memory and concentration difficulties. These symptoms are rated on a scale of increasing severity with the particular rating depending on the intensity, frequency and duration of the symptom in question. In this manner, a score can be derived for each individual which serves as a rough index of his symptomatology. Although this approach is admittedly more subjective than the psychometric tests described above, it can provide useful additional information.

A third type of assessment which has been utilized in studies of solvent-exposed workers is the standard neurological examination.[7] This normally involves examination of cranial, motor and sensory nerve functions. For example, examination of the motor system includes testing the strength of various muscle groups in the extremities. Coordination can be evaluated by observing rapidly alternating movements of the fingers or finger-to-nose and heel-to-shin tests. In addition, various reflexes can be tested as well as the senses of light touch, pain and vibration. At the completion of a full neurological examination, the findings may be classified as normal, slightly pathological or clearly pathological.

The final broad category of tests which have been applied in studies of occupational solvent exposure are those which involve rather sophisticated neurophysiological methodology.[12] Most commonly they are electroencephalography (EEG) and electroneuromyography (ENMG). EEG is the recording of the electrical activity of the brain. According to an international system, electrodes are placed on anatomically-fixed regions of the scalp and varying electrode combinations are typically recorded for 30 minutes, which provides ample opportunity for examining different areas of the brain. The neurophysiologist then interprets the EEGs according to standard principles. Although different types of EEG abnormalities can be identified, the most usual ones involve slow wave abnormalities of varying degrees or paroxysmal abnormalities such as spike and wave discharges.

Electroneuromyography (ENMG) includes the measurement of nerve conduction velocities or, stated differently, the velocity at which stimulus-induced nerve action potentials are conducted by peripheral nerve fibers. The rationale for this approach is based on the observation that nerve conduction velocities are slowed in cases of peripheral neuropathy. Different nerves conduct impulses at different speeds depending on their diameter and degree of myelination. To measure motor nerve conduction velocity (MCV), the nerve is stimulated with a skin electrode at two separate spots and the motor response is picked up with skin electrodes and amplified with an electromyograph. The latencies from the stimulus to the response are measured and the MCV is calculated by dividing the distance between the stimulation points by the difference of the latencies. Although the techniques necessary are somewhat more difficult, the conduction velocity of sensory nerves can also be measured. In summary, EEG techniques can be used to reveal central nervous system lesions while ENMG techniques can be used to reveal lesions at different levels of the peripheral nervous system.

The various tests described above are illustrative of the types which have typically been utilized in Scandinavian studies of solvent-exposed workers. It should be evident that these tests range in nature from relatively subjective questionnaire-type approaches to more objective and sophisticated evaluations of neuroelectrophysiology. Hopefully, this survey of methodology will provide an adequate background for the discussion of specific studies which follows.

IV. FINDINGS IN SOLVENT-EXPOSED WORKERS

This discussion focuses on the results of studies which have been published from 1976 to the present. The exposed populations consist of car painters, industrial painters, aircraft workers (exposed to jet fuel vapors) and workers exposed to styrene during industrial operations. In most instances, the investigations have been conducted by individuals associated with either the Institute of Occupational Health in Finland or the National Board of Occupational Safety and Health in Sweden.

A. Painters

1) In a series of studies published between 1976 and 1980[3,6,7,14], the Finnish Institute of Occupational Health reported on the psychological, neurological and neurophysiological effects of solvent exposure among car painters. The exposed group consisted of 100 car painters from 27 different repair garages in Helsinki. The subject's exposure times varied from 1 to 40 years (mean 14.8, S.D. 8.5), and their age, from 20 to 65 years (mean 35, S.D. 11). The nonexposed age- and sex-matched reference group was chosen from the employees of the Finnish State Railways. During spray painting operations the workers were exposed to vapors and particulate aerosols. The solvents and thinners consisted of aromatic hydrocarbons (toluene, xylene), aliphatic hydrocarbons (white spirit), alcohols (ethanol, isopropanol, butanol), esters (ethyl acetate) and ketones (acetone, MEK, MIBK). Solvent concentrations were measured at six randomly selected garages which were assumed to be representative of all garages. The mean concentrations of the separate solvents, measured over a 1-hour sampling period, were between 0.3 and 15.3 percent of the corresponding Finnish TLVs (which are close to those of the ACGIH). The possibility of higher exposures in the past could not be ruled out, however. In order to eliminate the potential acute effects of the solvents, all test batteries were always administered at least 16 hours after cessation of the last exposure.

<u>Subjective Symptoms</u>: Before the clinical part of the examination began, all subjects filled out a questionnaire concerning general subjective symptoms (chronic) and symptoms occurring during the workday (acute). The objective of this part of the study was to determine whether adverse symptoms existed in solvent-exposed workers and to test the usefulness of the questionnaire approach in revealing early signs of solvent effects on the CNS. The results have been reported by Husman.[6] In the category of questions concerning chronic symptoms, the car painters more frequently reported signs of fatigue, concentration difficulties and disturbances in vigilance than the railway engineers. The results of a pairwise comparison of these symptoms in the two groups indicated that the differences

were statistically significant for fatigue and concentration difficulties. Acute symptoms were probed with questions about irritation of the mucous membranes and skin, and the prenarcotic effects of solvents. When acute symptoms (those occurring during the workshift) were compared, signs of irritation and prenarcosis (i.e. nausea, dizziness, headache) were reported significantly more often among the exposed than among the control group. The implications of the latter findings may be very important, since they would seem to indicate that, at some point(s) during the day, significant excursions above the TLVs occurred. This would weaken the case for observable chronic effects at levels below TLV concentrations because the effects may be attributable to multiple short-term exposures at concentrations considerably above TLV levels.

Psychological Changes: A psychological test battery was also administered to both groups which included evaluations of intelligence, memory, psychomotor performances and personality.[3] The results indicated impairments in psychological performances as well as personality changes in the exposed groups. Impairments in visual intelligence (as measured by the Block Design Test from the Wechsler Adult Intelligence Scale) and a reduction in emotional reactivity were the central features, but the behavioral disturbances also involved several other functions, including performance on a verbal intelligence test. Significant differences in mean reaction times between exposed and nonexposed subjects were not observed. It should be pointed out that although the differences between the average test performances of exposed and nonexposed subjects were statistically significant, the impairments discovered were rather slight. There were more poor performances among the exposed subjects than among the controls, but the individual test results were, in general, within the limits of normal variation for both groups. The authors of this study stated that this does not necessarily mean that the behavioral changes found are harmless. The long-term practical consequences of mild memory impairment, diminished intellectual capacity or slight changes in emotional reactivity are difficult to evaluate.

Neurological: In addition to psychological testing, both groups underwent a complete neurological examination.[7] The results indicated that a decrease in the sense of light touch and pain and an increase in the vibration threshold were more frequent among the car painters than among the referents (the observed differences in frequencies were statistically significant). Significant differences were not observed between the groups in testing of cerebellar and extrapyramidal tract function or in evaluations of cranial nerve and peripheral motor system integrity. The authors concluded that sensory functions (vibration and light touch) seem to be the most vulnerable part of the nervous system in workers chronically exposed to organic solvents.

Neurophysiological: The final test battery conducted on these workers consisted of EEG recordings and measurements of motor and sensory nerve conduction velocities in the upper and lower extremities.[14] In this study, there were no definite EEG features which separated the car painters from the referent group. The frequency and type of EEG abnormalities were similar in both groups (in both groups approximately one third of the individuals exhibited some form of EEG abnormality). However, the authors pointed out that the prevalence of abnormal EEGs in both groups was clearly higher than expected for a "normal" population (approximately 10 percent according to the EEG literature) and speculated that the car painters' abnormal EEGs may have been due to solvent exposure.

"Abnormally" slow motor or sensory conduction velocities were found in 20 percent of the car painters but in none of the controls. However, these reductions in nerve conduction velocity were not large, as evidenced by the fact that mean conduction velocities in the two groups did not differ. The authors concluded that their findings indicated signs of slowed nerve conduction velocities among the car painters.

In summary, the findings reported in these four papers represent a comprehensive evaluation of a group of Helsinki car painters. The authors of these studies collectively imply that the psychological and neurophysiological effects observed may have been due to mixed solvent exposure at concentrations below the TLV standards in Finland. At most these effects were mild and as suggested could have been representative of effects from excursions above the TLVs. These studies do not demonstrate an association between occupational solvent exposure at current TLVs and deleterious CNS effects.

2) In a different study on painters, the Swedish Board of Occupational Safety and Health conducted a cross-sectional epidemiologic investigation on occupationally-exposed car and industrial spray painters. The results have been published by Elofsson, et al.[1] In this study 80 car or industrial spray painters with long-term low level exposure to mixed organic solvents were examined and compared with two matched reference groups of nonexposed industrial workers. The investigation included psychiatric interviews, psychometric tests and neurophysiological evaluations.

The results of questionnaires and controlled psychiatric interviews indicated that the exposed subjects exhibited more "neurasthenic symptoms" (fatigue, worry, memory and concentration difficulties) than the reference subjects. Furthermore, the psychometric tests revealed statistically significant differences between the groups with respect to reaction time, manual dexterity, perceptual speed and short-term memory. In each of these categories, the exposed group performed less well than the reference group. It is of note, however, that a correlation could not be established between the length of solvent exposure in years and test performance (i.e., a lack of dose-response correlation).

In tests of neurophysiological function, the exposed group was found to have significantly slower nerve conduction velocities and higher vibration thresholds than the control group. The authors acknowledged that even though these differences were statistically significant, the differences were small and all the mean values were within normal limits. Therefore, the neurophysiological findings in these subjects may not have been associated with obvious functional disturbances during ordinary activities. No significant differences were found between the groups with respect to the EEG recordings.

In concluding, the authors of this study stressed that the results all pointed in the same direction (i.e., impaired psychological/neurophysiological function), and that solvent exposure appeared to have been the cause for these effects. They also emphasized that the measured solvent concentrations in the workshops sampled were less than half of the Swedish TLV standards.

3) Psychological changes among house painters have been evaluated by Hane et al.[2] This study is much more limited in scope than the studies on car painters described above, in that it is concerned primarily with the results of a single battery of psychological tests. A more serious problem with this study is the lack of concern with documenting exposure concentrations. The paper simply states that, "It can be estimated that the painters had been exposed to several hundred parts per million of hydrocarbon solvents, as such concentrations seem to be common." The exposed group consisted of 52 house painters with more than five years experience who were randomly drawn from a trade union register. These painters were compared with a group of age-matched industrial workers who were unexposed to solvents. The exposed group had significantly lower mean scores on various psychological tests measuring memory, reaction time and psychomotor coordination. A correlation could not be established between length of exposure ("painter years") and degree of functional change. The results of this study are similar to those described above in that a dose-response effect could not be demonstrated.

4) Seppalainen and Lindstrom[16] recently reported the results of a neurophysiological evaluation of house painters exposed to solvents. The subjects of this study consisted of 72 house painters and 77 concrete workers who served as controls. The painters had worked in their occupation for an

average of 20.2 years. The average long-term air concentration, determined as white spirit, was given as 40 cm^3/m^3 (i.e. 40 ppm). This estimate of exposure was based on information collected about the paints and from measurements of the workplaces made during the study. The frequency of abnormal EEGs among the painters was similar to that found for a normal population. The means of the nerve conduction velocities were similar among both groups of workers and were in close agreement with normal values established historically in the laboratory. In summary, there were minimal differences between the solvent-exposed and control groups. The authors concluded that an average concentration of 40 ppm of white spirit "seems to be a no-effect level for sensitive neurophysiological methods."

B. <u>Exposure to Jet Fuel</u>

In a series of studies conducted by Knave <u>et al</u>.[8,9,10], the Swedish National Board of Occupational Safety and Health examined aircraft factory workers occupationally exposed to jet fuel for signs of possible nervous system effects. The controls and the exposed subjects were matched with respect to age, employment duration and education. Among the exposed subjects the mean exposure duration was 17 years and 300 mg/m^3 was calculated as an approximate time-weighted average exposure level. The fuel, which contained no lead compounds, was composed of the following: saturated hydrocarbons (87.5 vol.%), aromatic hydrocarbons (12 vol.%), and olefin hydrocarbons (0.5 vol.%).

The vast majority of subjects in the exposed group reported recurrent acute symptoms upon exposure to fuel vapors during work (dizziness, fatigue, headache, nausea and respiratory tract symptoms). The incidence of neurasthenia, anxiety and/or depression during employment was significantly higher in the exposed than in the nonexposed groups as recorded in (a) the medical history and standardized interview and (b) notations in the medical records of the factory health department. The prevalence of symptoms in both groups was also assessed in formal psychiatric interviews and ratings. The interview and evaluation were designed to yield a numerical score which served as an indication of the severity of symptoms. The results showed that the exposed individuals had significantly more adverse psychiatric symptoms than the controls. Neurasthenic symptoms (fatigue and emotional instability) showed the largest differentiation between the groups, followed by neurotic disturbances. In addition, a battery of psychological performance tests were conducted on all individuals. The exposed subjects had 1) a greater irregularity of performance on a test of complex reaction time, 2) a greater performance decrement over time in a simple reaction time task and 3) poorer performance in a task of perceptual speed than the nonexposed subjects. In summary, differences were found in tests which made high demands on attention and sensorimotor speed. The investigation did not reveal any difference between the groups in tests concerning memory or manual dexterity.

Neurophysiological evaluations were also conducted on individuals of this study. The EEGs recorded were considered clinically normal in most cases examined. (Although a computer assisted spectral analysis of the EEGs revealed certain significant differences between the groups, this finding is of questionable biological significance.) The results of the examination of peripheral nerve functions indicated that the nerve action potentials in sural nerves (sensory) were significantly smaller than in controls. Although Knave et al. make much ado over "trends" towards slower conduction velocities and higher vibration thresholds in exposed individuals (possibly indicative of polyneuropathy), that emphasis is considered to be of questionable merit.

Knave et al. concluded that the differences observed between the two groups in these psycho- and neurophysiological evaluations were probably related to exposure to jet fuel.

C. Styrene Exposure

The effect of styrene exposure on CNS function has been investigated in a series of studies conducted by the Finnish Institute of Occupational Health.[4,11,13] The exposed subjects consisted of 98 male laminating workers from 24 plants manufacturing polyester plastic products. Their median age was 28 years (range 16-54 years) and the duration of their exposure varied from 0.5 to 14 years (median 5.1 years). Based on previous work, urinary mandelic acid concentrations were used as a measure of styrene exposure. The urine samples were collected individually at the end of the workday, once a week, on consecutive weekdays, for 5 weeks prior to the clinical examination. The mean of the five determinations was used for the estimation of the intensity of individual exposure. The mean varied from 7 to 4,715 mg/l (median 808 mg/l). The various parameters examined in these subjects were studied in reference to different exposure categories. The control subjects were matched with respect to age and education.

According to the symptom questionnaire survey, the exposed group complained significantly more often of tiredness, concentration difficulties and irritation symptoms. The functions measured in the psychological test battery were general intelligence, visuomotor accuracy, memory, vigilance and psychomotor performance. In general, the comparison between exposed and nonexposed workers revealed few significant differences. However, visuomotor inaccuracy

(Bourdon-Wiersma Test and Symmetry Drawing Test) and lowered psychomotor performance (Mira Test) were parameters which showed a statistically significant relationship to the mean mandelic acid concentration. The first change in visuomotor accuracy became discernible when the urinary mandelic acid concentration exceeded 800 mg/l while a more pronounced decrement appeared in both visuomotor accuracy and psychomotor performance when the mandelic acid concentration exceeded 1200 mg/l. The latter concentration corresponds to an 8-hour TWA of styrene exposure of about 55 ppm.

An increased prevalence of abnormal EEGs (about 30 percent) was found for the subjects whose urinary mandelic acid concentration exceeded 700 mg/l, while the number of abnormal EEGs among the subjects with less exposure (below 700 mg/l) was not above that found in the general population. According to the data, a mandelic acid concentration of 700 mg/l corresponds to an 8-hour TWA styrene exposure of about 31 ppm. Nerve conduction velocity measurements performed on 40 subjects did not reveal any definite relationship between styrene exposure and peripheral nerve function.

In concluding, the authors recognized that the interpretation of these findings in terms of health impairment and work capacity is difficult. The studies did demonstrate an exposure-response relationship between EEG/psychological changes and styrene exposure. However, the psychological changes that occurred were rather mild and were confined to a narrow area of functions. Furthermore, it was not possible to determine to what extent occasional peak concentrations or elevated exposure levels in the past may have contributed to the changes observed.

D. "Solvent Poisoning"

Seppalainen et al.[15] reported on neurophysiological and psychological findings in 107 patients previously diagnosed as having occupational disease due to solvent exposure. The majority were exposed to halogenated hydrocarbons, mostly to trichloroethylene or to paint solvents. The mean length of exposure to solvents was 9.6 years for the men and 7.6 years for the women. The exposure level of each subject was graded as low (Level I), intermediate (Level II), or high (Level III), based on information given by the subject, his employer or on hygienic measurements taken in the workplace. High level exposure was defined as being close to the Finnish Threshold Limit Value and seldom exceeding it. Subjects were evaluated by means of electroencephalography, nerve conduction velocity measurements, and a psychological test battery.

The frequency of abnormal EEGs was high among the subjects. A total of 70 out of 107 subjects had abnormal EEGs with 67 percent of the men and 64 percent of the women showing some abnormality. In most cases, the abnormalities were slight in degree and represented an excess of slow waves in the waking record. None of the subjects with low-level exposure had an abnormal EEG. Moderately severe, diffuse slow wave abnormalities were noted only among subjects with high-level exposure. The authors felt that the increased frequency of abnormal EEGs observed in this study (compared to the 10-15 percent of abnormal EEGs occurring in the general population) indicated "toxic encephalopathy."

At least one abnormally slow nerve conduction velocity (CV) was found in 48 out of 77 subjects. The frequency of subjects with abnormal CVs tended to increase with higher exposure levels, although the difference was statistically significant only when comparing exposure Level II to Level III. Conduction velocity scores were not found to be correlated with length of exposure or age. Although none of the subjects had clinical palsy, the authors concluded that the slowing of nerve CVs was a sign of early neuropathy.

Scores from several subtests of the psychological test battery were significantly lower than in the Finnish standardization sample. A comparison of the solvent-exposed groups to a standardized sample revealed weaknesses in variables usually associated with memory and concentration. However, psychological performance test scores in patients with abnormal EEGs were not found to be significantly different from those of patients with normal EEGs.

In conclusion, the authors felt that the findings observed were due to occupational solvent exposure, even though the correlations between exposure level and neurophysiological/psychological results were relatively weak.

V. GENERAL CONCLUSIONS

Taken as a whole, it could be argued that this body of literature provides evidence for an association between adverse CNS effects and chronic occupational solvent exposure. In fact, some Scandinavian researchers have recommended lowering existing solvent TLVs on the basis of this literature. There are, however, certain facets of these data which need to be considered in drawing final conclusions.

- In many of the reported studies the observed effects have been slight. For instance, in the study by Hanninen et al.[3], the authors stated that although the differences between the psychological test performances of the exposed and nonexposed subjects were statistically significant, the impairments discovered could be considered rather slight. They also added that although there were more poor performances among the exposed subjects than among the nonexposed ones, the individual test results were in general within the limits of normal variation. Marginal effects such as these make interpretation of the findings quite difficult. A similar situation exists in the studies by Knave et al.[8,9] in which the authors reported "trends" toward slower nerve conduction velocities in jet fuel-exposed workers. In spite of these "trends," however, the differences in nerve conduction velocities between the groups were not statistically significant. Once again, the long-term practical consequences of such observations are difficult to evaluate.

- Compounding the problem of marginal differences between groups are the nature of the symptoms themselves. The "neurasthenic syndrome," which has often been used to describe these symptoms, is a set of subjective and somewhat vague conditions (i.e., fatigue, anxiety, concentration difficulties) which do not readily lend themselves to objective analysis. Furthermore, the unbiased objectivity of the participating subjects may have been compromised in some studies since the results of preliminary epidemiological reports attracted considerable attention from the general Scandinavian public.

- A fundamental tenet of pharmacology/toxicology is the concept of dose-response. With the exception of a few instances, it has not been possible to demonstrate dose-response type data in the reported studies. That is, there has been no relationship between the length of solvent exposure in years and the severity of the CNS effects observed. Although the lack of dose-response does not invalidate these findings, it does weaken the argument for chronic CNS effects of solvents following low-level exposure.

- Appropriate matching of control and exposed groups is crucial in studies of this nature. Subjects should be selected and matched such that both groups are similar with respect to age, duration of employment, level of education, alcohol intake, drug use and general state of health. A criticism of some of the Scandinavian research is that matched control groups were not chosen carefully enough. Although it is unfair to level this criticism at all of the Scandinavian studies, there are, nonetheless, certain of these studies in which insufficient attention was paid to selection of subjects.

- The possible influence of confounding factors must be eliminated before the reported effects can be attributed to solvent exposure per se. Many of the symptoms described as occurring in solvent-exposed workers may have been due to other environmental influences, such as age, stress, alcohol and drug abuse or other chemicals. Chronic alcohol intake, in particular, may lead to varying degrees of CNS dysfunction. In general, these factors have not been well enough controlled to eliminate their possible influence in most of the studies which were reviewed.

- Even if one accepts as fact that the reported effects are real, a question regarding exposure concentrations remains. Many of the published reports acknowledge that detailed records of solvent exposure are usually lacking, particularly in reference to exposure levels of the past. Unfortunately, this issue is of fundamental importance to the question at hand. The CNS effects being observed may be a result of repeated exposures to solvent levels well in excess of current TLV standards. The fact that some of the subjects in these studies reported symptoms during work such as dizziness, nausea and irritation would tend to support this supposition. The effects being observed may then be a result not of chronic exposure to TLV levels of solvents, but to an accumulation of high concentration insults. In the future, industrial firms should be encouraged to keep more accurate records of solvent exposure, both quantitatively and qualitatively.

In conclusion, it is the opinion of the present authors that the body of literature currently available is <u>not</u> adequate to demonstrate an association between chronic solvent exposure at existing TLVs and adverse CNS effects. However, the sheer number of reports available purporting to show such effects does raise concern over this issue and commands that these findings not be dismissed lightly. This potential problem cannot be ignored since occupational exposure to solvents is widespread. Research should continue in the area of behavioral toxicology in order to identify appropriate animal models for predicting chronic behavioral changes following exposure to chemicals.

VI. RECOMMENDATIONS

1) The current scientific literature on this subject should be monitored.

2) The solvent-related health effects described in this review are not widely recognized outside Scandinavia. However, the potential medical-legal implications to the solvent industry are serious and pressures to give this "occupational disease" formal recognition are rapidly spreading throughout Europe. The impact of these developments on solvent use in Europe should be monitored, particularly in regard to any changes in European TLVs.

3) It is our assessment that the current information does not indicate cause for a blanket lowering of solvent TLVs/OELs. However, in recognition of the public pressure which may be brought to bear on this issue in the near future, Solvents Division may wish to review the impact that reduced TLVs would have on normal operating procedures.

4) It is critically important to recognize the distinction between the CNS effects of acute solvent exposure (i.e., CNS depression) and the purported chronic effects discussed in this report. Experiments utilizing short-term exposure of humans (or animals) cannot reliably predict long-term hazards. Attempts to draw conclusions regarding chronic hazards based on information obtained from acute or short-term exposures should be approached cautiously.

5) The subjective nature of the health effects reported in the Scandinavian literature make it difficult to design meaningful animal experiments for investigating this problem. Although a variety of tests are available for evaluating neurobehavioral toxicity in animals, the interpretation of data obtained from such tests is sometimes open to question. Therefore, we do not recommend that an extensive animal testing program be initiated at the present time. However, research should continue to better understand the implications of the reported changes observed in humans and to identify appropriate animal models that will reasonably predict these events.

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