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# Chronic Neurotoxicity of Solvents

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# CHRONIC NEUROTOXICITY OF SOLVENTS

## CONTENTS

**SUMMARY**

This review addresses the question whether a discrete specific neurological syndrome that is causally related to chronic low-level exposure to organic solvents actually occurs. The review discusses the available information on solvent exposure, human neurotoxicology and animal neurotoxicology and demonstrates that only a small proportion of it is relevant to this particular question. Chronic low-level exposure has only been experienced in a few well controlled environments, sub-clinical effects in subjects exposed to these environments have only been investigated in a few studies and most animal work has been conducted at high levels of exposure.

A secondary objective is to review the natural history of those adverse effects that have been attributed to solvents, whatever the levels and frequency of exposure may have been. Several studies have been published which examine whether these effects are stable, reversible or progressive.

Thirdly, the information on specific solvents has been summarised within a framework for critical appraisal of the epidemiological literature on solvent neurotoxicity.

For a chemical to be considered neurotoxic, in contrast to narcotic, evidence needs to be obtained for a consistent pattern of neurological dysfunction in man or animals. Lesions may be shown in the nervous system or sense organs which account for the neurobehavioural disorder. Five solvents have previously been shown to cause structural lesions, namely, carbon disulphide, n-hexane, methyl n-butyl ketone, toluene and impure trichloroethylene.

The industrial exposure data, both in manufacture and use, have been examined for the above solvents (except carbon disulphide) together with that obtained for 1,1,2-trichloro-1,2,2-trifluoroethane, methyl ethyl ketone, styrene, tetrachloroethylene, white spirit and xylenes. The above thirteen solvents represent those most commonly used in industry. Historical data on industrial exposure has been generally inadequate for the investigation of possible neurotoxicity. Recent data revealed that there are circumstances where short-term exposures can exceed occupational exposure limits, often markedly so, but that on a time weighted average basis exposure levels were below the OEL with a tendency to progressively lower exposures over recent years.

The earlier epidemiological data (pre-1984) suggested that professional house painters and varnishers exposed to high doses suffer more from dizziness, forgetfulness, irritability and fatigue compared with those either not or minimally exposed to solvents. The data suggested that at high dose levels there was evidence of minor, non progressive deficits for memory, perception and coordination in some solvent exposed workers.

Epidemiological data since 1984 have been reviewed against two criteria, their ability to tackle the objective of this review, and the validity of their conclusions. Many studies are irrelevant because they consider populations exposed to high concentrations of solvents, because the populations studied have not had lengthy exposure, or because the health condition studied has many known causative factors other than solvent exposure. The remainder have been assessed as to their treatment of bias and confounding factors, their estimates of exposure levels and the validity of their investigative techniques. Criteria for the assessment of the neurobehavioural and neuropsychological content of study protocols have been defined by WHO. Conforming to these can be regarded as a necessary minimum but since they have subsequently been enhanced and extended by several investigators they cannot be regarded as a standard requirement.

A single neurotoxicological syndrome, as claimed by some to exist in man, does not occur in laboratory animals as a consequence of solvent exposures. The limited animal neurotoxicological data related to solvents has been reviewed in terms of chronic neurotoxicity or other evidence that would support the hypothesis that long-term low-level solvent exposure is causally related to chronic neurobehavioural effects in man. None of the studies support the hypothesis that low-dose chronic exposure to solvents, at or below the recent or current OELs, causes encephalopathy or profound changes in behaviour or performance. Frequent bouts of high, possibly narcotic, exposure over short periods, similar to exposures seen in human solvent abuse result in neuropathy and irreversible behaviour changes in the case of impure trichloroethylene and toluene. Exposure pattern is important for the induction of peripheral nervous system damage caused by n-hexane and methyl n-butyl ketone.

It is concluded that there is no basis for a neurological syndrome in man that is causally related to low level organic solvent exposure (as defined by recent or current OELs).

Whilst it is likely that further epidemiological studies will be reported it is doubtful whether they will be of any great value unless rigorous attention is paid to conforming with the WHO protocols coupled with adequate characterisation of exposure. It is recommended that resources are better deployed on the control of exposure rather than conducting further epidemiological examinations.

## SECTION 1. INTRODUCTION

The term "organic solvents" in the context of this review covers a wide group of chemicals, extensively used in many industrial and domestic situations, often in large volumes. They have three characteristics in common, namely they are all volatile liquids at normal temperature, strongly lipophilic and can produce depression of the central nervous system in man if a sufficiently large dose is administered. There are many reports of acute intoxication resulting from exposure to organic solvents. Such episodes are usually the result of accidental high exposure in work situations or deliberate exposure from solvent abuse.

One of the earliest reports of neurotoxicity after occupational exposure was recognised at the end of the 19th century. Workers exposed to carbon disulphide developed a syndrome, which was characterised by abnormal fatigue, difficulties in concentration, impairment of memory, general irritability and alcohol intolerance. This syndrome, sometimes called "neuraesthenic syndrome" was also described in workers exposed to other solvents such as trichloroethylene, xylene and turpentine. It is only for carbon disulphide that there exists clear evidence of neurotoxic damage detectable by clinical and pathological examination as well as neurophysiological measurements or neuropsychological techniques.

Although control of hazardous substances in the workplace has progressively improved during this century there is still occasional evidence of high acute exposures in excess of occupational exposure limits. These occur in certain occupations and situations, manifested by the presence of symptoms of acute exposure, pre-narcosis, and occasionally death.

A neurological dysfunction produced by long term exposure to neurotoxic agents will manifest itself as deficits in neurobehaviour and/or neuropsychological performance in animals as well as man.

When examining data for the chronic neurotoxicity of solvents the Task Force was set the following terms of reference:

- review critically published and unpublished epidemiological and experimental studies on the neurobehaviour and neuropsychological effects of exposure to organic solvents;
- evaluate the evidence in terms of hazard to man of long-term exposure to solvents at concentrations likely to occur in the industry.

To address the question of whether or not there is a discrete specific neurotoxicological syndrome,

characterised by adverse functional or structural effects manifested in a consistent manner and which is causally related to chronic low-level exposure to organic solvents the Task Force has concentrated on three areas of study: solvent exposures, human health data and experimental animal data. This report is therefore presented under these headings.

Human exposure data available for individual solvents varies and is only widely available for white spirit, toluene, methylene chloride, tetrachloroethylene, styrene and n-hexane while the remaining solvents are components of mixed solvents. For n-hexane peripheral neuropathy associated with exposure is clearly understood and exposure is well controlled.

When evaluating the animal data we have concentrated on the following 13 solvents that are most commonly used in industry: 1,1,1-trichloroethane, 1,1,2-trichloro-1,2, 2-trifluoroethane (fluorocarbon 113), n-hexane, methyl n-butyl ketone (MnBK), methyl chloride (chloromethane), methylene chloride (dichloromethane), methyl ethyl ketone (MEK), styrene, tetrachloroethylene, toluene, trichloroethylene, white spirit, and xylenes. We have looked for adverse functional and structural effects of the nervous system manifested in a consistent manner.

Wherever possible we have attempted to avoid the use of acronyms, but in a review of this nature some use is inevitable. All have been defined in the text at time of first use and in the glossary. Repeatedly throughout the text we use the phrase Occupational Exposure Limit (OEL) to cover published values otherwise termed Threshold Limit Values (TLVs), Maximale Arbeitzplatz Konzentration (MAKs), Permitted Exposure Limits (PELs) as well as OELs. Although the different sources change the OEL values from time to time for the purposes of our evaluation we have standardised on the 1991-1992 ACGIH TLVs (ACGIH, 1991).

## SECTION 2. EXPOSURE TO SOLVENTS

### 2.1 INTRODUCTION

A major difficulty highlighted in many papers addressing the issue of neurobehavioural effects of organic solvents has been the lack of data, and in particular historical data, quantifying worker exposure to solvents in the workplace. The purpose of this review therefore, was to gain an overall picture of current and historical solvent exposures, by collation of available occupational hygiene data during manufacture and use. The review includes a considerable body of data relating to paint manufacture and use because of the prominence of the issue within this industry. The exposure data included are derived from solvent manufacture and use in activities such as printing, paint stripping, cleaning, degreasing, dry cleaning, adhesive manufacture and use, plastics manufacture and use, boat building and tyre manufacture. The information so obtained will be of value for placing in context the biological responses seen in animals and the observations reported in man.

### 2.2 EXPOSURE TO ORGANIC SOLVENTS - A QUALITATIVE REVIEW

In the absence of quantitative data attempts have been made to characterise exposures by use of measures such as the number of years exposure, or the amount of solvent used. However the problems in addressing solvent exposure, particularly for painters, are numerous and investigations clearly demonstrate that the number of years exposure, which is a widely used surrogate for degree of exposure, is grossly inaccurate because it is not representative of cumulative exposure and difficult to analyse because it is highly correlated with age (Fidler *et al*, 1987a). It is clear from the published studies that solvent exposure has very often been in excess of the OELs, sometimes markedly so, as evidenced by the symptoms reported. For example in a study of solvent exposure in construction and maintenance painting in Finland it was reported that between 1960 and 1973 the feeling of drunkenness was estimated to have occurred on average 46 times per worker per year; between 1974 and 1978 it had fallen to 27 times per worker. In the same study 8% of the 231 workers reported experiencing drunkenness 100 or more times per year (Riala *et al*, 1984). On the basis of 200 working days this means that for 50% of the time the solvent exposure was in excess of the OEL. Similar feelings of drunkenness were reported from the Erlangen painter study in West Germany where 2% of the workers were affected (Triebig *et al*, 1988).

### 2.3 EXPOSURE TO ORGANIC SOLVENTS - A QUANTITATIVE REVIEW

Quantitative information concerning exposure to a variety of solvents, indicating ventilation systems, type and number of samples taken, and monitoring period, is summarised in Appendix A (Tables A-1 to A-8). It is stressed that the hygiene data reported were generated using a variety of measurement

and analytical techniques, and were collected for a variety of purposes. Comparisons between the data must therefore be made with caution.

Exposure to chemical substances can occur by inhalation, ingestion or absorption through the skin. However, inhalation is usually the main route of entry. Occupational exposure limits (OELs) have been developed to determine the adequacy of the control of exposure by inhalation. An OEL for an individual airborne substance is defined as the concentration, averaged over a reference period, at which, according to current knowledge, there is little or no risk of injury to the exposed individual. As OELs relate to the amount of a particular substance inhaled by an individual, any assessment of exposure should estimate as closely as possible the amount inhaled by the individual. Monitoring the amount inhaled is best done by attaching a portable sampling device to the exposed person, which, whilst allowing them to carry out their normal work activities, samples air from their breathing zone for later analysis. Data derived from such personal sampling allows a direct comparison with the OEL and hence an assessment of the adequacy of control over inhalational exposures.

Alternative sampling strategies can also be used. For example, where it is difficult to attach sampling equipment to an individual because of the nature of their work, fixed (or static) sampling equipment may be placed in a position that is, as far as possible, representative of the area in which the individual works. Clearly the results will not be a direct measurement of an individual's exposure and so interpretation of compliance with a particular standard has to carried out with care. Fixed (or static) sampling is also often used to evaluate the efficacy of a particular control system (eg an exhaust ventilation hood) and typically would involve placing the sampling equipment close to or actually within the exhaust hood itself. Such measurements are generally not representative of any particular individual's exposure, and are usually significantly higher than in the actual workplace.

Where fixed sampling has been used it is essential that an accurate description of the purpose of the sampling is available in order that a judgement can be made of its value as an indicator of personal exposure.

Whether personal or fixed sampling have been employed, exposure to chemical substances should be carried out using approved methods. These are typically issued by national regulatory bodies (eg UK-HSE, OSHA, NIOSH) and will detail the measurement method, the equipment to be used, the sampling period, sample volume and analytical methods and any other relevant information. Such approved methods will give results of a known precision within their working ranges, allowing an acceptable level of confidence when assessing compliance with OELs. Approved methods exist for all of the solvents of interest in this study.

In evaluating exposure data most weight should be given to data derived from personal monitoring

where the samples have been collected using an approved method. Data derived from fixed monitoring should be regarded with caution unless there is positive confirmation that the data was taken to assess an individual's, or group's exposure to the substance of interest, and that the authors have expressed confidence that data does in fact give a reasonable approximation to the individual' or group's exposure. This is normally done by reference to personal samples carried out within the area monitored which has produced comparable results.

Other factors of importance are the number of samples taken and the duration of the sampling period. Clearly the greater the number of samples taken in a particular situation the greater the statistical reliability of the results produced. Results based on a small number of samples (< 5) should be treated with caution. Sampling over longer periods (usually greater than 4 hours) is carried out to assess compliance with long-term OELs (8 hours time weighted average). Sampling over short periods is usually carried out to assess compliance with short-term OELs (15 minutes time weighted average) or to monitor specific activities to identify issues of potential concern. Long term monitoring will give an average exposure over a working shift and depending on the pattern of exposure, will generally include periods of higher and lower exposures. Short term monitoring is usually targeted at activities that are thought to give rise to particularly high exposures. Such activities may not be representative of exposure over the remainder of the work period, hence unless confirmation is given that the short monitoring periods are representative, such monitoring will tend to give higher results than full shift monitoring. Care must be taken when comparing data collected over markedly different monitoring periods.

Unfortunately most of the authors have failed to report in detail the measurement and analytical techniques employed thereby reducing the value of the publications; where details were provided they were generally to recognised standards (NIOSH, UK HSE or other National Standards). As a general guide the papers published in occupational hygiene journals gave most detail concerning the actual monitoring and analytical methods used. Clearly these papers are aimed principally at professional hygienists and in addition will have been peer reviewed by hygienists and are most likely to have had the closest scrutiny of the hygiene methods employed. As such more confidence can be placed on the results published. Papers published in the Scandinavian Journal of Work Environment and Health also tended to give more detail relating to sample collection and analysis. The remaining publications varied enormously in the detail given. The only comment that can be made is that there was generally insufficient information to conclude that the results were derived using inappropriate methods.

The results of the measurements have been reported either as concentration levels for individual solvents or for mixtures of solvents, or as a cumulative index for mixtures of solvents. The cumulative index is based on the assumption that the health effects of the individual solvents are similar and can

be added (UK HSE, 1989; ACGIH, 1991). The mixed exposure is assessed by means of the formula:

$$\frac{C1}{L1}+\frac{C2}{L2}+\frac{C3}{L3}\ldots<1$$

where C1, C2 etc are the time weighted average concentrations of the constituents in air and L1, L2 etc are the corresponding OELs. Where the sum of the C/L fractions does not exceed one, the exposure is considered not to exceed the notional exposure limit for the mixture.

In addition to the cumulative index for mixed solvents, many of the individual results are also expressed as the ratio of the exposure concentration to the Occupational Exposure Limit (OEL). Both are reported in the tables in the column headed CONC/OEL. Where these ratios are given they are based on the OELs current at the time the exposure measurements were made. It should be noted that OELs for solvents have varied over time; there is a general downwards trend (Table 1). Consequently, the reported ratios should be interpreted with care.

Exposure data are presented where a single or major solvent can be identified (Appendix A); when this is not possible because several solvents are present, data is presented for 'mixed solvents'. In the main exposure data is taken from work reported during the 1980's, nevertheless considerable data is included from the 1970's with occasional reports from earlier years.

Most of the data relate to personal exposures measured in the breathing zone with little information on the use of any respiratory protective equipment. In the absence of specific information it is assumed that protective equipment has not been used and the data reflects actual exposures.

## 2.4 SOLVENT EXPOSURE DATA

### 2.4.1 Methylene Chloride (Appendix A: Table A-1).

Exposure during solvent manufacture is normally below the OEL (< 15 ppm), but with occasional exposures up to 5 x OEL (ICI, 1991b). The majority of papers listed by IARC (1989) dealing with methylene chloride exposure relate to degreasing, paint stripping, printing and unspecified cleaning operations. The highest exposure reported occurred during tank cleaning in the printing industry (>100 x OEL) (Rivera, 1975); over 50% of papers report exposures in excess of the OEL.

**TABLE 1. Historical Occupational Exposure Limits, expressed as ACGIH TLVs set on a basis of life time exposure 40h/w, 40 weeks/year, 40 years)**

| COMPOUND | 1947 | 1959 | 1962 | 1963 | 1965 | 1971 ACGIH | | 1975 ACGIH | | 1980 ACGIH | | 1984/5 ACGIH | | 1989/90 ACGIH | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | TWA | STEL | TWA | STEL | TWA | STEL | TWA | STEL | TWA | STEL |
| N-Hexane | | | | | | 500 | | 100 | | 100 | 125 | 50 | | 50 | - |
| Methyl n-Butyl Ketone | | | | 100 | | 100 | | 100 | | 25 | 25 | 5 | | 5 | - |
| Methyl Chloride | | 100 | | | 100 | 100 | | 100 | | 100 | 125 | 50 | 100 | 50 | 100 |
| Methylene Chloride | | 500 | | | 500 | 500 | | 200 | | 200 | 250 | 100 | 500 | 50 | - |
| Methyl Ethyl Ketone | | | 200 | | | 200 | | 200 | | 200 | 300 | 200 | 300 | 200 | 300 |
| Perchloroethylene | 200 | | 100 | | 100 | 100 | | 100 | | 100 | 150 | 50 | 200 | 50 | 200 |
| Stoddard Solvent | | | 500 | | | 150 or 200 | | 100 | | 100 | 125 | 100 | 200 | 100 | - |
| Styrene | | | | | 100 | 100 | | 100 | | 100 | 125 | 50 | 100 | 50 | 100 |
| Toluene | | | 200 | | 200 | 200 | | 100 | | 100 | 150 | 100 | 150 | 100 | 150 |
| 1.1.1-Trichloroethane | | 500 | 500 | | 500 | 350 | | 350 | | 350 | 450 | 350 | 450 | 350 | 450 |
| Trichloroethylene | | | 100 | | 100 | 100 | | 100 | | 100 | 150 | 50 | 200 | 50 | 200 |
| Xylene | | | 200 | | 100 | 100 | | 100 | | 100 | 150 | 100 | 150 | 100 | 150 |
| Fluorocarbon 113 | | | | | | | | | | | | | | | |

[1] by analogy with heptane and octane

**2.4.2 Styrene** (Appendix A: Table A-2).

The industrial use of styrene has been subject to extensive investigation in particular in its use in the reinforced plastics industry. Exposures above the occupational exposure limit were reported in 10 out of the 21 papers reviewed. Out of these 10 papers 3 reported high exposures despite the use of local exhaust ventilation systems. High exposures were reported during the manufacture of fibre reinforced plastic boats (IARC, 1979; Crandall *et al*, 1985; Jenson *et al*, 1990) and with the manufacturing of bathware (Galvin *et al*, 1990; Rappaport *et al*, 1991). When monitoring times were detailed the majority of samples were taken over significant periods indicating prolonged exposures to styrene. In addition peak exposures up to 7 times the short term exposure limit were reported (Galvin *et al*, 1990).

A major review of styrene exposure in Denmark, principally as a result of boat building, reported exposures above the standard from the mid- 1950's to the end of the 1970's (Jensen *et al*, 1990). High exposures continue to be reported in the 1990's (Galvin *et al*, 1990; Rappaport *et al*, 1991).

**2.4.3 Tetrachloroethylene** (Appendix A: Table A-3).

Only four papers were identified when concentrations in use were measured; three report on exposures during dry cleaning and degreasing operations and one during solvent manufacture. The manufacturing data indicated average exposures well below the OEL (< 1.5 ppm) with occasional exposures to 4 x OEL. The dry cleaning and degreasing data indicated the majority of exposures below the OEL with significant numbers of results below 0.5 x OEL.

**2.4.4 Toluene** (Appendix A: Table A-4).

Exposure data relate principally to the use of toluene during printing and industrial painting during the 1980's. Half the papers reported long term monitoring of 4 hours or greater (Greenberg *et al*, 1942; Tokunaga *et al*, 1947; Maki-Paakkanen *et al*, 1980; Matsunaga *et al*, 1983; de Rosa *et al*, 1985).

The highest solvent levels reported (11 x OEL) occurred during spray painting of aircraft (Greenburg *et al*, 1942) with exposures above the OEL also being reported during spray painting of vehicles (Matsunaga *et al*, 1983). Five of the eight exposures involving printing operations also reported exposures above the OEL (Ikeda and Ohtshji, 1969; Veulemans *et al*, 1979; Maki-Paakanen *et al*, 1980; Lindstrom, 1981; Angerer, 1985).