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Chronic Neurotoxicity of Solvents

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CHRONIC NEUROTOXICITY OF SOLVENTS

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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).

It appears that a significant potential for exposure above the OEL exists in spray painting. It is normal in these situations for personal protective equipment to be used thereby reducing the effective exposure. Printers are also exposed by aerosols but in this situation such protective measures are not normally employed.

2.4.5 White Spirit (Appendix A: Table A-5).

The reported estimates of exposures principally relate to the use of white spirit in decorative paints (ie. household and building painting applications). Although some data refer to the situation in the 1960s and 1970s (Seppalainen and Lindstrom, 1982) the majority originate in the 1980's. All of the papers (cf. Appendix A: Table A-5) reported exposure periods of 3 hours or less, with most of the sampling being carried out to evaluate exposure during paint application. There is only one paper that describes exposure during a full working shift, this relates to a vehicle spray painting operation within a spray booth and reported a low average exposure (< 10 ppm) (Bradley and Bodsworth, 1983).

The data show that during the application of white spirit based paints, under conditions of poor ventilation, the OEL for white spirit can readily be exceeded and that the use of natural ventilation can significantly reduce solvent levels (Riala *et al*, 1984; Dearling *et al*, 1989; ICI, 1991d). Nevertheless natural ventilation is not always effective in reducing exposures below either the short term or long term OELs (Dearling *et al*, 1989; ICI, 1991d).

Much of the exposure data relating to decorative painting was produced during special research projects or by paint manufacturers. Routine monitoring of exposures by end users of paint does not appear to have been common.

The pattern of solvent exposure among painters is of great relevance as only part of the working time is spent using solvent borne paint; the amount of time spent doing other tasks (cleaning, preparing surfaces, etc.) or using water based paint may be significant. Estimates of solvent exposure by Finnish decorative painters between 1960 and 1973 indicated equivalent daily average exposures of 0.4 x OEL, with this figure reducing to 0.25 x OEL by 1977 (Seppalainen and Lindstrom, 1982). Whilst these values show that the time-weighted average exposure has reduced it is likely that the pattern of short-term and peak exposures is of greater significance for chronic neurotoxicity.

2.4.6 Mixed Solvents (Appendix A: Tables A-6 - A-8).

Mixed solvents generally incorporate xylenes, methyl n-butyl ketone and methyl ethyl ketone;

exposure data in isolation for these solvents is not easily obtainable and hence mixed exposure is addressed in this section.

The most frequently reported type of exposure is from mixed solvents in paints, varnishes, glues, degreasers, and printing operations. In the spray application of paints to aircraft where mechanical control of exposure is difficult, the average exposures reported were above the cumulative OEL (Hervin and Thorburn, 1975; Okawa and Keith, 1977; O'Brian and Hurley, 1981). In such circumstances it would be normal to wear respiratory protective equipment. Spray application of paints in industrial situations, the majority of which are carried out in booths, did not in general give rise to long term exposures in excess of the cumulative OEL (cf. Appendix A: Tables 6 - 8). In general the highest exposures (up to 54 x OEL) were recorded during house painting with the higher values associated with short monitoring periods; ie. a similar situation to white sprit exposure (Byggforlaget, 1975; Molhave and Lajer, 1976; Riala, 1982; Riala *et al*, 1984; Scheffers *et al*, 1986; ICI, 1991).

Furthermore high peak exposures during decorative painting was reported throughout the last two decades suggesting similar exposure patterns over that period (Byggforlaget, 1975; Molhave and Lajer, 1976; Riala, 1982; Riala *et al*, 1985; Scheffers *et al*, 1985; ICI, 1991). There is evidence that exposure levels in paint manufacturing were reducing over the same time period (Lundberg, 1986; Orbaeck *et al*, 1985).

2.5 EVALUATION

As far as we are aware the data compiled in Appendix A is the most comprehensive review of quantitative solvent exposures available at this time. When evaluating the data it is possible to categorise the situations giving rise to such exposures into three broad groups:

- Occupational Exposure Well Controlled: manufacturing operations for solvents themselves or formulated products, eg. paints, where the data indicates effective implementation of occupational hygiene practices and good control of exposure both in terms of peak and 8 hour-time weighted averages;

- Occupational Exposure Generally Well Controlled: certain industrial and commercial operations, e.g. aircraft spraying, some vehicle spraying, dry cleaning, using solvents or solvent based products where occupational hygiene standards are established, exposures in general are well controlled, but where there are possibilities of excursions above the OEL;

- Occupational Exposure Poorly Controlled: other industrial and commercial operations using solvents and solvent based products where occupational hygiene practices are not well established, eg. some boat building, interior painting, some vehicle spraying, some paint

stripping and degreasing operations as well as printing; in these circumstances there is a likelihood of exposure occurring for either long or short-term above the OEL.

By contrast with the manufacturing situation the paucity of quantitative exposure information for household and industrial painting operations confirms that occupational hygiene practices are not well established in these areas. Recent exposure assessments have relied upon simulated situations; in particular exposure resulting from the use of solvent based paints in confined spaces, on large surface areas, or in other circumstances of poor ventilation has been shown to be high and above the OEL. The reduction of exposure seen in the manufacturing situation has not been mirrored by the users of paint products or in other areas characterised by lack of professional occupational health supervision.

SECTION 3. EVIDENCE FOR NEUROTOXICOLOGICAL DAMAGE IN MAN

3.1 INTRODUCTION

Organic solvents have been extensively used over the last 30 - 40 years in paints, lacquers and as cleansing agents resulting in the exposure of a large number of workers to their vapours. Skin contact with liquid solvents also occurred frequently so that absorption must have taken place both by inhalation and percutaneous routes. The knowledge that acute exposure to organic solvents results in symptoms resembling drunkenness led to the concern that low-levels might lead to chronic irreversible damage to the nervous system. This concern was underlined by the fact that an important, and at one time, an extensively used solvent, carbon disulphide, produced serious and progressive damage. The possibility that brain damage may be caused by prolonged exposure to relatively low-levels of organic solvents was investigated in numerous epidemiological studies. These studies varied considerably in depth and in quality and this must be taken into account in evaluating their conclusions.

Grasso *et al* (1984) reviewed the clinical and neuropsychological studies carried out on workers exposed to solvent vapours during the previous two decades. They concluded that abnormal neuropsychological changes were detected more frequently in occupations involving an exposure to solvents. However, a cause-effect relationship could not be established because of a number of deficiencies in study design, such as identity of the solvent or solvents to which the workers were exposed, duration and levels of exposure, particularly information on "peak" exposure (eg. levels, duration, frequency) and failure to take sufficient account of confounding factors (e.g. age, medicaments, alcohol). No adequate dose-response or follow-up studies had been done up to that time and it was not known whether impairment of psychological functions improved on removal from exposure. Nevertheless the authors accepted that the solvent exposure may be causally associated with the neuropsycological deficits observed.

Spencer (1984) also reviewed the epidemiological studies on workers exposed to solvents and concluded that "The argument that the nervous system of these workers had been adversely affected is often based on heroic use of statistics to manipulate grouped data obtained by interviews, questionnaires and psychometric tests of dubious reliability, however, sufficient data are unavailable to refute the claims of the large number of Scandinavian workers that have published on this subject". In a subsequent publication, Spencer and Schaumburg (1985) analysed the neurotoxic effects of solvents on the nervous system and drew attention to carbon disulphide, n-hexane, and tetrachloroethylene as examples of classical neurotoxic agents with unmistakable clinical symptoms and morphological evidence of brain or nerve damage. Turning to the psycho-organic syndrome found in painters, they pointed out its very mild nature, compared with that produced by the three

neurotoxic solvents mentioned, and the absence of any evidence of a morphological basis. They also pointed out that most studies on the "painters syndrome" have relied on self-administered questionnaires and others on psychometric tests and neurological examination, "disparate findings [from these investigations] are often grouped together and reliance is placed on statistical techniques to yield small differences between those exposed and the referents".

Errebo-Knudsen and Olsen (1986) brushed aside any connection between the psycho-organic syndrome and solvent exposure. Neuropsychological deficits found in painters are also found in the general population and they pointed out that individuals with these deficits may have found it easier to take up painting as an occupation than other more intellectually demanding jobs thus providing differential information bias. They also emphasised that high alcohol consumption could have caused these deficits rather than solvent exposure thus confounding the information.

In contrast, Hogstedt and Axelson (1986) came to a different conclusion from the previous authors. They reviewed four major Scandinavian epidemiological studies (Axelson *et al*, 1976; Mikkelsen, 1980; Olsen and Sabroe, 1980; Lindstrom *et al*, 1984) and estimated that the risk for painters and some other solvent-exposed workers to develop an incapacitating neuropsychiatric disorder before the age of retirement was roughly doubled. They concluded that the majority of the design deficiencies seemed to work in the direction of diluting the risk estimates, making it more difficult to detect the true risks.

Baker and Fine (1986) arrived at a similar conclusion but their statements are more guarded. Reviewing the literature up to 1986 they said that there appeared to be a number of syndromes of solvent-related CNS dysfunction that vary in severity but have similar qualitative features. They noted an absence of consistent dose-response relationships in epidemiological studies so that they were unable to determine whether concentration of solvents below current permitted levels of exposure present any hazard. They cited a study by Maizlish *et al* (1985) who reported that there were no consistent neurobehavioral deficits at or below current exposure levels.

In a subsequent review Hogstedt (1994) concluded that the evidence linking high cumulative solvent exposure to disability pensions due to neuropsychiatric disease and hospitalisation for psychiatric treatment was convincing, but other aspects of what he called "the Scandinavian Solvent Syndrome" required further research.

3.2 UTILITY OF EPIDEMIOLOGICAL STUDY PROTOCOLS FOR ASSESSING EFFECTS OF SOLVENT EXPOSURE

Before reviewing the data published after 1984 (i.e. after the review of Grasso *et al*, 1984) it is

important to note some common features in the above reviews:

- all populations examined showed some minor deficits in long term memory and coordination;
- no psychiatric changes were seen;
- the severity of the deficits was not consistently related to the concentration or duration of exposure;
- a clear no effect level could not be established;
- workers exposed to solvents below the current (1991) OELs did not show any consistent deficits;
- there was no consensus regarding the aetiology of the deficits;
- all reviewers agreed that there was a need for further epidemiological studies.

In reviewing the literature, the terms neuropsychology, neuropsychiatric and neurobehaviour are frequently used and they are also reflected in this document. The terms are defined in the glossary. It is important to note that we have always used the original terms as quoted by the author, although in many instances the terms are interchangeable and do not necessarily agree with the definitions in the glossary.

Attempts have been made to draw up a standard set of investigations for use in neurological studies. The benefits of standardisation are that the tests can be validated, normal values can be calculated and the results of different studies can easily be compared. A pathfinding initiative on the question of validity was the publication of criteria by WHO in 1989 (the WHO Neurological Core Test Battery (NCTB)). These criteria covered experimental design, protocol, conduct, evaluation and particularly exposure assessment. In addition they recommended a number of neurophysiological tests to be used to ensure standardisation. Subsequently further research, and crucially, computerisation, have meant that the WHO recommendations can be adopted as minimum, but not definitive, criteria. The features examined in the WHO-NCTB are:

Obligatory Tests	Strongly Recommended Tests
Digit-symbol (WAIS-R)	Aiming
Trail making A and B (Halstead-Reitan)	Simple reaction time
Block design (WAIS-R)	Santa Ana
Vocabulary (WAIS-R)	Digit Span
	Profile of mood states
	Other tests of verbal and visual learning.

For a description of these tests see WHO (1989).

A disadvantage of standardisation is that development is constrained and improvements cannot easily be introduced. The above WHO-NCTB is widely used in field studies particularly in less developed countries, but many investigators prefer to use computerised batteries because of the time saved and the need for fewer observers. Most studies contain all or some of the following elements:

- clinical examination, including full neurological examination;
- symptoms and mood questionnaires;
- neuropsychological tests (computerised or otherwise);
- neurophysiological measurements;
- neuroradiological examinations, e.g. tomography.

The reported studies have been categorised according to their design, and it is shown that only cross-sectional studies can approach the level of detail needed to address the review's precise objective. It is also shown that only studies that avoid the traps of bias and confounding can produce valid results.

Many epidemiological studies of the neurotoxicological effects of solvents have been published. Although each study contributes to the debate about the nature and degree of the risks presented by solvent exposure, few of them shed much light on the specific topic of this report. The reason is that the design of some studies is such that they only serve to generate hypotheses rather than test them, whilst only the most sophisticated of designs is suitable both for testing a hypothesis about solvents and adverse effects and for providing evidence about the dose-response relationship (Bradford-Hill, 1971).

The aim of this report is to address the question of whether a discrete, specific neurological syndrome that is causally related to chronic low-level exposure to organic solvents actually occurs. This syndrome may occur as a neurobehavioural, neurophysiological or neuropsychiatric syndrome. With this aim in mind, each study has to be examined under two distinct criteria:

- did the study address this particular question, or any aspect of it ?
- was the study conducted in a sufficiently valid manner for its results to be meaningful?

To meet the first criterion, a study must clearly exhibit the following properties:

- it must exclude subjects exposed to high-level (acute) exposure; if a study is only to contain persons experiencing exposures below the OEL, then it must be restricted to employment in solvent manufacture, formulation and certain industrial and commercial operations in which exposure has been well controlled (see Section 2.5); studies of boat

building, interior painting, vehicle spraying, paint stripping and degreasing are unlikely to meet the criteria;

- it must exclude the effect of recent exposure by allowing an adequate interval between exposure and examination;
- it must contain a reasonably large number of subjects who have experienced low-level exposure for a considerable period, say a minimum of 5 years;
- it must study health parameters in a way that will identify a discrete specific neurological syndrome rather than health effects known to be attributable to a number of causes; it is likely that a range of investigations will be required and that sub-clinical effects will need to be studied; the criterion is unlikely to be met by a study that limits investigation to a clinical examination and a questionnaire of symptoms.

Other investigators have defined similar criteria. Most of the controversy about the existence of low-level solvent effects centres on the use and interpretation of neuropsychological tests. There are several validated test batteries which are not necessarily comparable.

Establishing whether a study meets the criterion of validity is more complex and must remain to some extent a matter of judgement. This is because the most important issues in judging validity are bias and confounding, and it is not easy to recognise their presence in a study or to assess their impact on the results (Checkoway *et al*, 1989).

Systematic error, or bias, occurs if there is a difference between what the study is actually estimating and what it is intended to estimate.

Confounding occurs when the exposed and control groups are not comparable because of inherent differences in background diisease risk, usually because of other risk factors. A confounding factor must be associated with both exposure and disease lacking exposure.

Bias can occur as

- selection bias, which arises from the procedures by which the study subjects were chosen from the total population at risk; common examples of selection bias are the use of volunteers, and the use of working populations which exclude leavers;
- information bias, which involves misclassification of study subjects with respect to disease or exposure status; it can occur as
  - differential information bias, which occurs when exposure depends on disease, or *vica versa*, or
  - non-differential information bias, which occurs when the misclassification is the

same in both control and exposed groups.

Differential information bias is present if exposed subjects tend to feign or over-report or are differentially screened for ill-health, or if unhealthy subjects claim, wrongly, to have been exposed. Differential information will bias the study in favour of an association between exposure and ill-health. Non-differential information bias can occur, for example, if a question about ill-health is ambiguous, or if the categorisation of exposure is unreliable. It will always lead the bias towards finding no effect when indeed an effect exists. Information bias can also be sub-divided into observer bias, introduced by the investigation team, and subject bias, introduced by those being studied.

Confounding occurs when the exposed and non-exposed groups are not comparable because of differences in background disease risk (usually other risk factors). To be a confounder, a factor must be related to both exposure and disease lacking exposure. Confounding is part of the same phenomenon as selection bias. The relationships between the confounder and exposure, and the confounder and disease, do not both have to be logical, one of them could be a statistical relationship peculiar to the study but not generally true. Confounders can, therefore, be divided into known confounders and potential confounders.

A valid study of solvents and neurological effects should at least take account of the following, known, confounding factors:

- age: this is known to be related to neurological disease and possibly related to exposure because subjects with long-term exposure to solvents will probably be above average age for a working population; age is usually accounted for by matching exposed subjects to those unexposed;
- pre-existing disease: this may obviously be related to present disease status and perhaps related to exposure because of recruitment policy into industry which usually depends upon health status; it is usually accounted for by excluding subjects with pre-specified health conditions, e.g., experiencing a coma;
- alcohol intake: this is known to be related to disease and possibly related to exposure for maybe social reasons; it is usually allowed for in the analysis, although if known alcoholics are excluded the spread of intake in the remainder may not be of any consequence;
- pre-morbid (innate) intelligence: this is known to affect the results of neuropsychological tests and is possibly related to exposure if the occupational demands do, or do not, require a certain level of intelligence; it is usually accounted for by including one or more tests that are a good measure of innate intelligence whether or not solvent exposure has been harmful.

It is never possible to preclude the presence of bias or confounding, but the validity of the study can be judged from the efforts the investigators have made to overcome them. Control can be exerted at the design stage by matching or random selection of participants, or at the analysis stage by stratification, smoothing or multivariate techniques. The same procedures should be used to collect information from both exposed and unexposed participants, and the investigator should, where necessary, be blind as to the subjects* exposure status.

Three further indications that the conclusions of a study may be invalid are a small sample size (in a study reported as negative), the use of many statistical tests in a study reported as positive, and a study which is reported as "positive" on the basis of a few statistically significant differences amongst many observations. Small studies lack the statistical power to demonstrate the existence of clinically important adverse effects in the exposed subjects. Small studies may show clinically significant deficits in performance, yet dismiss them as not statistically significant. Some small studies can be considered as hypothesis-generating epidemiological studies and may identify areas for further research. Such areas may be detected by correlating every response variable with every exposure variable, or by analysing the results for every conceivable sub-group of subjects. Any statements about statistical significance in such studies are highly suspect in such circumstances.

3.3 CATEGORISATION OF EPIDEMIOLOGICAL STUDIES FOR ASSESSING EFFECTS OF SOLVENT EXPOSURE

The published epidemiological studies of solvent exposure can be divided into five categories, and the essential features of these categories can be linked quite closely to the criteria above.

3.3.1. Case Reports

These are usually reports of a small number of cases of clinical findings in a highly exposed group of subjects. Often a known condition is being linked to an exposure hitherto regarded as harmless, or the exposure is being linked to a condition with which it had not previously been associated.

These reports have little or no epidemiological aspirations and they contribute nothing to the main aim of this report.

Definition of the painters syndrome would be assisted by the publication of good case reports; these have not been found in the literature.

3.3.2. Descriptive Studies

These are a quick way of studying relationships between solvent exposure and health conditions by using data routinely collected for more general purposes. Evidence about the incidence of diseases is available from mortality records, hospital records and records maintained by community physicians and general practitioners. Evidence about solvent exposure is available from the occupational entries on mortality and hospital records and from census data. Linkage of these records of ill-health and occupation allows a comparison to be made between ill-health in exposed and unexposed occupations. In some studies this comparison is achieved by a case-control approach.

Descriptive studies contribute nothing to the aim of this report because they usually study clinical conditions with a multiplicity of causes and they usually involve little attempt to make any estimate of exposure level or duration.

3.3.3. Case-Control Studies

In a case-control (or case-referent (Breslow and Day, 1980)) study the histories of exposure of subjects meeting a specific definition of ill-health (the cases) are compared to the equivalent histories of carefully selected subjects not meeting the ill-health definition (the controls or referents). Details of exposure are usually collected at the time of the study instead of relying on routinely collected data that may not be sufficiently informative. In the case of dead or severely ill cases the occupational histories have to be collected from relatives or other contacts. Information bias can occur when collecting retrospective exposure histories particularly if the purpose of the study is known and has a high profile. It can also occur if exposed persons are more likely to find their way on to the lists of cases than unexposed persons because, perhaps, of referral by an occupational physician.
Most case-control studies are only suitable for hypothesis generation although recent advances in the retrospective assessment of exposure are extending their use to hypothesis testing and dose-response analysis. For this report, case-control studies are of little value because the ill-health conditions studied in them will have multiple causes if the referents are similar to cases in respect of exposure to confounders but dissimilar in respect of the exposure of interest and will be broader than a discrete, specific neurological syndrome.

3.3.4. Cross Sectional Studies

Cross sectional studies with a control group

In these studies the health of a population of solvent exposed subjects at the time of examination is compared to that of an unexposed group at the same time and in the same way (Checkoway *et al*,

1989). The advantage of a cross-sectional study in the present context is that, in theory, any ill-health condition can be studied provided a suitable measurement device can be developed. Disadvantages, that may be real or apparent, are that the use of employed persons may involve a selection (survival) bias because the unwell will have left, there may be a selection bias due to non-participation, and the choice of control group may introduce confounding factors.

Cross-sectional studies with a control group, in which the exposed group is treated as a single entity, do contribute to the aim of this report, although they do little to identify a dose-response relationship. If however, assessments of exposure are attached to the individuals in the exposed group, then the study can be analysed with the control group all having zero exposure and some indication of a dose response curve can be obtained.

Cross sectional studies without a control group

Either there has to be a scalar health endpoint (e.g. the score in a psychometric test) which can be correlated with a scalar measure of exposure (e.g. TLV.years), or if there have to be two levels of exposure between which the frequencies of a non-scalar endpoint can be compared. The health of the population of solvent exposed subjects at the time of examination is related to estimates of their solvent exposure to produce a dose-response relationship. This approach minimises the effects of selection bias and confounding by using a single population. Its validity is highly dependant upon the quality of the exposure estimates. Inaccurate estimation of exposure will introduce non-differential information bias and will lead to an under-estimate of the effect of exposure.

These studies do contribute to the aims of the report as they give the best available approach to the determination of a dose-response curve, and hence, a no-effect or acceptable level of exposure.

3.3.5. Follow-up Studies or Retrospective Cohort Studies

Successive cross-sectional studies in which the results are linked to one another are better described as a single longitudonal study.

Truly prospective cohort studies are ideal buut they take so long that they are rarely possible. Rerospective cohort studies have also been termed historical prospective studies but the terminology is a bit elaboorate.

In these studies the health of a group (or cohort (Breslow and Day, 1987)) of solvent exposed subjects is studied at two time points several years apart. If the second time point is some time after exposure has ceased, after retirement for example, then the effect of withdrawal from exposure can

be estimated. The aim of these studies is to demonstrate whether health decrements noted at the first examination are stable, reversible or progressive.

These studies make little contribution to the principal aim of this report because they assume that an ill-health effect does exist, but they are the best approach to establish whether any effects of solvents are reversible, persistent or progressive.

3.3.6. Evaluation.

In summary, as the painters syndrome is poorly defined and comprises multiple scalar endpoints, only cross-sectional studies can contribute to the principal aim of this report and these must be judged against the criteria of their relevance and validity (c.f Section 3.2).

3.4 CHRONIC LOW-LEVEL EXPOSURE AND FOLLOW-UP STUDIES

In this section the studies addressing the aim of this report will be discussed in detail. In the following section the studies related to specific compounds will be summarised.

3.4.1 Studies on Paint Manufacturers

Only two published studies of solvent exposure can be clearly seen to meet the criteria of Section 3.2 and 3.3. These are the studies of paint manufacturing in the USA, reported by Bolla *et al* (1990) and Bleecker *et al* (1991), and in the UK, reported by Glass *et al* (1994) and Spurgeon *et al* (1994). The former will be used to exemplify the principles of design and analysis involved in studying chronic low-level exposure to solvents.

Bleecker *et al* conducted a cross-sectional study without a control group of employees at two paint manufacturing plants in the USA. 187 male workers from a total of 247 employees volunteered to participate. A medical questionnaire was used to measure health status and to assess common symptoms of peripheral neuropathy. Neuropsychiatric status was assessed by means of the Present State Examination (PSE), a structured psychiatric interview, the Zung Depression Scale (used to assess depression) and Scandinavian Questionnaire 16 (Q16) containing questions related to neurasthenic symptoms associated with the solvent exposure. The neurophysiological battery consisted of tests measuring different functional domains selected from various sources. Neurophysiological status was assessed by vibration threshold measurements using a modified Optacon Tactile Tester. The exposure of each subject was estimated by linking occupational history to a file of 13-15 years of personal breathing zone samples. Two measures of exposure for combined selected solvents were calculated, the cumulative exposure (CE) and the lifetime working average

exposure (LWAE). For all analyses, only 176 workers with at least 5 years of job tenure were used. The confounding factors allowed for were vocabulary score (as a measure of pre-morbid intelligence), age, race, education, smoking and alcohol consumption. Analysis was by linear regression. The results were:

Clinical:	no significant findings;
Neuropsychiatric:	no significant findings, although a subset of the PSE concerned with depression was related to exposure;
Neuropsychological:	significant relationships between LWAE exposure and digit-symbol substitution, serial digit learning, truncated reaction time, trails A and trails B (c.f. WHO-NCTB, Section 3.2);
Neurophysiological:	significant relationship between LWAE and vibration threshold measured at the toe.

The authors concluded that their study demonstrated sub-clinical dose-related effects of chronic solvent exposure on neurobehavioural outcomes, but that typical symptoms characteristic of solvent syndrome were not found. The LWAE values in this study were all 27 ppm or less, and the geometric means of the exposure measurements for the various jobs held by the study subjects varied between 0.4 and 31.2 ppm based on available measurements of the average instantaneous exposure. These figures are well below the OEL values for the solvents and the equivalent value for a solvent mixture.

Spurgeon *et al* (1994) considered a cross-sectional study of 110 male employees at two sites in a large paint manufacturing company in the UK, and a control group, individually matched for age, from a plant in the same company making nylon fibre. The response rates at the two sites were 43% and 42%. Exposed subjects had at least three years exposure to solvents. A questionnaire was used to exclude exposed subjects or controls with relevant previous or existing medical conditions, a history of alcohol or drug dependence, and those who did not have English as their first language. Neuropsychiatric status was assessed by means of the General Health Questionnaire (GHQ) described by Goldberg, and the Scandinavian Q16. The neurophysiological battery contained a range of tests from the computer administered neurobehavioural evaluation system (NES). Two measurements of pre-morbid ability, the national adult reading test (NART), and the NES vocabulary test were included, as were assessments of computing experience and job satisfaction. Exposure measurements had been collected at the two sites for 15 years. These measurements were typically well below present compliance standards, although there were a few excursions above the standards. Individual exposure assessments were calculated by combining job histories, plant histories, a job-exposure matrix and the relevant historical measurements. Three measures of exposure were calculated: duration, cumulative exposure, and intensity of exposure, obtained by dividing cumulative exposure by duration of exposure. Homogeneous sub-groups were formed for each measure of

exposure by dividing the men into three or four similarly sized sets by using natural break-points in the distributions of results. Analysis of covariance was used to calculate coefficients for each sub-group for each test measurement whilst allowing for confounding factors. No statistically significant adverse effects were found for the exposed men, but controls were reported to have performed less well on two tests, continuous performance and colour word vigilance. The intensity of exposure varied from 2.6 to 60 ppm as an 8 hour TWA. The authors concluded that their study supported the view that long term exposure to solvent at or below the current compliance levels does not result in damage to the central nervous system. They admit that the low participation rate could have introduced selection bias, but the results of a questionnaire given to non-participants suggested that it was the fitter workers who had opted out.

The difference in the outcomes of these two similar studies could simply be attributed to the inherent variability of an observational science, or to the use of slightly different tests in slightly different circumstances. At a deeper level, the difference could be attributed to the use of a control group in one study and not in the other. Perhaps there is a subtle effect of increasing solvent exposure on the performance of certain distinctive tests, but that effect is marginal compared to divergences found between apparently comparable groups of workers.

3.4.2 Studies on Painters

Several studies have been carried out on painters. Whether these studies meet the criteria of Section 3.2 and 3.3 depends on whether the populations of painters involved had been exposed to high levels of solvent vapour during their work. The results are summarised in Table 2; the following descriptions apply to the methods employed and subsequent comment.

Fidler *et al* (1987b) conducted a cross-sectional study of 101 construction painters in Boston, USA. The participants had responded to an invitation sent by post to 615 eligible subjects. Originally a control group of dry wall tapers from the same eligible population was to have been used, but they were subsequently considered not to be comparable and the analysis excluded them. Each participant completed a comprehensive health questionnaire and a solvent history questionnaire, from which an exposure index of lifetime paint use was derived. A questionnaire based on Q16 was used to assess neurological symptoms. The neuropsychological tests were chosen from the computer administered neurobehavioural evaluation system (NES) to assess psychomotor function, memory, verbal abilities and mood. The number of variables for analysis was reduced by applying factor analysis to the neurobehavioural test results and the symptom reports. Linear regression was then used to investigate relationships between the exposure index and the basic measurements and factors after allowing for the confounding effects of age, education, vocabulary score, social status (as measured by the Hollingshead Index) and alcohol intake. An exposure index (EI) was calculated for

each individual, and used to rank them as to their lifetime average paint use. The index was calculated from a solvent history questionnaire which collected information about paint application rates, frequency by method (spray, roll, brush), respirator use and ventilation. Similar indices for recent exposure were also calculated. No actual measurements of exposure were available. It would appear that past exposures had been in excess of the OEL because many of the painters answered positively to a question about getting "high" at work.

Baker *et al* (1988) studied 254 painters in a cross-sectional study without a control group in two cities in the USA selected after a three stage survey of union leaders, contractors and local union members. The participation rate from the two populations involved was 37.1%. Exposure intensity indices were calculated from occupational histories detailing such data as time spent spraying, rolling and brushing, indoors and outdoors. Nine neurobehavioural tests from the NES battery were administered to test verbal ability, psychomotor performance, memory and mood. A variety of analyses were used including regression analysis allowing for the confounding effects of vocabulary, education, age, race and alcohol, residual analysis and comparisons between the most and least exposed. Indices of exposure were calculated as in Fiddler *et al* (1987a). The units of these indices were 1,000 equivalent gallons (relative to brushing, outdoors, without a respirator, 100% of work time). Exposure categories used were the lowest 10%, 10-25%, 25-50%, 50-75%, 75-90% and highest 100%. No actual measurements were available. As in the study by Fidler *et al* (1987b), many of the painters reporting getting "high" at work, a condition described parenthetically by the authors as "acute intoxication".

Table 2. Results of Studies on Painters

	Cherry *et al*, 1985	**Fidler *et al*, 1987b**	**Baker *et al*, 1988**	**Triebig *et al*, 1988**	**Triebig *et al*, 1992a,b**	**Spurgeon *et al*, 1992**
Symptoms	Q16	Q16	Not stated	Own questions	Q16	Q16 and CFQ
Results	- ve	+ ve	+ ve	+ ve (Age?) Paraesthesia	- ve	- ve
Neuropsychology	Various	NES	NES	WHO	WHO	NES
Cognitive results	+ ve (but not valid, see author's comments	+ ve SDS/DS	+ ve	+ ve memory	- ve	+ ve SDS/PAL
Mood results	None	- ve	+ ve	+ ve personality	- ve	none
Neuropsychiatry	None	None	None	Own questions	PSE	GHQ
Results	-	-	-	- ve	+ ve depression	- ve
Neurophysiology	Nerve cond	None	None	Nerve cond.	Nerve cond.	None
Results	- ve	-	-	- ve minor	Not stated	-
Neuroradiology	None	None	None	CAT	CAT	None
Results	-	-	-	- ve	+ ve atrophy	-

Triebig *et al* (1988) conducted a cross-sectional study of 105 house painters and a control group of 53 workers from various professions matched for age, occupational training and socio-economic status. The participants were almost all the eligible workers at several randomly selected companies in Erlangen, Germany. Nineteen painters and 14 controls were excluded because of non-occupational confounding factors. Each participant responded to a symptoms questionnaire, carried out a battery of neurobehavioural tests similar to those recommended by WHO, and had conductive velocities measured. An EEG and a CAT scan was also administered. Analyses were by suitable tests for differences between two groups. The index of exposure used was the proportion of the day spent applying solvent based paints. Five categories of this index were formed (0-10%, 10-30%, 30-50%, over 50% and spraying). A lifetime index was also calculated by multiplying the daily index by duration. Ambient air monitoring data were collected for working day exposures at 30 different workplaces including some small, badly ventilated rooms. The highest mixed solvent exposure recorded was 0.5 of the maximum allowable level. The maximum exposure levels recorded for individual solvents were about 10% of the relevant OELs.

Triebig *et al* (1992a,b) conducted a cross-sectional study of 105 spray painters and 58 control subjects not exposed to solvents. Participation was voluntary, 72% of spray painters in 52 German companies who met the qualification of 10 years exposure took part. Twenty two painters and 16 controls were excluded mainly because of high alcohol consumption. Participants were given the Q16 Questionnaire, the PSE psychiatric investigation, a battery of neuropsychological tests and nerve conductive velocities were measured. Various indices of solvent exposure were calculated from the answers to an occupational history. The analyses included comparisons with the control group and tests for a dose-response relationship. Three solvent exposure indices (SEI) were calculated, years of exposure multiplied by proportion of time spent spray painting (SEI1), SEI1 multiplied by a protective factor (SEI2) and SEI2 multiplied by a symptom factor (SEI3). Measurements of exposure were collected at 10 different worksites. The measurements were all well below the current limit values. Biological monitoring data for spray painters and controls indicated that the spray painters had experienced recent, but not current, exposure to xylene. One painter in two suffered from dizziness at work, but half of those who suffered did so rarely, that is, once a year. Dizziness was, however, not usually associated with spray painting, but usually occurred when using chlorinated hydrocarbons in cleaning operations.

Spurgeon *et al* (1994) report the results of two studies of solvent exposed populations. In the first study 90 brush painters employed in the UK were age-matched to controls selected randomly from maintenance workers at the same sites who had no exposure to solvents. Of the available population of painters, 29% were unwilling to take part and 4% were excluded. In the second study 144 solvent exposed workers in the UK, 83% of the available subjects, were age-matched to randomly selected unexposed maintenance workers on the same sites. In both studies, all the participants completed

the General Health Questionnaire (GHQ) to screen for psychiatric morbidity, the cognitive failures questionnaire (CFQ) to assess self-reported memory difficulties and the Q16 to assess symptoms. They were also given a selection of neuropsychological tests from the NES. Analysis was by paired comparisons and by tests for dose-response effects. Exposure was measured by duration of exposure which was categorised into less than 10 years, 10-20 years, 21-30 years and over 30 years. No exposure measurements were given in the publication.

Cherry *et al* (1985) reported the results of two studies, in one of which 44 painters employed in dockyards were compared in a cross-sectional study to controls, who were joiners in the same yards, and were matched individually to the painters on age and sex. The painters were selected at random from those who had participated in a previous study. Participants completed a slight variation on the Q16 symptoms questionnaire, were given a clinical examination and performed a series of behavioural (neuropsychological) tests drawn from various sources. As no exposure data were available, duration of exposure (mean 11.7 years) was used as the exposure index. Data from a separate investigation indicated that exposures when working in enclosed spaces exceeded the OEL. The paper underlined the importance of correcting the results of neuropsychological tests for pre-morbid intelligence. The painters performed poorly on several of the tests compared with controls; they also performed significantly less well on reading score. When their test results were compared to another control group with similar reading scores, no significant deficiencies were observed. The exposure of the painters in this study was difficult to quantify because of the varied nature of work.

Despite the similarities in the designs of the above studies and their similar population sizes, their is disparity in results (c.f. Table 2). To some extent the greater number of positive results in Fidler and Baker might be due to the different analytical procedures employed, an example of more analyses producing more statistically significant findings. The differences in the outcomes for symptoms, however, are too great for statistical methodology to be the explanation. Perhaps the strict exclusion criteria imposed by Triebig predispose his studies towards a negative outcome for symptoms. It seems more likely, though, that the subjects in the Fidler and Baker studies were reporting the effects of acute, high exposure during their working lives, whilst the monitoring data in the Triebig studies correctly position his groups of painters at the lower end of the spectrum of exposure for painters as documented in Section 2. The pattern of results in Table 2 could, therefore, be demonstrating a dose-effect relationship across studies, but the monitoring data are not available to test this possibility.

Unfortunately, in almost all these epidemiological studies, no accurate data on occupational levels of exposure to solvent are provided. Indeed, the problems in assessing solvent exposure particularly for painters are many as discussed by Fidler *et al* (1987a), and their investigations clearly demonstrate that number of years of exposure, which is widely used as a surrogate for degree of exposure is grossly inaccurate. They also found that the estimates of relative exposure from different types of

painting, made by experienced occupational hygienists, varied by 300% Other critical factors such as the use of respirators that can significantly reduce exposure are rarely reported. Furthermore adequate description of samples as personal or fixed (area) is often missing making it difficult to assess whether measured concentrations of solvents represent actual exposure. The other important factor to be considered is the pattern of exposure. Although many studies report the estimated exposure to be below the OEL-TWA, this is unlikely to represent continuous exposure. The pattern is likely to follow a pattern of repeated acute, high-level exposures as evidenced by the frequent occurrence of acute symptoms of pre- or actual narcosis.

The greatest relevance of these studies of painters as far as long-term, chronic exposure is concerned is that they largely demonstrate the same adverse outcomes, i.e. sub-clinical dose-related effects, for neuropsychological tests as described by Bleecker *et al* (1991) (c.f. Section 3.4.1). The finding of poorer performance in the symbol digit substitution test in several studies is particularly noteworthy. Thus, although there are consistent findings across the studies suggesting they are genuinely related to the occupation of painting, the neurological symptoms found in these painters* studies cannot reasonably be attributed to chronic low-level exposure alone in the light of the monitoring data for painters tabulated in Appendix A. The consistent reports of repeated exposure to pre-narcotic levels of solvents by painters leaves open the possibility that the effect results from repeated high exposures rather than chronic low exposure.

3.4.3 Follow-up Studies

The value of these studies is to indicate whether the neurotoxicological observations in solvent exposed workers are reversible, persistent or progressive. Given that neurological symptoms as well as neurophysiological deficiencies can be caused by the type of exposure experienced by painters, the follow-up studies are relevant to the long-term health experience of this and similarly exposed occupations.

The following paragraphs describe the nature of the investigations made; the effects observed are subsequently tabulated and evaluated.

Bowler *et al* (1991) studied former microelectronics workers who had been exposed to multiple organic solvents and referents matched individually on age, education level, sex, ethnicity and family size. All the former microelectronics workers had passed extensive pre-employment examinations, but had subsequently suffered work related illness as evidenced either by the Occupational Health Clinic or successful litigation. Sixty-seven matched pairs were formed from an initial group of 180 workers and 157 potential referents put forward by the workers themselves. The former workers had ceased working an average of 6.5 years at the time of commencing the study. The

neurophysiological tests used were a revised version of the California Neurophysiological Screening Battery (CNS-B). Analysis was by appropriate matched pairs techniques. The method in which referents are put forward by the exposed workers is gaining credence, but the extent to which it introduces selection bias is impossible to judge.

From the clinical records of 6 Swedish departments of occupational medicine, Edling *et al* (1990) formed a cohort of 65 men with symptoms but no test impairment (Group 1) and 46 men with symptoms and test impairment (Group 2B). All the men had worked with solvents for at least 10 years. Sixty-two men in Group 1 and 45 men in Group 2B were re-examined at least 5 years after their initial diagnosis. The psychometric investigation used the test battery for investigating functional disorders (TUFF) and 13 different symptoms were assessed by the subjects and by a clinician, The study was analysed by t-tests for group data and by linear regression. The study group contained subjects still exposed to solvents and subjects whose exposure had ceased. The paper discussed the problems inherent in comparing the responses to questionnaires by subjects in work and the same subjects out of work.

Flodin *et al* (1989) studied 21 men with between 6 and 21 years exposure at work to about 50 mg/m^3 of styrene and re-examined 17 of the men 7 months after exposure had ceased. Neuropsychiatric symptoms were assessed by the Scandinavian Q16 and the TUFF battery of psychometric tests was used. Simple tabulations and group comparisons were used to analyse the results. The authors discuss the potential confounding effects of threatened unemployment at the time of the first examination and unemployed status at the second examination.

Gregerson (1988) studied the prevalence of psychiatric and neurological symptoms in 65 exposed workers and 33 controls, and re-examined those still available after intervals of 5.5 years (59 exposed and 30 controls) and 10.6 years (53 exposed and 30 controls). The exposed workers included employees in painting, lacquering, dry cleaning, photogravure and polyester boat building. Appropriate statistical tests were used for analysing scored data. The authors acknowledge the possible existence of volunteer bias in their study.

Juntenen *et al* (1982) re-examined 80 of a possible 106 subjects, 3 to 9 years after they had been diagnosed with chronic organic solvent intoxication. The subjects had been exposed to solvents an average of 10.7 years at the time of diagnosis. Forty-one of the group were women and 39 were men. Forty-nine of the group had left solvent exposed work on diagnosis, and only 4 subjects were still occupationally exposed to solvents at the time of re-examination. The examination included assessments of symptoms, neurophysiological tests and a battery of psychological tests described by Hanninen (1979). Analysis was primarily by regression analysis in which allowance was made for several potential confounding factors. The authors discuss the problems involved in using a patient

as his own control and admit to the possibility of inter-observer error due to using different neurologists at the two examinations.

Orbaek and Lindgren (1988) re-examined, after a median period of 4 years, 32 of 62 men who had been diagnosed with chronic toxic encephalopathy. The men had at least 7 years solvent exposure at the time of diagnosis, and all had virtually ceased exposure at the time of re-examination. A full clinical examination to assess neurological symptoms was conducted and a battery of psychometric tests drawn from various sources was applied. The data were analysed by appropriate non-parametric tests. The authors discuss the extent of bias that might be introduced when administering tests to subjects who lack motivation.

Gade *et al* (1988) re-examined after an interval of 2 years, 20 solvent exposed workers, mainly painters, diagnosed with toxic encephalopathy. A battery of neurophysiological tests was administered to the patients and to 20 controls individually matched on age, sex and education, drawn from a pool of 120 non-exposed subjects. Results for the patients were compared with those of controls and also, to the extent possible, with their own results at the time of diagnosis. Regression analysis of the data for the pool of 120 non-exposed subjects was used to correct the patient's results for pre-morbid intelligence. The authors discuss the possibility that, in the absence of a correction for confounding factors, the patients had been wrongly diagnosed.

All of these follow-up studies of small cohorts of subjects with symptoms and, in some cases, deficient performance in tests, suffer from severe problems of interpretation due to the near certainty that they are subject to bias. It is, therefore, surprising that the results, summarised in Table 3, are remarkably consistent. At the clinical level of diagnosis, prognosis and management there remains room for much further debate and argument. On the surface, however, it would appear that the subjective symptoms improve if exposure ceases, and objective test results remain stationary if exposure ceases.

3.4.4 Evaluation

Paint manufacture is a most suitable setting for the study of health effects and chronic low-level solvent exposure. Two studies of paint manufacturers in the US and the UK are supported by industrial hygiene data that allow each participants cumulative exposure to be estimated. These studies used validated investigative techniques and included measures to minimise the influences of bias and confounding. They showed no increase in solvent induced symptoms. The only adverse effects demonstrated were subclinical and only detectable on a group basis in large studies.

Several studies of painters have been published that meet validity criteria but their relevance is

difficult to assess because painters are exposed at varying frequencies to peak exposures. These studies report a variety of outcomes including an increased incidence of symptoms. Their inconsistency could be due to differences in exposure or to differences in study protocol and conduct.

Table 3. Results of Follow-up Studies (Test employed: A, symptoms/clinical; B, neuropsychological)

Exposure	Tests Used	Results	Reference
Mixed	A	Subjective improve, objective worsen	Juntunen *et al*, 1982
Mixed	A,B	Symptoms improve; tests unchanged	Orbaek and Lindgren, 1988
Mixed	B	Persistent but erroneous	Gade *et al*, 1988
Mixed	A	Recovery if no exposure	Gregerson , 1988
Styrene	A,B	Recovery	Flodin *et al*, 1989
Mixed	A,B	Persistent	Edling *et al*, 1990
Mixed	B	Persistent	Bowler *et al*, 1991

Follow-up studies are valuable in the context of this report because they aim to determine whether solvent induced effects are reversible, stable or progressive. The published follow-up studies suggest the subjective symptoms improve and objective tests remain stationary if exposure ceases.

3.5 EXPOSURE TO SINGLE SOLVENTS

This section deals with the exposure of man to single solvents in the same sequence identified in the introduction (Section 1); for some substances no evidence for the effects of exposure has been found although multiple exposure data with other substances may exist. All the reported human neurological studies are discussed, whether or not they meet the criteria defined in Sections 3.2 and 3.3.

3.5.1 1,1,1-Trichlorethane (methyl chloroform)

There do not appear to be any epidemiological studies on neurobehavioural effects from long-term low-level exposure to this solvent.

3.5.2 1,1,1-Trichlor-1,2,2-Trifluoroethane (Freon 113)

Rasmussen et al (1988) conducted a cross-sectional study of all degreasers using halogenated solvents in Aarhus. Of 116 eligible men, 99 participated. Three men who had been working exclusively with Freon 113 were diagnosed as having psycho-organic syndrome of a slight degree

after being given a medical examination and psychological tests. Exposure to Freon 113 was high. In the absence of a control group, this case finding exercise raises the possibility that a few years exposure to high levels of Freon 113 can cause slight neurological harm.

3.5.3 N-Hexane

There do not appear to be any epidemiological studies on neurobehavioral effects from long-term low-level exposure from this solvent. There are studies which have examined peripheral nerve damage which is a well characterised hazard, however, there appear to be no reports evaluating the exposure effects of this solvent over long-term periods.

3.5.4 Methyl n-Butyl Ketone (MnBK)

No data on epidemiologic studies concerning neuropyschological disorders and exposure to MnBK have been found although studies on acute exposure have been reported.

3.5.5 Methyl Chloride (Chloromethane)

There do not appear to be any epidemiological studies on neurobehavioral effects from long-term low-level exposure to this solvent when used in isolation.

3.5.6 Methylene Chloride

Lash *et al* (1991) selected from a population of retired airline employees those who, in their working lives, had experienced the greatest and least cumulative exposures to methylene chloride. They conducted a cross-sectional study of 25 high exposed and 21 low exposed retirees in which physiological, psychophysical and psychological variables were measured. They analysed exhaustively to exclude bias and confounding factors. They reported no significant difference for any variable, but they commented on interesting differences in groups of attentive and memory tests. They concluded that exposure to high levels of methylene chloride showed no persistent neurological effects. This conclusion may not be reliable because the study is small and lacks power.

3.5.7 Methyl Ethyl Ketone (MEK)

A study of psychomotor effects of acute exposure (Dick *et al*, 1989) could not demonstrate any significant changes; there do not appear to be any recent studies of chronic neurobehavioural effects.

3.5.8 Styrene

It has been demonstrated in several studies (cf. Grasso *et al*, 1984) that workers chronically exposed to levels of about 125 ppm of styrene (1990 TLV - 50 ppm) show a higher frequency of neuraesthenic symptoms and delayed reaction times. Recent studies (Cherry and Gautrin, 1990) have confirmed the neurological findings mentioned in earlier reports consisting of mild sensory nerve conduction deficits in 23% of people exposed to 50 ppm and 71% for exposures higher than 100 ppm.

As part of a study of acute effects Edling and Ekberg (1985) administered a neuropsychiatric questionnaire designed to identify symptoms arising from long-term exposure to this solvent. Workers who had been exposed to 10 - 12 ppm for 2.5 years showed no abnormalities.

Triebig *et al* (1989) conducted a cross-sectional study with two control groups to assess the chronic and acute effects of styrene. In the chronic study 23 of 36 men with a median of 7 years exposure to styrene in the manufacture of reinforced polyester resin products used for boat manufacture were compared to controls matched on age, socio-economic status and pre-exposure intelligence level available from a previous study. Participants were given an adaption of the Q16 for symptoms, a variety of neurobehavioural tests before and after a shift that followed 72 hours free of exposure and biological monitoring tests. Analysis was by parametric and nonparametric tests for group differences with a covariance correction for premorbid intelligence. Ambient exposure levels had a median level of 18 ppm but levels during lamination of the inside of the boots ranged from 140 to 600 ppm. There were no significant differences between the exposed group and controls in the neurobehavioural tests. The authors concluded that exposures up to 100 ppm cause no acute or chronic effects on the central nervous system.

In addition to the reports of nausea and headaches, as well as the objective signs of neurological impairment in man exposed to high concentrations of styrene, there are reports that high exposures to styrene may be associated with hearing loss in experimental animals (cf Section 4.2.8). A recent study employing 299 persons exposed to 26 ppm failed to find any evidence to suggest that acute or chronic exposures to styrene was associated with any type of hearing loss (Sass-Kortsak, 1993).

In summary there is no evidence from the few studies available that at low-level exposure to styrene (up to 100 ppm) performance on standardised neuropsychological test batteries is affected whilst the evidence relating to symptoms is contradictory.

3.5.9 Tetrachloroethylene

Ferroni *et al* (1992) conducted a cross-sectional study of 60 female workers exposed to tetrachloroethylene in dry-cleaning shops and 30 female controls in an industrial cleaning plant where solvents were not used. The controls had comparable ages and vocabulary tests scores but they were not matched. Participants performed five computerised neurobehavioural tests taken from the Italian version of SPES. Exposure levels varied from 1 to 67 ppm with a median of 15 ppm. Analysis was by t-tests for differences between groups. The exposed group performed significantly less well than the controls on tests of simple reaction time, vigilance and response to stress. No effort was made to exclude the effects of acute exposure in this study. It was apparently a volunteer study and therefore has the attendant risk of selection bias. Exposed and unexposed participants were examined by the WHO core battery of neurobehavioural tests. The vocabulary scores between test and control were comparable but a statistically significant difference was observed in simple reaction time, vigilance and response to stress. The air and blood concentrations of tetrachloroethylene showed no correlation with results of the neurobehavioural studies. In the author's opinion, the design of the study does not allow a distinction to be made between effects during current exposure and possible chronic effects. It should be noted that the authors did not take into account the possibility of peak exposure in their study.

Cai *et al* (1991) conducted a cross-sectional study of 56 workers (29 male, 27 female) exposed to tetrachloroethylene in dry-cleaning shops and control group of 69 workers (32 male, 37 female) of comparable age in workshops with no solvent exposure. Duration of exposure ranged for 0 to 10 years. A symptom questionnaire designed by Inone was used to test for symptoms at and away from work. The questionnaire was applied towards the end of the working week to ensure maximal exposure conditions. Exposure levels had a geometric mean of 20 ppm. Analysis was by chi-squared tests. The exposed group reported significantly more symptoms both at and away from work.

3.5.10 Toluene

Orbaek and Nise (1989) investigated the effects of chronic exposure to toluene in a cross-sectional study of 30 out of 35 male employees most of whom had a least 10 years experience in rotogravure printing plants. A control was formed from 50 workers in a sugar refinery and 22 employees in railway carriage repairs who had been examined on previous occasions. After the weekend, the exposed group were given a symptom questionnaire of 60 questions and 9 neuropsychological tests from various sources. Exposure levels were currently below the OEL but previous exposures had been well in excess of the OEL. Analysis was by various tests for mean differences and for the effects of covariates. The exposed group reported significantly greater prevalence rates for many of

the symptoms. The exposed group performed less well on many of the tests including the synonyms test. When the results were corrected for performance in the synonyms test, there were no longer any significant differences in scores on the other tests. Both exposed workers and controls with high alcohol intake performed less well on the tests. Since there was a correlation between symptom score and poor test performance, the authors conclude that there is evidence of a toluene exposure effect on test performance.

Antti-Poika *et al* (1985) studied 43 male rotogravure printers exposed to toluene in a cross-sectional study with a control group of 31 male offset printers. The exposed group had all worked with toluene exposure for more than 10 years. A wide range of tests including a symptom questionnaire, EEG, and unspecified psychological tests was applied and an alcohol consumption history was taken. Exposure to toluene had been about 100 ppm for many years. Analysis was by tests for group means and correlation techniques. No significant differences were found between the exposed group and controls on any tests. The exposed group had a highly significant increased alcohol intake and it included several men who might have been excluded from many of the studies in this report.

Hanninen *et al* (1987) analysed the neuropsychological test data from the Antti-Pika *et al* (1985) study in more detail. Eleven tests from various sources had been used. The exposed group performed less well on two tests of visual intelligence. There was almost no difference in mean pre-morbid intelligence as measured by a synonyms test. When analysed for both toluene exposure and alcohol intake, it was found that the small groups with either high exposure or high intake had poor results but the small group with both did not. The authors suggest that the different jobs held by the two groups may explain the difference in visual intelligence.

In a psychiatric study Larsen and Leira (1988) compared 22 photogravure printers exposed to toluene with 19 controls. The printers had been exposed to toluene for at least 12 years for which current exposures were below the 1990 OEL (100 ppm, 8/hr TWA), although there was evidence of very high exposures (10 x OEL) less than 5 years earlier. There was some clinical testing of cognitive functions, but the tests were not named and there was no correction for age or primary intellectual level. The psychiatric assessment was described as a "semi-structured interview" but there is no reference to the use of any standardised method, as recommended by WHO. Heavy drinkers, defined as those who had a history of alcohol intake that interfered with their capacity for work, were excluded from the study. The authors claimed to have found a significantly greater prevalence of mild chronic encephalopathy and organic affective syndrome in toluene exposed workers.

Winchester and Madjar (1986) studied 42 workers, from 12 plants, who had been occupationally exposed to solvents. Toluene was the major component of these solvents and average exposure figures showed that they were below the then current OEL. Forty two controls, matched for age, were

included in the study. The exposed group complained of eye irritation, nausea, skin irritation and lightheadedness more frequently than the controls; the difference was statistically significant but clinically the condition of eyes and skin in both groups were the same. There was a significant slowing of simple reaction time. The weekly consumption of alcohol for the exposed group was noticeably higher than controls and may have contributed to some of the symptoms including the slower reaction time. In our opinion, high exposures must have occurred to account for eye irritation. Except for alcohol, other confounding factors were not considered.

In a report that also discusses a study of painters, Cherry *et al* (1985) describe a cross-sectional study of 59 workers exposed to toluene at an asbestos products factory and controls from elsewhere in the factory matched individually on age, race and duration of employment. The exposed workers had mostly been exposed for 5 years or more. Participants were given a symptoms questionnaire and a battery of behavioural tests from various sources. Exposure to toluene was about 100 ppm at the time of the study but it had been 3 times or more higher in the past. Analysis was by t-tests for matched pairs. The scores of the exposed group on neuropsychological tests were somewhat lower but their pre-morbid intelligence score was significantly lower. After allowance for pre-morbid intelligence no significant differences in performance was found.

The UK Health and Safety Executive (UK-HSE, 1989) has published a detailed literature review of toluene. They concluded that the published studies of painters were of limited value because of mixed exposures and possible misdiagnosis of pre-senile dementia, while studies of printers and rubber-matting workers show no clear evidence of central nervous system dysfunction after repeated toluene exposure at air concentrations in the range 50 - 200 ppm. In 1990 the OEL was set at 100 ppm (UK-HSE, 1990).

Foo *et al* (1990) studied 30 females exposed to toluene in the course of electronic assembly work. In a cross-sectional study they compared them with 30 controls matched on age, sex and ethnicity from another section of the factory. A battery of 8 neurobehavioural tests was undertaken by the participants before work on a morning in the second half of the working week. The exposed group was exposed to a mean toluene concentration of 88 ppm and the control group was exposed to a mean of 13 ppm. Analysis was by Student's t-test and covariance analysis. The analyses were adjusted for years of education because the exposed group was less well educated but there was no measure of pre-morbid intelligence in the study. The exposed group performed significantly less well on 6 of the 8 tests and there was a dose-response relationship with toluene exposure for these tests. The authors attribute the differences to acute exposure.

In summary, most of the toluene studies are deficient in good exposure data. Several studies highlight the importance of alcohol as a confounder and few have used the recommended WHO

neurobehavioural tests in part. There is no evidence of adverse chronic central nervous system effects from low-level exposure to toluene, that is below the 1991 OEL of 100 ppm (8 hour TWA): some studies reported better performance in exposed groups.

3.5.11 Trichloroethylene

Kadushin *et al* (1988) examined 10 people with long-term occupational exposure to trichloroethylene, 7 showed low scores on motor agility tasks and had other signs of CNS dysfunction. There were no data on exposure, age, intellectual level, alcohol intake or details of testing methods.

In China, Liu *et al* (1988) studied 79 men and 24 women exposed to trichloroethylene either in manufacturing or degreasing operations and a similar number of unexposed controls, by means of a questionnaire, a physical examination and laboratory tests. No neurobehavioural testing was carried out. Personal air sampling was done; exposures varied from 1 to 100 ppm. Although there were no differences between the groups on physical examination or laboratory investigation, there were significant differences for symptoms of nausea, forgetfulness, tremor and cramp.

In our opinion these papers suggest that exposed groups reported symptoms associated with solvent exposure more frequently than those non-exposed, but in both cases the study design is inadequate to establish if neurobehavioural abnormalities were present.

3.5.12 White Spirit

White spirit is the main solvent which has been used, since 1930, as a replacement for turpentine in decorative paints. As such, it has been the major contributor to solvent exposure in house painters where it has been implicated as the cause of the so-called "Painters' Syndrome". The acute effects of high exposure are well documented (Grasso *et al*, 1984) and include headache, nausea, giddiness, lack of concentration, eye and throat irritation and narcosis.

Bazylewicz-Walczak *et al* (1990) studied 226 persons (202 female, 24 male) exposed to white spirit while gluing footwear elements in a cross-sectional study with 102 controls (91 female, 11 male) drawn from hosiery plants and compatible on age, sex educational level and length of employment. The exposed group had all worked for at least years and the exposures had been close to 500 mg/m^3 for 13 years. The participants undertook 7 neuropsychological tests and 3 tests of psychomotor function. Analysis was by tests for differences in mean values and discriminant analysis. The exposed group performed significantly less well on several tests, in some cases in all age groups and in others only in the oldest, and longest serving group. The study did not include a test for pre-morbid intelligence and the report does not say when the tests were carried out. The exposure data in this

study are poorly reported. No idea of frequency and location of sampling has been provided. It is quite possible that high peak exposures may have occurred on several occasions during the exposure period.

3.5.13 Xylene

Acute studies (Savolainen *et al*, 1985) have demonstrated the influence of xylene on the sense of balance. The effects of acute exposure to xylene or toluene or to a mixture of these two solvents were investigated by means of a neurobehavioural test battery similar to that recommended by WHO (Dudek *et al*, 1990). Ten male volunteers aged 22 - 35 years were enclosed in a chamber for 4 hours and exposed in rotation to 100 ppm toluene, to 100 ppm xylene, to a mixture of 50 ppm toluene and 50 ppm xylene or to normal ambient air. In this way each participant served as his own control. An interval of 7 days was allowed between each exposure. Tests for memory, cognitive function, motor-visual co-ordination, speed and precision of hand movement and psychomotor efficiency (Simple Reaction Time - SRT; Choice reaction time - ChRT and Santa Ana-test), were carried out before exposure commenced and 1 and 3 hours during exposure. Toluene produced an improvement in the memory test after 1 hour but no change from control values at 3 hours. Xylene and the xylene-toluene mixture produced no effect. Only xylene significantly caused a deterioration in the performance of SRT and ChRT tests, the xylene-toluene mixture and toluene did so only slightly. Performance in other tests, including the Santa Ana test was unaffected. It should be noted that the Santa Ana test measures eye-hand co-ordination and co-ordination between wrists and fingers. It, therefore, demands a higher degree of skill than SRT or ChRT. The negative results with this test throws some doubt about the validity of the study.

In another short-term study by Seppalainen *et al* (1991) nine healthy volunteers were exposed to a TWA concentration of 200 ppm xylene during a 4-hour period under a varying or constant concentration of xylene or under conditions of rest or exercise. Each subject participated in 4 exposure and 2 control sessions. EEG was recorded before and during exposure. No significant differences were observed in the EEG taken before exposure compared with those taken during exposure. Kilburn *et al* (1985) found high rates of acute non-specific symptoms in histologists but these were probably due to formaldehyde rather than xylene. There do not appear to have been any neurobehavioural studies on workers exposed to xylene for prolonged periods. In one study on long-term exposure has been done (Sukhanova *et al*, 1969) in which no neurobehavioural changes were reported.

3.5.14 Evaluation

These studies provide useful information to those handling these specific solvents but as they all fail

to exclude the possibility of high exposures they do not contribute to the objectives of this report.

3.6 OTHER STUDIES ON MIXED EXPOSURES

Many studies of workers exposed to mixed solvents have been published since 1984. Although these are considered not to contribute to the main objectives of this report they all have some relevance to solvent induced neurotoxicity.

3.6.1 Studies on Paint Manufacture

An in-depth clinical and psychological examination, supplemented by EEG and rCBF (regional cerebral blood flow) was conducted by Orbaek *et al* (1985) in a cross-sectional study on 50 workers aged 27 - 64 years (mean 42 years) from a paint factory. They were matched with 50 unexposed subjects (referents) according to age and educational level in three groups. The workers had been occupationally exposed to a mixture of solvents over 10 - 20 years. Nine solvents were frequently used in the factory: acetone, butanol, butyl acetate, ethanol, ethyl acetate, white spirit, methyl isobutyl ketone, toluene and xylene along with several others that were not identified. No details were given of atmospheric concentrations for these solvents but occupational exposure was higher in 1969 - 1978 than it was in 1982 when control measures were introduced including the lowering of atmospheric concentrations of these solvents in order to conform with occupational hygiene standards. The psychiatric examination consisted of well established procedures employed in the investigation of psychiatric patients; although not stated in the paper the context indicates that this examonation was not blind. The replies of the participants and the observations made were scored on a rating scale by the examiner. Analysis of the scores obtained from these scales revealed striking differences in magnitude between the cases and referents for symptoms concerning memory function, concentration difficulties and fatigue-ability as well as "inner tension", "worrying over trifles" and hostile feelings. In the psychological examination, the test battery included a vocabulary test of multiple-choice questions, Block Design, Digit Symbol, Serial Reaction Time, Visual Retention Test (Benton form C), Figure Classification (reasoning ability) and Dots Test (perceptual speed and accuracy). No changes were observed between exposed and unexposed groups in the vocabulary test and in tests measuring reasoning (figure classification) and perceptual speed and accuracy (digit symbol). In the other tests, the cases performed less well than the referents but with the exception of the Dots Test, the difference in the scores was not statistically significant. The Dots Test results were significantly poorer in the exposed group. The EEG studies were conducted under the standardised conditions available in the department of Clinical Neurophysiology. Quantitative analysis of frequency bands in the EEG recordings (measured in Hz) showed that the dominant background activity did not differ significantly between the exposed and referent groups, although there tended to be greater activity in higher frequency bands in the exposed groups. The authors state that the neuro-biological

background of these changes is completely unknown, and they "tentatively suggest" that variations may be related to long-term exposure to solvents but conclude that this is speculative. Measurement of the rCBF indicated that it was 4% (p=0.05) lower in the exposed groups than in the referents but the difference was not statistically significant. There was a considerable overlap in results of the rCBF between separate individuals that made it impossible to distinguish between exposed and non-exposed on an individual basis. The authors conclude that the primary role of the rCBF measurements is to exclude other possible causes of neuraesthenic syndrome such as vascular brain disease rather than diagnose solvent encephalopathy.

3.6.2 Studies on Painters

An in-depth neuropsychological examination conforming with WHO recommendations was made of 15 workers (both sexes) from 3 different sites exposed to mixed solvents, toluene, xylene, methyl ethyl ketone, acetone and white spirit (Linz *et al*, 1986). The level of exposure was not measured but was sufficiently high to cause acute intoxication. Nine of the workers had an exposure history to lead formulated paints, but only 1 showed abnormal biomonitoring data. The workers were matched 1:2 with controls for age, sex and education for the interview but not for the neuropsychological tests. For the latter, historical data, presumed to be normative, was used instead of control data. Some significant loss in performance for the neuropsychological tests (simple motor speed, visuo-motor coordination and memory) was observed from which the authors concluded the existence of chronic encephalopathy. However, the effects reported and the lack of any data on exposure free periods before testing suggests that the observations were more likely to be the result of acute exposure rather than chronic effects. Thus the historical lead exposure, the lack of matched controls for the neuropsychological examination, the lack of exposure details and the very small numbers of participants make it difficult to draw any meaningful conclusions from these data.

Seventy four-male painters selected from 3 shipyards were clinically examined (Valciukas *et al*, 1985); 55 of them were also examined using a neuropsychological test battery (Block Design, Digit Symbol and Embedded Figures). Thirteen of the painters were less than 50 years old, 17 were between 51 - 60 years, 23 between 61 - 70 years and 2 were over 71 years. The solvents most frequently used included methyl isobutyl ketone, xylene, tetrachloroethylene, ethylene glycol and white spirit. Historically the painters had been also exposed to other chemicals. Each painter was matched with controls of the same age, race and education. Controls were examined clinically and psychologically. More painters complained of acute symptoms (unspecified) than their matched controls and the difference was statistically significant. On the other hand there was no difference in chronic symptoms (unspecified) between test and controls. The results of the psychological tests showed a poorer performance in Block Design and Embedded Figure tests. According to the authors, these findings support the view that exposure to solvents used in the painting trade is

associated with impairments in CNS function. From the data presented, the only significant difference was for acute symptoms and this would suggest that they were the effect of acute exposure.

In a small study of 22 solvent-exposed men attending an occupational medicine clinic, Morrow *et al* (1989) administered the Minnesota Multiphasic Personality Inventory (MMPI) and found significantly abnormal scores. Over a quarter of the men reported that they had previously experienced at least one episode of acute over exposure, but there were no measured exposure data available. Estimates of solvent exposure levels obtained from questionnaires did not correlate with scores on the MMPI, but some correlation was observed between these scores and duration of exposure. The authors state: "we cannot speculate whether the symptoms reported in our sample of exposed patients results from the psychologic effect of knowing one has had an exposure". This study highlights the difficulty of making any sensible observation in the absence of reliable exposure data. Indeed the data presented, where the only significant difference was in acute symptoms, would suggest that the observations were the result of acute exposure.

The effects of chronic occupational exposure to a mixture of xylene, toluene, n-butanol, butyl acetate, n-butyl acetate, ethyl acetate and cyclohexanone was studied by Waszkowsk and Bazylewiez-Walezak (1992). Exposure levels conformed to MAK values. Thirty four paint shop workers and 34 controls matched for sex, age, education and type of work performed were examined by Neurobehavioural Core Test Battery (WHO). A longer simple reaction time as well as reduced manual dexterity were found in exposed workers when compared with controls.

Arlien-Soborg *et al* (1982) compared the results of a neurobehavioural study (WHO test battery), CT scan and cerebral blood flow (131XE) on 9 house painters occupationally exposed to organic solvents for a mean of 22 years with those of 11 controls. The painters showed a mild intellectual impairment but no cerebral atrophy. On the other hand there was a slight, but statistically significant impairment of cerebral blood flow ($p < 0.05$).

Van Vliet *et al* (1989a,b) administered questionnaires for acute and chronic symptoms to a group of 379 solvent exposed painters and construction workers and compared the results with 443 controls. Exposure estimates were derived from questionnaires. Out of 13 questions for symptoms of acute exposure, 3 questions had significantly more positive responses in the exposed group. Out of the 33 questions for chronic effects, a further 3 attracted significantly more positive responses in the exposed group. There was no correlation between chronic symptom score and level of exposure. As the authors state, some statistical significant differences are likely to arise by chance when such long lists of questions are used. There was no mention of correction for alcohol consumption.

3.6.3 Studies on Floor-Layers

A cross-sectional study of floor-layers was conducted by Ekberg *et al* (1986). In Sweden, floor-layers had been exposed to relatively high levels of ethanol/methanol based glues and to contact adhesives containing 75% solvents (benzene, acetone, toluene, ethyl acetate and xylene). During the 1970's water based glues containing less than 5% organic solvents have been introduced so that exposure to solvents was considerably reduced. Twenty-five floor-layers with more than 20 years service in the trade and 25 with 5 - 10 years only, were randomly selected for the study. Fifty carpenters matched for age and number of years in employment in the trade but with no known exposure to solvents were selected as controls. The floor-layers with more than 20 years experience had used large amounts (20 - 30 litre/day) of alcohol-based glues and were exposed to a mixture of the solvents at levels exceeding the OEL. Those employed for 5 - 10 years were exposed to a much lower concentration of solvents and had virtually no exposure to ethanol/methanol. At interview, the floor-layers performed worse than the carpenters when questioned about memory deficits, difficulties in concentration and changes in mood. Those with 20 or more years in the occupation did worse than those with 10 years or less of service. The clinical examinations showed no differences between the floor-layers and carpenters except that floor-layers with less than 10 years in the occupation had a higher blood pressure than their respective controls. The psychometric tests showed no meaningful differences between the groups except in the 20 year group where there was a slight difference ($p = 0.05$) in the Block Design Test and in the 10 year group in the Psychomotor Bolt Test ($p = 0.02$) compared to controls. No account was taken of alcohol intake or exposure to the ethanol/methanol mixtures. The increased prevalence of neuropsychiatric symptoms in both groups of floor-layers was attributed to recent exposure to solvents. The most striking conclusion was the absence of meaningful differences in the psychological examinations between the groups.

3.6.4 Studies on Sewage Workers

In a study on sewage workers Kraut *et al* (1988) administered five neurobehavioural tests to a small group of 19 workers. Some intermittent exposure data were available. Benzene was said to reach up to 50 ppm and toluene to exceed 200 ppm. Toluene exposure had been stopped some unspecified time before the investigation which was confirmed by the normal urinary hippuric acid level. Various symptoms (lightheadedness, fatigue, headache) were reported and 9 of the 19 workers had an abnormal result on at least one neurobehavioural test. The number of abnormal psychological tests correlated with a longer time of employment. No conclusions can be drawn from this small study because of failure to control for the major confounding variables and the absence of controls.

3.6.5 Studies on Micro-electronics Workers

Most of the studies on CNS dysfunction and solvent exposure have been conducted on male workers. Parkinson *et al* (1990) conducted a study by means of a questionnaire and a neuropsychological test battery on 567 female workers employed in a microelectronic company in which a variety of solvents were used for degreasing and as general cleaning agents. Within the total 73 had never been exposed to solvents (Group 1); 173 (Group 2) had been previously exposed but not for 1 year prior to interview; 60 (Group 3) had been exposed to solvents during the past year but not within 2 weeks of the interview; 121 (Group 4) were typically exposed less than 10% of the working day while 140 (Group 5) had been exposed for 50 - 80% of the time. All exposure was for multiple solvents. During interview participants were questioned about the occurrence of neurologic symptoms (memory loss, severe headaches, dizziness, tremors, incoordination, coldness of hands and feet, depression) and somatic symptoms (loss of appetite, palpitations, fatigue, rashes, cough and abdominal pain). The neuropsychological tests consisted of accuracy of design drawing (visuoperceptual functioning), connecting numbers and letters in consecutive order (Trial Making Test), tests for motor speed and manual dexterity. Smoking, alcohol consumption, history of CNS disease and exposure to chemicals other than solvents were taken into account. Results showed that after making allowances for confounding factors, women in Group 5 were "significantly more symptomatic with respect to depression, headaches, dizziness and tremors than control Group 1". Headache was the symptom which showed the only increase between the other exposed groups (2 - 4) and Group 1. Memory loss was reported significantly more often in Group 2 - 4 than in Groups 1 or 5. Change of appetite, weakness, rashes and abdominal pain were reported more frequently in Group 5 than in any of the other groups. The only effects seen in this study were in the higher exposure Group 5 who were exposed to solvents at the time of investigation and showed symptoms of acute exposure. Despite this, there was no significant difference in psychological performance between the groups. It is interesting to note that memory loss was reported in the lower or previously exposed groups so that this finding is probably of no relevance.

3.6.6 Studies on Varnishing Workers

Gupta *et al* (1990) investigated the neurobehavioural effects of a mixture of xylene and toluene on a group of 45 workers employed in various processes of varnishing in a heavy electrical manufacturing company located in India. Within this group 30 (average age 33 years) were continuously exposed to these solvents in the course of their jobs while 15 (average age 31.5 years) were only occasionally exposed. Twenty-five non-exposed (average age 34.5 years) workers with similar educational achievement were also included in the study. The psychological test battery consisted of Benton Visual retention test (visual perception and visual memory, immediate and short-term memory), Koh's Block Test (visual ability and visual disturbances due to brain injury), Digit Symbol Test (Visual

learning ability, motor speed and coordination of eye and hand) and mirror drawing. The continuously exposed and non-exposed had been at their job for approximately 9 - 10 years, the occasionally exposed for approximately 5 years. The mean concentrations of xylene and toluene were reported to be within recommended levels: average 43 ppm (16 - 146 ppm) and average 28 ppm (1.6 - 104 ppm) in air respectively. There was a statistically significant difference between the continuously exposed group and the non-exposed ($p < 0.001$) for all the psychological tests. The same statistical difference was observed between the occasionally exposed and the non-exposed for the Benton Visual Retention Test and Koh's Block Test. The Digit Symbol Test and Mirror Drawing did not show any significant difference. According to the authors, long-term exposure to xylene and toluene in concentrations that have been recommended as safe have been found to result in dysfunction of the CNS. Peak exposures are likely to have been significant in this application, but their occurrence, duration and level have not been recorded and other confounding factors have not been taken into account.

3.6.7 Studies on Mixed or Unspecified Occupations

A cross-sectional study was conducted by Maizlish *et al* (1985) on 124 solvent-exposed and 116 non-exposed employees from 4 industries, 2 of which manufactured office furniture and one made automotive parts and the last was a printing plant. The subjects were young (average age 35) mostly males [numbers of males/females not given] and had been employed in their current job less than 10 years (mean 6 years). Exposure or non-exposure was based on job description and on analysis of atmospheric concentration by means of a personal sampler. Ten solvents were identified which made up 80 - 100% of the solvent mixture inhaled: isopropanol, methylene chloride, trichloroethylene, acetone, methyl ethyl ketone, naphta, toluene, xylene, ethyl benzene, n-hexane. The average solvent concentration was 302 ppm in the printing plant and 6 - 13 ppm in other plants over the working day. Alcohol intake was described as one drink a day. The test procedures employed were described as similar to those recommended by WHO (1989) and consisted of Santa Ana, Block Design, Digit Span, Digit Symbol and ability to ignore distraction and verbal stimuli. Results indicated that except for memory span there were no statistically significant deficiencies among the exposed group. Comparison of results from printing plant workers with those of the other three plants showed no dose/response relationship.

The consequences of prolonged exposure to mixed solvents were investigated by Morrow *et al* (1990). Thirty-two solvent-exposed workers self referred to an occupational medicine clinic between October 1986 and January 1989. Each solvent-exposed worker was matched on age and education to a control subject randomly selected from a pool of healthy blue-collar workers who had no history of exposure to heavy metals, solvents or toxic inhalants. The neuropsychological examination consisted of the Pittsburgh Occupational Exposure Test (POET) battery which contains the WHO

(1989) recommended tests and a questionnaire based on MMPI. There was no difference between the two groups in tests for General Intelligence but the performance of the exposed group was significantly less than controls in learning and memory, visuo-spatial ability and psychomotor speed (POET) while the pattern of response in the MMPI indicated the presence of somatic concern, anxiety, depression, poor concentration and disturbance in thinking. Duration of exposure or recent exposure did not correlate with a poor performance in the POET test but a history of peak exposure was related to poor performance in several tests of learning and memory. The solvent-exposed participants constituted a self-referred group to the clinic and hence the study is confounded by self-selection which was triggered by concern over health. The effects on learning, memory and other endpoints studied will not necessarily occur in unselected groups.

3.6.8 Studies on Construction Workers

A case-control study from data in the register of an Employment Pension Fund was conducted by Lindstrom *et al* (1984) on 374 construction workers who had been granted a disability pension due to a neuropsychiatric disorder between 1978 - 1980. The controls were selected from construction workers who had been granted a disability pension for some other disorders. Results indicated that the incidence of neuroses (but not other neuropsychiatric disorder or alcoholism) among the group deemed to be occupationally exposed (painters and carpet layers) was higher than in other occupations (odds ratio 5.5, $p = 0.05$). The assumption that painters and carpet layers only represent an exposed grouping within the construction workers on the register introduces an unavoidable bias to the study and reduces its value.

3.6.9 Studies on Unspecified Occupations

In a cross-sectional study, Rasmussen and Sabroe (1986) employed a self-administered questionnaire with the aim of identifying neuropsychological deficits in workers exposed to a mixture of halogenated hydrocarbons. The main components of the mixture were trichloroethylene, 1,1,1,-trichloroethane, methylene chloride, tetrachloroethylene and fluorocarbons. The questionnaire was sent to 590 workers and was returned completed by 462. Of these 94 were "non-exposed" (although it is given as 196 in a separate table) and 364 were occupationally exposed to organic solvents. Adjustments were made for age, alcohol consumption, neurologic events (eg. head injuries) and exposure to other organic solvents. An increased prevalence was found for the following symptoms: dizziness, drunkenness, abnormal fatigue, forgetfulness, "often goes back to check things", difficulty in concentration, irritability. The authors concluded that there was a highly significant association between exposure and response when adjustment for the effect of potential confounding factors was made. No distinction was made between symptoms indicative of recent exposure and those thought to be associated with neuropsychological disorders.

3.6.10 Studies based on Data from Records and Questionnaires

Data originally collected in the UK between 1970 - 1971 as part of a morbidity survey in general practice were used by Cherry and Waldron (1984) to estimate the prevalence of minor psychiatric illness among workers exposed to organic solvents. The frequency of consultation for mental illness in any solvent-exposed group, either male or female, was not different from that in groups not exposed to solvents. Although the data used for the analyses were unbiased, in so far as they were collected for purposes other than that of examining any effect of solvents on mental illness, the authors acknowledge that there are important deficiencies in this study: many of those in apparently exposed occupations may have little or no solvent exposure and there is no information on the number of years the patients spent in exposed occupations.

A case-control study was conducted by Rasmussen *et al* (1985) on patients seeking admission into a nursing-home geriatric ward; 207 cases with psychological disorders were selected for examination. They included pre senile dementia and mental disorders due to cerebral atrophy, hypertensive vascular disease, ischaemic atherosclerosis, psychiatric illness and alcohol related conditions. History of exposure to solvents was deduced from their occupational history so that cases were divided into categories of always exposed, often exposed, rarely exposed and never exposed. Controls (210) had no past or present history of mental disorder. Each condition leading to impaired psychological function listed above was excluded in turn and adjusted rate ratios were estimated. The authors concluded that the categories of "often" and "always" exposed showed a higher rate ratio than other categories. In this paper, confounding causes of dementia were not adequately excluded. The number of cases in the "always exposed" group is too small to allow valid conclusions to be made.

A case-control study using death certificates was conducted by O'Flynn *et al* (1987) to investigate the extent to which pre senile dementia occurred in those occupationally exposed to organic solvents. The death certificates of all men under 65 years bearing pre senile dementia as cause of death were collected for the years 1970-1979 (n = 557). Control death certificates (in which the cause of death was some disease other than senile dementia) were also collected and matched based on age and sex. Thirty cases had possible exposure to solvents and 13 had probable exposure. The corresponding figures for the controls with possible and probable exposure to solvents were 22 and 17 respectively. Virtually no difference in occupational exposure to lead (Pb) was present among the two groups. There was no indication that exposure to either solvents of lead increases the risk of dying from "pre senile dementia".

A case-control study was conducted by Brackhill *et al* (1990) from the records of the U.S. Social

Security Disability Insurance Programmes for the years 1969 - 1976; 3,565 cases (males) were selected. They were listed as having been employed as painters for at least 10 years and were over 35 years of age when they received their disability pension; 83,245 males were selected as controls from the same source. Exposure to solvents was judged from the job description. Painters were given a high ranking for solvent exposure relative to other occupations. After adjusting for age, education and "time period", calculation of the odds ratio revealed that it was greater than unity for all neuropsychiatric diseases except pre senile dementia. According to the authors, the study "does not stand alone given the inherent biases in this sort of study" but provides support for the hypothesis that there may be a relationship between exposure to organic solvents and "chronic disabling neuropsychiatric disease".

According to Heine *et al* (1990) questionnaire studies may be criticised because the objectives of the study are known to the participants and consequently bias could have led to the over reporting of symptoms, their severity and the degree of occupational exposure to organic solvents. To avoid this objection the authors conducted an epidemiological study on cerebral dysfunction and solvent exposure from replies to a questionnaire intended to study the frequency of cardiovascular disorders. In this questionnaire, the participants were asked to state any exposure they may have had to organic solvents and its duration in years and to report symptoms considered to be associated with such exposures (headache, dizziness, loss of memory and concentration). A clinical examination was carried out on the participants as part of the study. Out of the 3,303 men who provided valid answers to the questionnaire, 295 men, mainly degreasers in metal workshops, had been occupationally exposed to mixed organic solvents over 5 years or more. Of these 178 had retired while 117 were still employed and exposed to solvents. After excluding confounding factors such as smoking, head injury, alcohol, age, social class and psychiatric drugs it was found that more complaints of loss of memory and concentration were found among both groups of men exposed to solvents than those who were never exposed. The difference was statistically significant. Headaches were found occurring more often in both groups of solvent-exposed workers than in the non-exposed while dizziness was reported more often in those still exposed to solvents than in any other group. No indication of degree of exposure was given by the authors but it should be noted that solvent exposure was mainly in degreasing operations where it had been shown that high acute exposures have been common (cf. Appendix A, Tables A-3 and A-4).

3.6.11 Studies on Solvent exposed and Non-exposed Monozygotic Twins

The performance of 21 monozygotic twins exposed to organic solvents was compared with that of their non-exposed co-twins using a psychological test battery (Hanninen *et al*, 1991). A further 28 monozygotic twin pairs were examined as a reference group. This study was based on the hypothesis that monozygotic twins show less interindividual variation than individuals randomly

chosen from the general population in the absence of other factors affecting neurological or behavioural conditions. Exposure to solvents was determined by occupation. Duration of exposure was said to be 5 - 30 years but there was no reliable information on the level of exposure or on the type of solvent or solvents to which they were exposed. The occupations comprised skilled, semiskilled, or non skilled factory workers, (9), painters (4), upholsterers (2), laundry worker (1), blacksmith (1), building renovator (1), laboratory worker (1), carpenter (1). The test battery comprised - Similarities test, Block Design, Digit symbol, Digit Span and tests for memory, manual dexterity, visual reproduction and associative learning. The reference pairs did not show any statistical difference in the performance of these tests except in the finger tapping test. On the other hand, the performance of the solvent exposed twins showed a significant poorer performance in associative learning and digit span than in their non-exposed co-twin. The authors are aware of the small numbers of participants in their study and of the paucity of information on exposure levels but considered these results to support the existence of the psycho-organic syndrome due to solvent exposure. Nevertheless, they also point out that "even in the presence of clear intrapair difference, most of the exposed persons still performed within the normal range, though at a lower level than their co-twins. They would have been considered as unaffected if assessed as single individual cases".

3.6.12 Evaluation

Mixtures of solvents are frequently used in both industrial and commercial operations; several epidemiological studies have been carried out on workers exposed to vapours from such mixtures. The presence of solvent mixtures makes the estimation of exposure more complex and it means that if an adverse effect is demonstrated it can only, logically, be attributed to the particular mixture experienced.

The above review illustrates the variety of approaches that have been adopted to examine the possible adverse effect of solvent exposure to the CNS. In most of these studies the exposure data are not sufficiently reliable to allow any meaningful conclusions to be drawn about chronic low-level exposure to solvents. Furthermore, in most of these studies, the investigative approach is flawed so the results do not contribute to the aim of the review. Nevertheless, they provide some measure of the efforts expanded in the attempt to define a specific neurological syndrome associated with solvent exposure.

3.7 ALCOHOL AND THE PSYCHO-ORGANIC SYNDROME

Alcohol has been acknowledged as a possible confounding factor in the production of the deficits in memory, concentration and mood observed in many epidemiological studies on workers exposed to

solvents. However, it could not always be adequately excluded, principally because of the difficulty in getting a reasonably accurate history of drinking habits.

In a recent review Hogstedt (1994) remarks that heavy alcohol consumption has a strong modifying effect on solvent related disorders. He states that it is unclear whether solvent exposure leads to higher alcohol consumption or whether solvent exposure and alcohol intake combine to increase the risks of neurological problems.

Lundberg *et al* (1992), in an attempt to assess the contribution of alcohol consumption to the "solvent syndrome" investigated the incidence of alcoholism in 767 house painters and 1,212 house carpenters who had been registered with their respective trade unions between 1960 and 1970. The investigation was conducted between 1965 - 1986. The alcohol crime register was used to identify severe alcoholics in the two cohorts studied. This register contains all persons who had broken any law regulating handling and consumption of alcohol. The medical reason for early retirement was obtained from another register while the registers of psychiatric disease provided the incidence of psychiatric illness among the participants. Results from the last two registers showed that there was an excess of diagnosis of all psychiatric disorder including "solvent syndrome" among painters compared with carpenters (relative risk = 6.5). The main psychiatric disorder diagnosed was alcoholism (relative risk = 8.0) even though the mean consumption of alcohol per person between the two cohorts was similar. As expected, painters had a much higher cumulative exposure to solvents than carpenters. The alcohol crime register, however, showed that this type of offence was not more marked among painters. Death due to alcoholism and alcohol related diseases were not more prevalent in painters. The results suggest that some factor linked to the painters occupation may interact with the alcohol consumed to increase the risk of developing symptoms of alcohol abuse. Occupational exposure to solvents seems to be the most likely interacting factor.

3.8 EVALUATION

The principal objective of this report is to address the question whether a discrete specific neurological syndrome that is causally related to chronic low-level exposure to organic solvents actually occurs.

The conditions required to meet this objective have been discussed (Section 3.2) together with the types of study that can deliver them (cf Section 3.3). It has been shown that very few of the published studies can really address this report's principal objective. Many studies have to be eliminated (cf Section 3.6) because they do not exclude acute (high) exposure, either at intervals during the working experience or shortly before the participants were interviewed and tested. Other studies failed to take account of confounding factors, of which pre-morbid intelligence is the one most often omitted and is

the one least easily dealt with Cherry *et al*, 1985). The inclusion of a control group, in other circumstances a criterion for a valid study, is complicated by the need to match for confounders including pre-morbid intelligence, for which years of education has been shown to be an inadequate surrogate measure (Gade *et al*, 1988).

A cross-sectional study without a control group, in which each individual's exposure is carefully estimated has been shown to be the best form of investigation, followed by a cross-sectional study with a carefully chosen control group and appropriate analysis.

The studies which best meet this report's objective are those of paint manufacturers (Bleecker *et al*, 1991; Spurgeon *et al*, 1994). Both of these studies are supported by carefully evaluated exposure data (Bolla *et al*, 1990; Glass *et al*, 1994). These show that if exposure is maintained consistently at low-levels there need be no increase in solvent induced symptoms and that if any adverse effects can be demonstrated they are sub-clinical and only detectable on a group basis in a large study.

Several studies of painters have been reported (e.g. Cherry *et al*, 1985; Fidler *et al*, 1987; Baker *et al*, 1988; Triebig *et al*, 1988, 1992a,b; Spurgen *et al*, 1992) that only fall short of the ideal in that the painters will have been subjected to acute exposures at frequency and intensity that is impossible to quantify. These studies demonstrate that, in the face of acute exposures, solvent related symptoms are reported at an increased prevalence rate and the reduced performance in certain neuropsychological tests, such as symbol digit substitution, become more detectable. However, the results of these studies of painters are far from consistent, so it is not surprising that the remaining studies in the literature, often deliberately concentrating on acute exposures, present a complex picture of a spectrum of diseases.

The second objective of the report is to review the natural history of those adverse effects that have been attributed to solvent exposure. Several follow-up studies have been reported that have this objective as their focus and their conclusions are quite consistent despite their varied protocols. It seems to be the case that, broadly speaking, persons with solvent related symptoms recover after removal from exposure but those whose neuropsychological performance is impaired do not recover but do not deteriorate further when exposure ceases (Juntunen *et al*, 1982; Orbaek & Lindgren, 1988; Gade *et al*, 1988; Gregerson *et al*, 1988; Flodin *et al*, 1989; Edling *et al*, 1990; Bowler *et al*, 1991). This lack of progression argues strongly against any organic basis as chronic encephalopies are characterised by rapid and often progressive deterioration. Furthermore the results obtained from rCBF and EEG examinations in exposed and non-exposed workers were normal confirming that no organic basis for the deficits can be demonstrated. Attempts to establish a correlation between cerebral atrophy, demonstrated by CAT scan analysis, and solvent exposure were equally disappointing since no consistent difference was obtained between solvent exposed workers and unexposed controls in the criteria employed for determining brain atrophy (Grasso *et al*, 1984; Triebig

et al, 1992a,b). In a study by Orbaek *et al* (1985) it was found that when patients with clinical radiological evidence of brain atrophy were subjected to a WHO Test Battery the scores were different from those obtained from a group of patients suspected to suffer from the so-called organic solvent syndrome. In another study Gade *et al* (1985) the scores obtained from a WHO Test Battery from patients showing evidence of brain atrophy were not significantly different from expected test scores. In fact, in another carefully controlled study Gade *et al* (1988) found that patients with brain atrophy performed better in psychometric tests including those measuring per-morbid intelligence.

Finally the report has reviewed studies of specific solvents (c.f. Section 3.5). It would seem that acute exposure to several solvents can lead to an increase in clinical symptoms, reduced psychomotor performance and impaired performance on neuropsychological tests. The information available, and its validity, varies considerably from one solvent to another, but the need to avoid extreme, acute exposures, and persistent exposures at or above the OEL is clear in several instances.

SECTION 4. NEUROTOXICITY STUDIES IN ANIMALS

4.1 INTRODUCTION

Whilst it is clear that adverse neurobehavioural effects are not seen in workers for whom solvent exposure has been controlled, it is clear that historically solvent exposure has not been well controlled and a variety of acute effects have been experienced by some workers.

In these circumstances it is appropriate to review the body of animal neurotoxicological data relating to solvents focusing on chronic neurotoxicity or any evidence of plausible mechanisms which would support the hypothesis that long term, low-level, solvent exposure is causally related to chronic neurobehavioural effects in man. The literature addressing neurotoxicity in animals is extensive. The following chapter critically reviews the relevant studies conducted with animals, which have investigated exposure to organic solvents with regard to adverse chronic effects to the central nervous system (CNS).

The endpoints specifically examined were: general toxicity, behaviour, neurophysiology, neuropathology and neurochemistry.

The criteria for selection of relevant studies were:

- repeated exposure, inhalation protocol;
- endpoints of effect to either behaviour, neurophysiology, neuropathology, or neurochemistry

Subchronic (defined here as ≥ 13 weeks) or chronic inhalation protocols with occupational type protocols (4-12 h/d) were used in preference to other exposure regimens. Routes of exposure other than inhalation were considered only for solvents with a limited subchronic/chronic toxicity database, or for endpoints of special interest.

In the context of addressing chronic effects it is important to differentiate between transient and permanent changes; irreversibility was selected as the necessary criterion for this purpose. NOAELs for CNS effects were identified for each solvent as the highest exposure concentration in the most sensitive study without observation of irreversible effect to behaviour, neurophysiology, neuropathology, or neurochemistry.

4.2 EFFECT OF SPECIFIC SOLVENTS

An appraisal of the neurotoxicity of individual solvents is reported in this section. Details of the studies reviewed and summary tables are found in Appendices B - N.

4.2.1 1,1,1,-Trichloroethane (Methyl chloroform) [Appendix B]

Specific neurotoxicological evaluations of the effects of inhalation exposure to 1,1,1-trichloroethane have been conducted in the rat and no evidence of irreversible behavioural, electrophysiological, biochemical or neuropathological changes has emerged.

Specific neurotoxicological data concerning chronic inhalation exposure of rats to 2,000 ppm 1,1,1-trichloroethane (6h/d, 5d/w, 13wks) has shown no irreversible behavioural, electrophysiological or neuropathological effects (Mattson *et al*, 1991). This concentration can be considered to be the NOAEL for neurotoxic effects.

4.2.2 1,1,2-Trichloro-1,2,2-Trifluoroethane (FREON 113) [Appendix C]

No studies were found which included specific neurological assessment following TCTFE exposures or studies which included exposure durations longer than 4 weeks. In all of the studies reported there was no evidence of neurotoxicity or toxicity at non-lethal dose levels. The only effect recorded was transient changes in neurochemical activity which were only monitored for 7 days following cessation of exposure.

The lack of toxicity from studies of a longer duration than 4 weeks makes determination of a NOAEL difficult. Nevertheless, no effects were observed in a number of species at a concentration of 5,100 ppm (Steinberg *et al*, 1969).

4.2.3 n-Hexane [Appendix D]

The neurological dysfunction of sensorimotor or motor neuropathy caused by n-hexane exposure is well documented in man and is reproducible in animal studies (Spencer and Schaumburg, 1985). In addition, the putative neurotoxic metabolite, 2,5-hexanedione, has been well studied in animal models (Spencer and Schaumburg, 1985). Chronic CNS effects of n-hexane in the absence of peripheral neuropathy have not been established in animal models. It has been clearly demonstrated in animal studies that the duration of inhalation exposure is more important than the exposure concentration on the severity and speed of onset of peripheral neuropathy. Cessation of exposure normally leads to partial or complete recovery.

In the relevant studies on n-hexane, CNS effects that were clearly permanent rather than transient were seen only under conditions > 12 h/d. The poor retention of hexane by inhalation, its very short half-life, and the requirement that it be metabolised to 2,5-hexanedione to be effective, can account for its lack of potency when administered for less than 12 hours/day or at very high dose levels intermittently. Exposure at levels of 10,000 ppm (13w, 5d/w, 6h/d) gave no significant neurotoxic or neuropathological changes (Cavender *et al*, 1984; Dunnick *et al*, 1989) and should be considered to be the NOAEL for occupational exposures. However, an overall NOAEL, assuming 22 or 24 h/d exposure, was established at 125 ppm (Spencer, 1982) based on exposure periods of 22 h/d, 7 d/w for 26 weeks.

4.2.4 Methyl n-Butyl Ketone (MnBK) [Appendix E]

Methyl n-butyl ketone causes an identical pattern of peripheral neurological damage as n-hexane with chronic inhalation exposures (Spencer *et al*, 1980).

A LOAEL for effects on averaged visual evoked potentials in monkeys can be identified for exposures to 1,000 ppm 6 h/d, 5 d/wk for 25 weeks (Johnson *et al*, 1977), equivalent to a cumulative exposure of 750,000 ppm-hrs. In the same paper a NOAEL of 100 ppm was established.

4.2.5 Methyl Chloride (Chloromethane) [Appendix F]

There have been several acute studies examining the effect of inhalation exposure but only a few studies have addressed the effects of chronic or subchronic exposure to methyl chloride and no specific neurotoxicity studies have been performed. Long term exposure to 300 ppm methyl chloride on an occupational exposure type pattern (6 h/d, 6 d/wk, for 64 weeks) was without systemic or neurotoxic effects in a wide range of species (rat, mouse, guinea pig, rabbit, dog and monkey) although specific neuropathological assessment was not performed (Smith and Von Oettingen, 1947). High exposure concentrations or long exposure periods examined in acute studies resulted in specific neurotoxic signs and/or neuropathology consisting of cerebellar necrosis, although, in general, neurotoxicity is only observed in association with general systemic toxicity, toxicity in other organs (kidneys) and/or death (Morgan *et al*, 1982). There are also specific species, strain and sex differences in the susceptibility to the brain lesions (Wolkowski-Tyl *et al*, 1983; Landry *et al*, 1985; Jiang *et al*, 1985). Nevertheless, a clear NOAEL of 50 ppm was established in the mouse following exposure of 22 h/d, 7 d/w for 11 days (Landry *et al*, 1985).

4.2.6 Methylene Chloride (Dichloromethane) [Appendix G]

A number of subchronic/chronic inhalation studies and a specific neurotoxicity study have shown no

evidence of neurophysiological, neuropathological or irreversible behavioural changes occurring as a consequence of exposure to methylene chloride. 'Irreversible' neurochemical changes have been reported but, as exposure was for 24 hours a day continuously for 3 months, significant exposure must have occurred as a consequence of oral and possibly dermal exposure (food and water contamination, grooming, contamination of cage etc). The relevance of these studies to occupational exposure is unclear. In addition, it has not been shown that such changes are associated with neuropathological or behavioural changes.

Thus, the NOAEL for methylene chloride is 2,000 ppm (Mattsson *et al*, 1988a, 1989a).

4.2.7 **Methyl Ethyl Ketone (MEK)** [Appendix H]

Methyl ethyl ketone does not form y-diketone metabolites, such as 2,5-hexanedione, therefore it fails to induce neuropathy in exposed animals (Spencer and Schaumburg, 1985). MEK can potentiate the neurotoxic potency of n-hexane and MnBK (Altenkirch *et al*, 1982).

Since MEK does not have any direct neurotoxic effects the NOAEL is determined from the study with the highest concentration which investigated neurotoxicity endpoints (Cavendar *et al*, 1983) and is 5,000 ppm.

4.2.8 **Styrene** [Appendix I]

Two studies (Kulig, 1989a; Albee *et al*, 1992a) have investigated the behavioural and neurophysiological effects of styrene systematically, the latter study also included a comprehensive neuropathological examination. Savolainen and Pfaffli (1977) was the only study identified that looked at neurochemical changes during subchronic inhalation exposure.

Savolainen and Pfaffli (1977) concluded that the biochemical changes measured were transient and adaptive. Consequently the Albee *et al* (1992a) study forms the basis for the hazard assessment of chronic CNS neurotoxicity of styrene. Frequency-specific hearing loss accompanied by cochlear hair cell lesions were observed and a clear NOEL was established. The NOAEL for this experiment was 200 ppm (6h/d, 5d/w, 13 wks).

4.2.9 **Tetrachloroethylene (Perchlorethylene)** [Appendix J]

Only one specific neurotoxicity study using an exposure pattern similar to occupational exposure has been conducted. The study included comprehensive evaluations of the nervous system (functional, electrophysiological and neuropathological) and revealed no evidence of irreversible behavioural,

electrophysiological or neuropathological changes (Albee *et al*, 1992b). The highest exposure in this study, 800 ppm (6h/d, 5d/w, 13wks) was established as a NOAEL.

4.2.10 **Toluene** [Appendix K]

No evidence of neurotoxicity was observed in a variety of studies in rats and mice which used occupational-type exposures. Exposure as high as 3,000 ppm were seen to be without irreversible behavioural or pathological effects (Rudy *et al*, 1978; Shigeta *et al*, 1978; API, 1980; Lewis and Holdsworth, 1982; Tahti *et al*, 1983; Bushnell *et al*, 1985; Huff, 1990; Ladefoged *et al*, 1991). Irreversible changes in theta-wave activity were noted by Naaslund (1985, 1986) following exposure to 500 ppm toluene (8 or 16 h/d, 5 d/w, 12 w). The functional significance of such changes is not clear. Electrophysiological and behavioural evidence of peripheral auditory damage has been demonstrated in rats (Rebert *et al*, 1983; Pryor *et al*, 1983, 1984b) when exposures were greater than 1,500 ppm or for more than 12 h/d. Nevertheless a clear NOAEL of 700 ppm (14 h/d, 7 d/w, 16 w) was established (Pryor *et al*, 1984b).

4.2.11 **Trichloroethylene** [Appendix L]

A variety of effects of trichloroethylene exposure have been reported in animals. Behavioural effects have been shown to be reversible shortly after termination of exposure with the single exception of improved performance, suggesting changes in emotionality, which was not seen to recover in 40 days following continuous exposure for 150 days. The relevance of this finding to occupational exposure is unclear but would not support memory loss as a significant feature of chronic exposure. A consistent or characteristic pattern of neuropathological lesions has not been seen to occur. The only lesions observed following inhalation exposure were at acutely toxic dose levels or were associated with increased performance. Again, the data do not support an encephalopathy.

Other changes, in neurochemical parameters, show no consistent pattern, have infrequently been measured for reversibility following termination of exposure and/or only occur following continuous exposure. No link between these changes and behavioural deficits have been shown.

The study of Rebert *et al* (1991), in which a high frequency hearing loss was observed, provided a NOAEL of 1,600 ppm (12h/d, 6-7d/w, 12 wks).

4.2.12 **White Spirit** [Appendix M]

Only Kulig (1989b; 1990) has investigated the behavioural and neuropathological effects of white spirit systematically and adequately; these studies therefore from the basis of the hazard assessment for chronic CNS toxicity of white spirit. This study is corroborated by other white spirit inhalation studies (Carpenter *et al*, 1975a; Philips & Egan, 1984), and similar studies with C9 aromatic hydrocarbons (Clark *et al*, 1989; API, 1988a; 1988b) which showed no histopathological abnormalities of the nervous system. The API studies were specifically designed to evaluate neurotoxicity, i.e., behaviour and neuropathology in line with the proposed EPA guidelines on neurotoxicity.

Since subchronic/chronic inhalation exposure to white spirit did not have any post exposure behavioural or neuropathological effects the NOAEL is determined from the highest concentration which investigated neurotoxicity endpoints. Rats were exposed to 800 ppm white spirit (8 h/d, 5 d/wk, 26 wks) without any evidence of chronic CNS damage (Kulig, 1989a; 1990).

4.2.13 **Xylenes** [Appendix N]

There have been no specific neurotoxicity studies using inhalation exposure to occupational-type exposure patterns. High frequency hearing loss has been reported following repeated 14 hour exposures at 800 ppm (7 d/w, 6 w) or single 8 hour exposures to 1,450 ppm (Pryor *et al*, 1987). Duration of exposure is clearly important for this type of lesion as, in the same study, single 4 hour exposure to 1,700 ppm was without effect. When occupational exposures were examined no effects on clinical condition or CNS pathology were observed in rats or dogs exposed to 810 ppm (6 h/d, 5 d/w, 13 w) (Carpenter *et al*, 1975b). In addition, the U.S. NTP 103 week chronic oral gavage studies with xylene (Hejtmancik *et al*, 1985), at the relatively high doses of 500 mg/kg/d for rats and 1,000 mg/kg/d for mice, showed no adverse effects in the histopathological examination of the brain. The NTP concluded that in their future studies with xylene, the brain would not be treated as a target organ.

The highest NOAEL that can be identified in an inhalation study which examined brain tissue is 810 ppm in both rat and dog (Carpenter *et al*, 1975b).

4.3 DISCUSSION OF ANIMAL TOXICITY DATA

Animal toxicity studies have been reviewed to identify data which would support the view that chronic exposure to organic solvents results in irreversible adverse effects to the central nervous system. A variety of specific neurological endpoints were identified (Section 4.1) as of special interest and studies using subchronic or chronic inhalation exposure were considered to be most relevant to the

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ECETOC Technical Report No. 70 - Erratum

Please note that on page 58 of the 'Chronic Neurotoxicity of Solvents' report, in section **4.2.12 White Spirits** the first paragraph should read:

Only Kulig (1989b; 1990) has investigated the behavioural and neuropathological effects of white spirit systematically and adequately; these studies therefore form the basis of the hazard assessment for chronic CNS toxicity of white spirit. This study is corroborated by other white spirit inhalation studies (Carpenter *et al*, 1975a; Phillips & Egan, 1984), and similar studies with C9 aromatic hydrocarbons (Clark *et al*, 1989; API, 1988a; 1988b) which showed **no** histpathological abnormalities of the nervous system. The API studies were specifically designed to evaluate neurotoxicity, i.e., behaviour and neuropathology in line with the proposed EPA guidelines on neurotoxicity.

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occupational exposure situation. For most of the solvents, specific neurotoxicity studies have not been performed in animals. In addition, many studies have only examined one endpoint e.g. activity level so that correlation of structural and functional damage has not been possible. Many of the functional parameters measured do not have a comparative endpoint in man, therefore it is worth noting that any effect may be quite different in rats and human beings. Of particular concern is the general lack of special studies to examine the more subtle deficits, such as memory loss and reduction in social skills, which have been reported in man following solvent exposure. There are very few primate studies which would be expected to be more predictive of human neurotoxicity.

Two of the solvents, n-hexane and methyl n-butyl ketone, are well known classical neurotoxicants which produce a peripheral "dying-back" sensorimotor neuronopathy in both laboratory animals and man (Spencer and Schaumburg, 1985; Spencer *et al*, 1980). The compounds have been extensively studied and characteristic clinical signs of peripheral neuropathy, electrophysiological changes and neuropathology have been observed in a variety of species. However, no evidence of chronic central nervous system effects have been established in any animal model.

Almost all of the other solvents reviewed are known to produce acute narcotic effects and acute effects were observed in many of the animal studies reviewed. These effects, demonstrated by such changes as altered activity levels, are reversible, usually within minutes of terminating exposure. Again, many of the animal studies demonstrated the reversibility of this type of effect. In some studies, however, observations of animals only occurred during or immediately following exposure and thus potential reversibility or irreversibility of responses could not be evaluated. For four of the compounds, styrene, trichloroethylene, toluene and xylenes, irreversible behavioural changes were reported. In general, these effects reflected hearing loss rather than a CNS deficit and were only seen following high levels of exposure or non-occupational types of exposure.

In the case of trichloroethylene, the effect reported was contrary to the expected result and showed improved performance in a radial arm maze used to assess spatial memory (Kjellstrand *et al*, 1980, 1981). The same authors saw conflicting effects in the two studies performed and concluded that the effects reflect changes in emotionality rather than memory. It should also be noted that the exposure to trichloroethylene was for 24 h/d for 5 months. Nevertheless, the effect does not support the hypothesis that trichloroethylene induces impaired memory.

Irreversible behavioural effects of toluene, indicating an impaired ability to learn and perform a complex task, were observed following exposure at 4,000 ppm for 2 h/d for 60 days. Such an exposure pattern reflects solvent abuse rather than occupational exposure and it is known that the former types of exposure can result in irreversible CNS deficits (Ikeda and Miyake, 1978). Effects on electrophysiological parameters have also been seen using abuse-type exposures (Mattsson *et al*,

1989c). Higher cumulative exposures (following an occupational exposure pattern) have been shown not to affect learning ability (Shigeta *et al*, 1979, 1986) suggesting that the exposure pattern is important in the ability to induce this type of effect.

Styrene, trichloroethylene, toluene and xylenes have also been shown to induce electrophysiological changes indicative of a high frequency hearing loss. In the case of toluene the effect was correlated with histopathological evidence of cochlear damage (Pryor *et al*, 1984a) confirming that toluene is ototoxic in young rats. The authors speculated that although toluene may well be ototoxic in workers exposed at similar levels (2,000 ppm and above) this is only likely to occur in accidental situations and, when exposure is maintained at or below the current TWA of 100 ppm, hearing problems should not occur. Toluene has also been reported to induce an irreversible change in the frequency of theta wave activity (Naaslund *et al*, 1986). The functional significance of such a change is not clear.

Trichloroethylene and xylene ototoxicity has also been demonstrated at high exposure levels (Pryor *et al*, 1987; Rebert *et al*, 1991). Pathological and electrophysiological evidence of styrene ototoxicity changes were observed in rats exposed to 800 ppm and above (Pryor *et al*, 1987; Albee *et al*, 1992a). Clear NOAELs were established; no hearing loss was observed in human beings exposed to 26 ppm (Sass-Kortsak, 1993).

Neurochemical changes have been examined by a number of workers in an attempt to investigate a mechanism of neurotoxicity for the individual solvents. No consistent pattern of changes has been shown to occur with the solvents as a group and even for individual solvents conflicting results have been reported. For many of the reported effects the changes have not been examined in conjunction with or correlated to other functional or structural deficits. The biological significance of small changes in many of the parameters are not understood, nor are they known to be of relevance to memory loss. Although this type of measurement is extremely sensitive and may give some insight into the biochemical basis of neuropsychological functioning they are not fully understood at present and extrapolation to the proposed human conditions can only be speculative until a consistent syndrome can be established in animals.

Neuropathological changes have been shown to occur as a consequence of exposure to trichloroethylene. Trichloroethylene has been variously shown to produce effects in the cerebellum or the hippocampus following oral, intra-muscular or inhalation administration. None of the studies, however, properly addressed the possibility of effects following occupational-type exposure. Studies which have used more relevant exposure patterns and similar, or higher dose levels, to those which have been reported to produce neuropathology indicate that any changes which may occur are not associated with decreased learning ability (Kulig, 1987).

In conclusion, therefore, very few animal studies investigating solvent neurotoxicity have been performed and of these only a small percentage have included endpoints which correspond to the reported effects in man. None of the studies performed would support the theory that low dose chronic exposure to organic solvents results in encephalopathy or in profound changes in behaviour or performance. Frequent bouts of high, possibly narcotic, exposure over short periods, similar to exposures seen in solvent abuse, have been shown to result in both neuropathology and irreversible behavioural changes for trichloroethylene. Irreversible behavioural and electrophysiological changes indicative of high frequency hearing loss changes have been observed for styrene, toluene and xylene. Exposure pattern has also been shown to be important for induction of peripheral nervous system damage by n-hexane and methyl n-butyl ketone. It is clear, however, that a single neurological syndrome, as claimed to exist in man, does not occur in test animals as a consequence of solvent exposures.

SECTION 5. EVALUATION, CONCLUSIONS AND RECOMMENDATIONS

At the start of its work this task force set out to address the question of whether or not there is a discreet specific neurotoxicological syndrome, which is causally related to chronic low-level exposure to organic solvents.

In reviewing solvent exposure it is clear that good quality historical data has been a major limiting factor in many studies of solvent exposed workers particularly in the use industries. It is possible to conclude that in the manufacturing operations using solvents or the production of formulated products containing solvents implementation of occupational hygiene practices has led to control of exposure so that both peak and time weighted OELs are not exceeded. In certain use situations, eg. aircraft and some vehicle paint spraying and dry cleaning, exposures are in general well controlled but with occasional excursions above the OEL. In other industrial and commercial operations where occupational hygiene practices are not well established exposures are not well controlled, and there are circumstances where current occupational exposure limits can be exceeded and often markedly so. This can occur particularly in the application of solvent borne paints to large internal surfaces, or in confined spaces, the use of solvent based paint strippers, some vehicle spraying, boat building and some printing, adhesive and degreasing operations.

Although most of the early studies of painters do not include reliable exposure data from measurements, it is possible to make sensible judgements of what exposure might have been based on the incidence of acute health effects in exposed workers and historically exposure have been at least as high as those exposures reported in Section 2.

In this context it is important to note that whilst occupational exposure limits for solvents have been progressively reduced over the last two decades the standard of implementation of workplace controls has not kept pace in some situations.

The other important factor to be considered is the pattern of exposure. Although it has been common to express exposure as annual time weighted averages it is highly unlikely that exposure actually occurs continuously at such levels. Most solvent exposures in workplace applications consist of periods of high peaks interspersed by periods of little or no exposure, as evidenced by the frequent occurrence of acute symptoms of pre- or actual narcosis. Thus any health effects consequent on such exposures cannot be claimed to represent the results of chronic low-level exposure.

With the above in mind the question is asked as to whether lesions are produced in animals under similar conditions of exposure and if lesions so observed are they reproduced in the nervous system of man. The experimental animal data show reversible non-specific acute effects to high exposure for

some of the solvents studied. For the neurotoxic agents studied the data is fragmented but supports the known neurotoxicity particularly for n-hexane and toluene. There is no significant pathological, physiological or mechanistic evidence which supports the premise of an organic neurotoxic syndrome related to low-level solvent exposure.

Any review of the epidemiological literature on solvent neurotoxicity must first make a judgement on the validity of the available studies. Studies cannot be considered to contribute to the argument unless they use validated techniques, such as the WHO core protocol, contain expert evaluations of exposure, and avoid the epidemiological pitfalls of bias and confounding. The body of literature covering human health effects is voluminous and variable. The acute effects of overexposure are well understood.

It follows that any studies in which high rates of acute effects are reported, or in which the setting is known to involve frequent peak exposures cannot be relevant to a discussion of chronic low-level exposure. For this reason, studies of floor-layers, micro-electronic workers, varnishing and other miscellaneous groups have been given little emphasis apart from the light they throw on the range of effects that might be attributable to high solvent exposure. Similarly studies based on health records and questionnaires have been given little weight because the effects reported were probably due to high exposure.

Studies of painters fall into an intermediate category because the exposure experienced by painters is difficult to quantify and is known to be very variable. These studies report inferior performance in neuropsychological tests, increased neurological symptoms and some evidence of depression and neuroradiological abnormalities. Inconsistencies of this sort may reflect differences in exposure levels between the studies but equally it may reflect subtle differences in their design and conduct.

The studies best suited to the evaluation of the health effects of chronic low-level solvent exposure have been judged to be those of paint manufacturers in which past and present exposure of each participant has been estimated by expert hygienists. A wide range of investigative techniques has been used in these studies, the debate about the existence of a chronic low-level effect has centred largely on the results of neuropsychological tests. Some studies have included psychiatric and additional neurological investigations but these have provided little or no evidence of a solvent effect. These studies have shown no increase in solvent induced symptoms and that if any adverse effects can be demonstrated they are subclinical and only detectable on a group basis in a large study.

There is no basis for a hypothesis of an existing discrete neurological syndrome that is causally related to low-level exposure (as defined by recent or current OELs) to organic solvents. Whilst it is likely that further studies will be reported these will not be of any value unless rigorous attention is

paid to conforming to the WHO protocols coupled with adequate characterisation of exposure.
It is our overall recommendation that resources would be better focused on control of exposure rather than conducting further epidemiological examinations.

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APPENDIX A. SOLVENT EXPOSURE DATA

TABLE A-1. SOLVENT EXPOSURE DATA: METHYLENE CHLORIDE

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Degreasers, Paint strippers, Cleaners. (General manufact-uring; 14 plants)	1973			P	Methylene Chloride		7	1,930		mg/m³	11.1	Burton *et al*, 1973
	1974			F	Methylene Chloride		10	28		mg/m³	0.16	Markel *et al*, 1974
				P	Methylene Chloride		14	101		mg/m³	0.58	""
	1974			F	Methylene Chloride		<2	136		mg/m³	0.80	Gunter *et al*, 1974
	1974			F	Methylene Chloride		<3.5	403		mg/m³	2.32	Hervin *et al*, 1974
	1977			F	Methylene Chloride		654	868		mg/m³	4.99	Kronoveter, 1977
	1980			P	Methylene Chloride		180	2,190		mg/m³	12.59	Lee, 1980
	1981			P	Methylene Chloride			27		mg/m³	0.16	Ruhe, 1981
	1981			P	Methylene Chloride		52	141		mg/m³	0.81	Ruhe *et al*, 1981
	1982			P	Methylene Chloride		1.3	467		mg/m³	2.68	Ruhe *et al*, 1982
				F	Methylene Chloride		2	240		mg/m³	1.38	""
	1977			P	Methylene Chloride		38	2,820		mg/m³	16.21	Okawa and Keith, 1987
				F	Methylene Chloride		81	1,379		mg/m³	7.93	""
	1980			P	Methylene Chloride		94	4,882		mg/m³	28.10	Crosteck, 1980
				F	Methylene Chloride			1,041		mg/m³	5.99	""
	1980			P	Methylene Chloride		45	698		mg/m³	4.01	Hartle, 1980
				F	Methylene Chloride		298	1,461		mg/m³	8.40	""
	1980			F	Methylene Chloride		55	930		mg/m³	5.34	Cohen *et al*, 1980
	1976			P	Methylene Chloride			25		mg/m³	0.14	Gunter, 1976
	1977			P	Methylene Chloride		30	503		mg/m³	2.89	Ruhe *et al*, 1977
	1981			P	Methylene Chloride		22	233		mg/m³	1.34	Crostek *et al*, 1981
	1981			F	Methylene Chloride		0.06	0.48		mg/m³		Pryor *et al*, 1981
				P	Methylene Chloride			2		mg/m³	0.01	Gunter *et al*, 1976
	1977			P	Methylene Chloride		30	412		mg/m³	2.37	Ruhe *et al*, 1977
	1978			P	Methylene Chloride			2.61		mg/m³	0.01	White & Wegman, 1978
				F	Methylene Chloride		1.1	70		mg/m³	0.40	""
	1981			F	Methylene Chloride		0.01	2.4		mg/m³	0.01	Pryor, 1981
	1982			P	Methylene Chloride		3.4	31.1		mg/m³	0.18	Albrecht, 1982

TABLE A-1. SOLVENT EXPOSURE DATA: METHYLENE CHLORIDE

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Printing inks etc. (Printing operations; 5 plants)	1980			P	Methylene Chloride			17		mg/m^3	0.10	Arenholz, 1980
	1981			P	Methylene Chloride		24	410		mg/m^3	2.36	Lewis *et al*, 1981
	1981			P	Methylene Chloride		5	560		mg/m^3	3.22	Quinn, 1981
				F	Methylene Chloride		17	257		mg/m^3	1.48	""
	1982			P	Methylene Chloride		8.2	37		mg/m^3	0.21	Gorman, 1982
				F	Methylene Chloride		2.7	16		mg/m^3	0.09	""
	1981			P	Methylene Chloride		360	1,550		mg/m^3	8.91	Quinn, 1981
				F	Methylene Chloride			356		mg/m^3	2.04	""
				P	Methylene Chloride		84	17,890		mg/m^3	102.82	Rivera, 1975
				F	Methylene Chloride		73	285		mg/m^3	1.64	""
Paint strippers	Industrial paint stripping; dockyard		1		Methylene Chloride				214.7	mg/m^3	1.23	Cherry *et al*, 1975
Solvent Manufacture	1988		301	P	Methylene Chloride	>180	0.1	861.4	10.91	ppm	0.22	}ICI, 1991b
	1989		175	P	Methylene Chloride	>180	0.1	712.3	14.64	ppm	0.27	}
	1990		65	P	Methylene Chloride	>180	0.1	100	5.96	ppm	0.12	}

TABLE A-2. SOLVENT EXPOSURE DATA, STYRENE

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	SAMPLE TYPE	SAMPLE NO.	SAMPLE TIME (mins)	RESULTS			UNITS	CONC /OEL	REFERENCE
						RANGE		MEAN			
						(min)	(max)				
GRP pipe construction						0.2	136		ppm	≤2.72	IARC, 1979 NIOSH, 1977
Tyre manufacture	Curing					0.06	0.15		ppm	<0.003	IARC, 1979; Ayer, 1975
Not Specified				4 2 11		6	<6 25 >25		ppm ppm ppm		Olsen & Seedork, 1990
GRP Bathware manufacture	Sprayer Nonsprayer		P P	28 35	60 60	11.9 187.4	761.8 666.9	514.6 245.9	mg/m^3 mg/m^3	2.42 1.16	Galvin *et al*, 1990
Plastics manufacture						70.7	164		mg/m^3	≤0.78	Dolora *et al*, 1983
GRP Bathware			P	2	20	210	280		mg/m^3	≤1.32	Kure *et al*, 1991
Field trials - not spec			P S	10 30		18.3 8	22.6 116.7		ppm ppm	≤0.46 ≤2.34	Brown *et al*, 1987
Resin manufacture			F/P	4	95-720	0.1	2		ppm	≤0.04	UK Paints Hygiene Report, 1991
Resin research			F/P	8	2-425	0.1	10		ppm	≤0.20	UK Paints Hygiene Report, 1991
Polystyrene manufacture		Local Exhaust	P P P P P F F F F F F	11 9 13 6 11 8 6 6 9 10 18	50-450 50-450 50-450 50-450 50-450	ND ND ND ND ND ND 0.025 ND ND ND ND	2.4 0.36 0.015 0.014 19.8 0.11 1.1 0.008 ND 0.023 0.13	0.44 0.12 0.002 0.006 2.3 0.053 0.296 0.001 0.006 0.017	ppm ppm ppm ppm ppm ppm ppm ppm ppm ppm	0.009 0.002 <0.001 <0.001 0.05 0.001 0.006 <0.001 <0.001 <0.001	Samimi & Falbo, 1982
Polyester resin handling				36	Shift Peak	3 10	251 600	18	ppm ppm	0.36 ≤1.14	Triebig *et al*, 1989

TABLE A-2. SOLVENT EXPOSURE DATA, STYRENE

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	SAMPLE TYPE	SAMPLE NO.	SAMPLE TIME (mins)	RESULTS			UNITS	CONC /OEL	REFERENCE
						RANGE		MEAN			
						(min)	(max)				
Pipe manufacture			P	12	60-120			43	mg/m³	0.2	Edling & Ekberg, 1985
				12	60-120			54	mg/m³	0.25	
Plastics manufacture						16	61		mg/m³	≤0.30	Dolora *et al*, 1984
Fibreglass manufacture		Local Exhaust	P	23	480	6	90	25	ppm	0.5	Schumacher *et al*, 1981
			P	21	480	4	179	39	ppm	0.78	
			P	57	480	1	399	112	ppm	2.24	
			P	19	480	13	382	84	ppm	1.68	
			P	100	480	2	509	123	ppm	2.43	
			P	94	480	26	745	119	ppm	2.38	
			P	19	480	11	371	92	ppm	1.84	
			P	37	480	10	161	33	ppm	0.66	
			P	77	480	30	466	109	ppm	2.18	
			P	70	480	43	214	42	ppm	0.84	
			P	18	480	64	187	33	ppm	0.66	
			P	97	480	1	226	49	ppm	0.98	
Styrene-butadiene rubber manufacture			P	159	240-360	0.08	65.16	1.71	ppm	0.03	Checkoway & Willians, 1982
GRP Boat building			P	37+		18	157		ppm	≤3.14	Kalliokoski *et al*, 1988
FRP Yacht building		Local Exhaust	P	10		21	72	44	ppm	0.88	Todd, 1985
			P	12		13	31	21	ppm	0.42	
			P	9		16	34	28	ppm	0.56	
			F	14		9	31	20	ppm	0.4	
			F	10		0.5	3	2	ppm	0.04	
			F	11		3	12	7	ppm	0.14	
FRP Yacht building		Dilution/ Local Exhaust	P	168	450	1.6	183	77.7	ppm	1.56	Crandall & Hartle, 1985
			P	114	450	12.3	160	73.4	ppm	1.46	
			P	70	450	9.3	130	45.4	ppm	0.9	
			P	45	450	5.3	103	47.5	ppm	0.96	

TABLE A-2. SOLVENT EXPOSURE DATA, STYRENE

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	SAMPLE TYPE	SAMPLE NO.	SAMPLE TIME (mins)	RESULTS			UNITS	CONC /OEL	REFERENCE
						RANGE		MEAN			
						(min)	(max)				
Plastic boat building								25-144	ppm	≤2.88	NIOSH, 1977; IARC, 1979
Occupational exposure period. (Principally Boat Building in Denmark)	1955-70		P	227		10	4,700	714	mg/m^3	3.4	Jensen *et al*, 1990
	1971-80		P	1117		4	1,905	274	mg/m^3	1.3	
	1981-88		P	1184		1	4,020	172	mg/m^3	0.82	
	1955-88		P	2528		1	4,700	265	mg/m^3	1.26	

TABLE A-3. SOLVENT EXPOSURE DATA: TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Solvent Manufacturing	1988 1989 1990		182 454 423	P P P	Perchloroethylene Perchloroethylene Perchloroethylene	>180 >180 >180	0.1 0.1 0.1	13.3 135 401	0.5 1.2 1.5	ppm ppm ppm	0.005 0.01 0.02	ICI, 1991
Solvent drycleaning	Drycleaning in unit shops; 114 units		441	P	Perchloroethylene		97% 86% 69%	<100 <50 <30		ppm ppm ppm		Handbook Occupational Hygiene,
Solvent drycleaning	Drycleaning in unit shops; 90 units		333	P	Perchloroethylene		97% 88% 74%	<100 <50 <30		ppm ppm ppm		Shipman and Whim, 1980
Solvent drycleaning	Drycleaning				Perchloroethylene		97% 80% 65%	<100 <50 <30		ppm ppm ppm		CEFIC, 1984
Solvent degreasing	Metal degreasing Metal degreasing	Enclosed machines Open topped machines			Perchloroethylene Perchloroethylene		97% 85% 35% 95% 77% 60%	<40 <20 <10 <100 <50 <30		ppm ppm ppm ppm ppm ppm		CEFIC, 1984

TABLE A-4. SOLVENT EXPOSURE DATA: TOLUENE

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Furniture manufacture; hand application				Toluene (+ acetone, isobutanol, ethanolethyl acetate)	4hr	27	182		mg/m^3		IARC, 1989; Apostoli *et al*, 1982
Paint	Vehicle refinishing; spray application	Spray booth (side-wall ventilated)			Toluene		410	660		ppm	-[1]	IARC, 1989; Matsunaga *et al*, 1983
	Vehicle refinishing; spray application	Spray booth (downdraft ventilated)			Toluene		28	87		ppm	-[1]	
Paint	Airplane manufacture; spray application[2]		106		Toluene	8hr	100	1,100		ppm	11.00	IARC, 1989; Greenberg *et al*, 1942
Solvent. Manufacture of asbestos matting; mixing, weighing, calender operator	1970				Toluene		300	>500		ppm	>5	Cherry *et al*, 1985
	1971				Toluene		300	>500		ppm	>5	
	1972				Toluene		300	>500		ppm	>5	
	1973				Toluene		300	>500		ppm	>5	
	1974				Toluene		300	>500		ppm	>5	
	1975				Toluene		300	>500		ppm	>5	
	1976				Toluene		200	>500		ppm	>5	
	1977				Toluene		200	>500		ppm	>5	
	1978				Toluene		100	300		ppm	3	
	1979				Toluene		100	300		ppm	3	
	1980				Toluene		100	200		ppm	2	
	1981				Toluene		0	200		ppm	2	
Printing	Rotogravure printing			P	Toluene	8hr	7	112		ppm	1.12	IARC, 1989; Maki-Paakkanen *et al*, 1980

1 Short painting periods resulted in full shift TWAs below OELs

2 Approx 60% of workers exposed to >200ppm

TABLE A-4. SOLVENT EXPOSURE DATA: TOLUENE

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Printing				P	Toluene Ethyl Acetate N-Hexane MEK	8hr	27.1 14.6 3 1	53.7 77.6 4.7 1.5		ppm ppm ppm ppm	0.54	IARC, 1989; Tokunaga *et al*, 1974
Printing				P	Toluene	7hr	37	229		mg/m^3	0.61	IARC, 1989; de Rosa *et al*, 1985
Printing	Printer 1 Printer 2 Helper		36 25 50	P Aliphatic hydroc. P Aliphatic hydroc. P Aliphatic hydroc.	Toluene Toluene Toluene		102 283 120 304 81 192	667 2,547 706 2,636 680 2,479	352 1,154 367 1,231 303 690	mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3		IARC, 1989; Veulemans *et al*, 1979
Printing				F	Toluene		13	49	23	ppm	0.23	IARC, 1989; Angerer, 1979
Printing				F	Toluene		4	240		ppm	2.4	IARC, 1989; Ikeda *et al*, 1969
Printing			200 workers		Toluene		60	200		ppm	2.00	Lindstrom, 1981
Printing				F	Toluene		36	269	139.8	ppm	1.4	IARC, 1989; Angerer, 1985

TABLE A-5. SOLVENT EXPOSURE DATA: WHITE SPIRIT

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME (mins)	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	1. Painting interiors		4		White Spirit				577.4	mg/m^3	1.1	Cherry *et al*, 1985
	2. Chlorinated rubber paint		3		White Spirit				124.6	mg/m^3	0.24	
Paint[1] (Brush application)	1. Lab	None	1	F	White spirit	50		520		ppm		ICI, 1991 (private communication)
	2. Lab	Fan on	1	F	White spirit	20		255		ppm		
	3. Lab	Natural	1	F	White spirit	20		105		ppm		
	4. Small booth	Limited	3	F	White spirit	30-60	180	1,040		ppm		
	5. Small booth	Limited	2	F	Low odour w/spirit	20-40	1,060	1,340		ppm		
	6. Small booth	Natural	1	F	Low odour w/spirit	20		140		ppm		
	7. House	Natural	3	F	White spirit	60-75	80	145		ppm		
	8. Toilet	Natural	1	F	White spirit	120		300		ppm		
	9. Toilet	Natural	1	F	Low odour w/spirit	60		260		ppm		
	10. Small booth	Natural	1	P	White spirit	75			206	ppm		
	11. Toilet	Natural	1	P	White spirit	150			130	ppm	1.3	
	12. Toilet	Natural	1	P	Low odour w/spirit	135			152	ppm	0.51	
Paint (Roller/ Brush application)	1. Studio	Nil	4	P	White spirit	40		603	310	ppm	3.1	Dearling *et al*, 1989
		Natural	4	P	White spirit	40		143	81	ppm	0.81	
	2. Office	Nil	2	P	White spirit	20		571	418	ppm	4.18	
		Natural	2	P	White spirit	20		280	166	ppm	1.66	
	3. Corridor	Nil	3	P	White spirit	30		480	316	ppm	3.16	
		Natural	3	P	White spirit	30		270	226	ppm	2.26	
	4. Darkroom	Nil	2	P	White spirit	20		635	436	ppm	4.36	
	5. Darkroom	Nil	2	P	White spirit	20		400	291	ppm	2.91	
Paint (Brush application)	bathroom walls	None	2	P	White spirit	69		349	270	ppm	2.02	ICI, 1991 (private communication)
			1	F	White spirit	68		213	213	ppm	2.13	
			1[2]	F	White spirit	62		790	400	ppm	4	
Paint	Maintenance painting				White spirit			1,200-1,500		ppm	12+	Bobjer and Knave, 1977

1 Samples 1-9; Continuous monitoring. Sample time indicates time to reach maximum value.

2 Continous, direct reading, monitor

TABLE A-5. SOLVENT EXPOSURE DATA: WHITE SPIRIT

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME (mins)	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Household painting				White spirit	10-75	270	6,140		mg/m^3	10+	ICI, 1989
Paint	Alkyd paint		7		Stoddard Solvent		22	65		ppm		Riala, 1982
Paint	Wood finishes Floor varnishing		4		Stoddard Solvent. Actone, ethanol, isobutanol, butyl acetate		68	280		ppm	0.6- 2.3	IARC, 1989
Paint	Spraying vehicles	Spray booth (pre-service)	2	P	Xylene White spirit	Full Shift		65 12	58.5 9.5	ppm	0.59 0.1	Bradley and Bodsworth, 1983
		Spray booth (post service)	2	P	Xylene White spirit	Full Shift		9 <5	8 <5	ppm	0.08 <0.05	
Paint	House painting Airless spray	Nil	1	P	White spirit Xylene Butyl acetate	16			44 9 3	ppm		Pearce, 1990
	House painting LPHV gun	Natural	1	P	White spirit Xylene Toluene	21			140 33 115	ppm		
Paint	Roller application to walls, doors, ceilings	0.25-2.0 changes/hr	20	F	White spirit	Cont.	300	800		ppm		Bygghalsan, 1983
	Spray application to walls, doors, ceilings	2 air changes/hr	1	F	White spirit	Cont.		900		ppm		

TABLE A-5. SOLVENT EXPOSURE DATA: WHITE SPIRIT

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME (mins)	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Roller/brush application to doors, walls, window frames etc.	Mech vent or natural draft	26	P	White spirit	15-180			38	ppm	0.38	Riala *et al*, 1984
	Roller/brush application to doors, walls, window frames etc.	No vent (only door open)	43	P	White spirit	15-180		300	194	ppm	1.94	
		Vent (as above)	5	P	White spirit	15-180			39	ppm	0.39	
	Spray application to ceilings	No vent (as above)	3	P	White spirit	15-180			235	ppm	2.35	
	Spray application to ceilings											
Paint	Estimated average exposure between 1960 & 1973										0.4	Seppalainen and Lindstrom, 1982
	Estimated average exposure in 1977										0.25	

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint (Ship painting)	1. Small shipboard structures											
	High exposure group		Min 6	F	Benzene	Grab 5ml		8	6	ppm		Mikulski *et al*, 1972
					Toluene	syringe		22	16	ppm	0.16	
					Xylene			365	256	ppm	2.56	
	Low exposure group		Min 6	F	Benzene	Grab 5ml		ND	ND	ppm		
					Toluene	syringe			7	ppm	0.07	
					Xylene			133	93	ppm	0.93	
	2. Large ship holds											
	High exposure group		Min 6	F	Benzene	Grab 5ml		11	9	ppm		
					Toluene	syringe		88	53	ppm	0.53	
					Xylene			538	398	ppm	3.98	
	Low exposure group		Min 6	F	Benzene	Grab 5ml		ND	ND	ppm		
					Toluene	syringe			11	ppm	0.11	
					Xylene			108	59	ppm	0.59	
Paint	Fireplace manufacture; spray application				Toluene		3	18		mg/m^3		Helliquist *et al*, 1983
					Isobutyl acetate		2	44		mg/m^3		IARC, 1989
Paint (Plywood industry)	Polyurethane paints		12		MIBK		2	28		ppm		Kauppinen, 1986
			12		Butylacetate		8	50		ppm		IARC, 1989
			12		Xylene		10	25		ppm		
			12		Cyclohexane		1	28		ppm		
			8		Toluene		2	3		ppm		
	Alkyd paints		8		Xylene		7	12		ppm		
			8		Isobutanol		7	11		ppm		
			8		Trimethyl benzene		1	9		ppm		

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint, Printing inks etc. (Furniture & manufacturing industry)	Painting		8[1]		n-Hexane			1-11		ppm		de Rosa *et al*, 1985
			5[1]		Cyclohexane			2-153		ppm		
			15[1]		n-Heptane			2-21		ppm		
			30[1]		MEK			1-376		ppm		
	Printing		28[2]		n-Hexane			2-143		ppm		
			7[2]		Cyclohexane			3-17		ppm		
			3[2]		MEK			3-277		ppm		
Paint refinish	Vehicle refinishing	Spray booth	54	P	Toluene	1hr		250	30.6	ppm	0.31	Kurppa and Husman, 1982
					Xylene	1hr		36	5.8	ppm	0.06	Husman, 1980
	Samples from 6 garages, 40 painters				Butyl acetate	1hr		130	6.8	ppm	0.04	Seppalainen *et al*, 1978
					White spirit	1hr		150	4.9	ppm	0.05	Hanninen *et al*, 1976
					MIBK	1hr		39	1.7	ppm	0.03	
					Isopropanol	1hr		85	2.9	ppm	0.01	
					Ethyl acetate	1hr		33	2.6	ppm	0.01	
					Acetone	1hr		25	3.1	ppm	0.00	
					Ethanol	1hr		27	2.9	ppm	0.00	

											0.53	
Paint	Vehicle refinishing; spray application	Spray booth	8	P	Xylol	30		35.3	16.4	mg/m³	0.04	Konzentrationsmessungen in der Spritzkabinenlift, 1987
					Ethylbenzol			10.9	6	mg/m³	0.01	
					C3-alkylbenzol			33.4	20	mg/m³	0.08	
					Butylacetat			23.3	16.5	mg/m³	0.02	
		Spray booth	18	F	Xylol	30		83.7	16.2	mg/m³	0.04	
	Vehicle refinishing; spray application				Ethylbenzol			25.6	5.3	mg/m³	0.01	
					C3-alkylbenzol			87.3	16.6	mg/m³	0.07	
					Butylacetat			43.9	12.6	mg/m³	0.01	

1 Number of occasions out of 155 samples that substance found

2 Number of occasions out of 111 samples that substance found

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Vehicle refinishing; spray application	Spray booth	13		Xylene Toluene Isobutanol Ethyl acetate	Full shift			8 19 5 6	ppm	0.38[1]	Takeuchi *et al*, 1982 IARC, 1989
	Vehicle refinishing; spray application	Spray booth	14		Mixed solvents (toluene major component)	Short term					>0.38[2]	
Paint	Aircraft maintenance; primer				Toluene MEK Butyl acetate N-butanol Isopropanol Cyclohexanone Ethyl acetate			179 77 130 47 132 23 857	112 39 72 25 51 10 333	mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3		Okawa and Keith, 1977 IARC, 1989
	Aircraft maintenance; top coat				MEK MIBK Butyl acetate Xylene Cellosolve acetate			219 117 210 49 46	69 44 80 21 18	mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3		

1 Combined exposure

2 For 10 of 14 workers

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Aircraft painting; spray application				Toluene	Short		1,230	583	mg/m^3		Hervin and Thorburn, 1975
					MEK	term		3,250	1,436	mg/m^3		IARC, 1989
					Ethyl acetate			3,520	1,231	mg/m^3		
					Naptha			120	44	mg/m^3		
					Butyl acetate			150	64	mg/m^3		
					Xylene			1,330	318	mg/m^3		
					Cellosolve acetate			25,170	4,843	mg/m^3		
					Dichloromethane			2,840	654	mg/m^3		
					Ethyl acetate	Long		1,100	264	mg/m^3		
					MEK	term		440	197	mg/m^3		
					Toluene			450	162	mg/m^3		
					Butyl acetate			50	11	mg/m^3		
					Naptha			160	10	mg/m^3		
					Xylene			270	69	mg/m^3		
					Cellosolve acetate			2,490	640	mg/m^3		
					Dichloromethane			760	100	mg/m^3		
Paint	Paint manufacture		23		Acetone	TWA	1	121		mg/m^3	0.05	Mergler and Blain, 1987
					MEK		3	170		mg/m^3	0.29	
					Toluene		1	172		mg/m^3	0.46	
					Xylene		3	142		mg/m^3	0.33	
					Styrene		1	10		mg/m^3	0.02	
					MIBK		16	192		mg/m^3	0.94	
					2-ethoxy ethanol		0	10		mg/m^3	0.27	
					2-ethoxy eth acetate		0	141		mg/m^3	2.61	
Paint	Truck manufacture; spray application		8	P	Xylene	1-3hrs	5	140		ppm		Vandervort and Cromer, 1975 IARC, 1989

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Light aircraft finishing; primer spray application		3	P	2-butanone Toluene Ethanol Isopropanol	25-41			42 60 26 19	mg/m³ mg/m³ mg/m³ mg/m³	0.90	O'Brian and Hurley, 1981 IARC, 1989
	Light aircraft finishing; top coat spray application		7	P	Ethyl acetate Ethoxyethyl acetate Aliphatic HCs	27-62			77 44 34	mg/m³ mg/m³ mg/m³	0.15	
	Vehicle refinishing; spray application		7	P	Toluene Xylene Petroleum Distillate Other solvents	15-45			39 10 21 <10	mg/m³ mg/m³ mg/m³ mg/m³	0.09	
	Railroad car; Spray application		14	P	Toluene Xylene Other aromatics Aliphatic HCs	15-60			188 14 217 840	mg/m³ mg/m³ mg/m³ mg/m³	1.30	
Paint	Paint manufacture; 1975-1976 7 factories; 42 employees monitored		44 43 36 35 33 32 31 18 11 5 5 3		Xylene Toluene Isobutanol N-butanol Ethanol Ethyl acetate N-butyl acetate White spirit Methyl acetate Dichloromethane MEK Isopropanol	8hr	1 1 1 1 1 1 1 5 3 10 8 6	6,070 1,260 1,040 1,540 1,090 767 1,680 74 169 242 124 258	82 10 4 6 12 26 9 44 13 719 39 129	mg/m³	 (0.40)	Lundberg and Hakansson, 1985 IARC, 1989 Anshlem Olsen, 1982
								38 Workers 9 Cleaners 47 Total			0.35 2.94 0.40	

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Paint manufacture (7 factories - 17 highest exposure workers of 47)		16 16 15 14 13 13 13 8 3 3 1		Xylene Toluene Isobutanol Ethyl acetate N-butyl acetate Ethanol N-butanol Methyl acetate Dichloromethane White spirit Isopropanol				111 11 5 20 14 13 7 12 719 45 129	mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3 mg/m^3		Haglund *et al*, 1980 IARC, 1989
Paint	House painting Airless spray	Nil	1	P	White spirit Xylene Butyl acetate	16			44 9 3	ppm ppm ppm		ICI, 1991 (private communication)
	House painting LPHV gun	Natural	1	P	White spirit Xylene Toluene	21			140 33 115	ppm ppm ppm		
Paint	Roller/brush application - 30 workplaces	Varied, incl small badly ventilated rooms	30	P	Ethylacetate Toluene Butylacetate MIBK Xylene Ethylbenzene	6-8 hrs		50 15 11 11 7 3		ppm ppm ppm ppm ppm ppm	0.13 0.15 0.06 0.09 0.07 0.03 --- 0.53	Treibig *et al*, 1988 Treibig, 1986
Paint	Paint manufacture 2 factories		31	P	Isophorone Toluene Xylene MEK Methanol Isobutanol White spirit Trichloroethylene	8hrs			377	mg/m^3	<0.1 <0.1 <0.1 <0.1 <0.1 <0.1 <0.1	Normand *et al*, 1990

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Vehicle refinishing; spray application	Spray booth (pre-service)	2	P	Xylene	Full		65	58.5	ppm	0.59	Bradley and Bodsworth, 1983
					White spirit	Shift		12	9.5	ppm	0.10	
		Spray booth (post service)	2	P	Xylene	Full		9	8	ppm	0.08	
	Vehicle refinishing; spray application				White spirit	Shift		<5	<5	ppm	<0.05	
Paint	Heavy electrical engineering; varnishing processes			F	Xylene			550	163.4	mg/m^3		Gupta *et al*, 1990
				F	Toluene			451.5	121.7	mg/m^3		
Paint	Heavy equipment; spray painting		12	P	Refined solvents	60		21-96		mg/m^3	0.01-0.05	O'Brian and Hurley, 1981 IARC, 1989
					Other solvents			<5		mg/m^3		
	Metal furniture; spray painting (solvent & waterborne paints)		5	P	Toluene	8hr		12-61		mg/m^3	0.10-0.46	
					Xylene			7-48		mg/m^3		
					N-butyl acetate			22-109		mg/m^3		
					Diisobutyl ketone			<1-23		mg/m^3		
					2-ethoxyethyl acetate			1-14		mg/m^3		
								33-180		mg/m^3		
	Metal furniture; spray painting (high-solids paints)		6	P	Aliphatic HCs	8hr		6-55		mg/m^3	0.07-0.31	
					Xylene			5-60		mg/m^3		
					Aromatic distillates			<10		mg/m^3		
			4	P	Other solvents	8hr		88-204		mg/m^3	0.38-0.79	
	Appliance finishing; spray painting				Toluene			112-225		mg/m^3		
					Xylene							
Paint	Bus manufacture; Paint mixing/ Spray painting				Petroleum naptha						0.03-0.32	Zey and Aw, 1984 IARC, 1989
					Toluene, xylene, MEK							
					Benzene, N-Hexane							

TABLE A-6. SOLVENT EXPOSURE DATA: SPECIFIC SOLVENTS

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC /OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint stripper Glue Lacquers					Methylene Chloride Total solvent Toluene Total solvent	10-30 15-60 10-30			1,580-7,030 3,870-6,490 2,040 732-3,130	mg/m^3 mg/m^3 mg/m^3 mg/m^3	40+	ICI, 1991 (private communication)
Varnish	Varnish production		12	P	2-ethoxyethanol 2-ethoxyethyl acetate 2-butoxyethanol 1-methoxypropan2ol 2-methoxypropyl-1-acetate Xylene			7.8 11.1 8.1 24.1 13.8 6.7	2.8 2.7 1.1 7 2.8 1.7	ppm ppm ppm ppm ppm ppm	0.14 0.14 0.06 0.07 0.14 0.02	Angerer *et al*, 1990
	Store		3	P	2-ethoxyethanol 2-ethoxyethyl acetate 2-butoxyethanol 1-methoxypropan2ol 2-methoxypropyl-1-acetate			0.4	<0.1 <0.1 <0.1 <0.1 <0.1 0.4	ppm ppm ppm ppm ppm ppm		
	Laboratory		2	P	Xylene 2-ethoxyethanol 2-ethoxyethyl acetate 2-butoxyethanol 1-methoxypropan2ol 2-methoxypropyl-1-acetate Xylene			2.3 0.4	<0.1 2.1 <0.1 <0.1 <0.1 0.2	ppm ppm ppm ppm ppm ppm		
Paint, Glue (Industrial painting & glueing of bowls, alters, furniture etc)	Hand spraying Brush application Screen painting Automatic spraying Glueing	LEV systems	77 4 17 9 10	F/P	Mainly Toluene + Xylene Ethyl benzene n-hexane	9 hrs direct read	0.02 0.04 0.11 0.24 0.11	0.75 0.42 0.7 2.02 0.48		Conc/ OEL		Ikeda *et al*, 1985

TABLE A-7. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint (Industrial spray painting manual)	Plant 1 Plant 2 Plant 3 Plant 4 Plant 5 Plant 6 Plant 7 Plant 8 Plant 9 Plant 10	 Spray booth Spray booth Spray booth Spray booth Spray booth Spray booth Spray booth		P	Mixed solvents (toluol, xylole ethylbenzol ethyltoluol trimethyl benzol styrol, iso butanol aceton, MIBK, MEK ethyl acetat butyl acetat etc)	30mins, -6hrs					<0.1 <0.1 <0.1 <0.1 <1.0 <0.1 1.40 2.70 1.90 2.10	Treibig, 1989[1]
Paint (Furniture manufacture, 50 factories, 1975-1984)	Spray painting Spray assistant Feeding curtain machine Operating curtain machine Receiving painted items (before oven) Receiving painted items (after oven) Cleaning m/cs	LEV/dilution LEV/dilution LEV/dilution LEV/dilution LEV/dilution	119 37 47 36 67 18 30	P P P P P P P	Mixed solvents (xylene, butanol, ethanol, toluene, butylacetate, ethylacetate, propanols, MEK, MIBK, cellosolve acetate, cellosolve, Solvessos, white spirit, styrene, methyl acetate)	30-90					0.43 0.41 0.51 0.69 1.10 0.1- 1.80 2.10	Priha *et al*, 1986
Paint (House painting)	Alkyd paint Wood finishes Floor varnishing		7 4		Stoddard Solvent. Stoddard Solvent. Actone, ethanol, isobutanol, butyl acetate		22 68	65 280		ppm ppm	 0.6- 2.3	Riala, 1982 IARC, 1989

[1] Results evaluated in accordance with TRG403

TABLE A-7. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint	Paint manufacture			P	Mixed solvents	2-4hrs		53	28.3	ppm	0.17	Winchester and Madjar, 1986
				P	(toluene, xylene,	2-4hrs		65	44.0	ppm	0.37	
				P	ethyl benzene,	2-4hrs		133	63.8	ppm	0.24	
				P	pentane, n-hexane,	2-4hrs		31	18.6	ppm	0.16	
				P	heptane, acetone,	2-4hrs		171	130.0	ppm	0.86	
				P	MEK, MIBK, ethanol,	2-4hrs		297	128.0	ppm	0.77	
				P	isopropanol, etc.)	2-4hrs			92.0	ppm	0.45	
Paint (Paint manufacturing)	1985	LEV/dilution	77	P	Mixed solvents (xylene, toluene, acetone, MEK, isobutanol, MIBK, white spirit, etc.)	5-9hrs		4.1	0.33	CONC/ OEL		Clark, 1990
	1990	LEV/dilution	72	P		6-8hrs		2.36	0.25	CONC/ OEL		
Paint (Decorative painting)	1. Brush, roller, spray application											
	Showroom		12	P	Mixed solvents	3-4hrs		176	59.6	mg/m^3	)	Van der Wal and Moerkerken, 1984
	Canteen		8	P	(toluene, xylene,	3-4hrs		204	99.8	mg/m^3	)	
	Hall & Corr		10	P	ethylbenzene,	3-4hrs		76	34.4	mg/m^3		
	Laboratory		4	P	propylbenzene,	3-4hrs		59	42	mg/m^3		
	Auditorium		2	P	trimethyl benzenes, etc)	3-4hrs		17.5	15.8	mg/m^3		
	Laboratory trials, brush application:	Windows shut	2	P	Mixed Solvents	14		64	61.5	ppm		
		a/c off	2	P	Mixed Solvents	11		49	41	ppm		
		As above + fan	2	P	Mixed Solvents	21		59	48.5	ppm		
		1 Window open, a/c off										

TABLE A-7. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Painting (Maintenance painting)	Brush/roller; house[1]		12	P	Mixed Solvents	3-4hrs					0.24	Scheffers *et al*, 1985
	Brush/roller; house		8	P							0.34	
	Brush/roller; office		6	P							0.06	
	Brush/roller; factory		8	P							0.41	
	Brush/roller; house		4	P							0.24	
	Brush/roller; factory		8	P							1.97	
	Spray; factory[1]		4	P							1.58	
Paint (Furniture manufacture, spray application)[2]	Base coat	Spray booth			Mixed solvents (MEK, isopropyl acetate, xylene, MIBK, isopropanol etc)	8hr					0.06-0.11	O'Brian and Hurley, 1981 IARC, 1989
	Glaze operations	Spray booth				8hr					0.06-0.10	
	Lacquer operations	Spray booth				8hr					0.08-0.24	
Paint (Vehicle refinishing, spray application)	Plant 1	Spray booth		P	Mixed solvents (Toluene, xylene trimethyl benzene ethyl benzene, butyl acetate, ethyl acetate, methyl acetate, isopropanol, MEK, MIBK, n-hexane etc)	30					0.06	deMedinilla and Espigares, 1988
	Plant 2	Spray booth		P		30					0.29	
	Plant 3	Spray booth		P		30					0.18	
	Plant 4	Spray booth		P		30					0.94	
	Plant 5	Spray booth		P		30					0.74	
	Plant 6	Spray booth		P		30					0.06	
	Plant 7	Spray booth		P		30					0.35	
	Plant 8	Spray booth		P		30					10.68	
	Plant 9	Spray booth		P		30					0.23	
	Plant 10	Spray booth		P		30					3.20	
	Plant 11	Spray booth		P		30					1.29	

1 exposure included chlororubber paints

2 27 samples in total

TABLE A-7. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint (Construction & maintenance painting)	1. Roller & brush application											
	Doors, walls, windows	Mech vent or natural draft	26	P	Solvent naptha	15-180			38	ppm	0.38	Riala *et al*, 1984
	Doors, walls, windows	Door open	43	P	Solvent naptha	15-180		300	194	ppm	1.94	
	2. Spray application											
	Ceilings	Mech vent or natural draft	5	P	Solvent naptha	15-180			39	ppm	0.39	
	Ceilings	Door open	3	P	Solvent naptha	15-180			235	ppm	2.35	
	Estimated average exposure between 1960 & 1973										0.40	Seppalainen and Lindstrom, 1982
	Estimated average exposure in 1977										0.25	
Paint (Bus manufacture)	Paint mixing/spray painting				Mixed Solvents (Petroleum Naptha, Toluene, Xylene Benzene, MEK, N-Hexane)						0.03-0.32	Zey and Aw, 1984 IARC, 1989

TABLE A-7. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint, Glue, Printing inks, etc.[1]	1. Office furniture manufacture											
	Spray painting & glueing	Spray booth		P	Mixed solvents [Isopropanol, methylene chloride, trichloroethylene,)	Full Shift			9	ppm	0.06	Maizlish *et al*, 1985
	Spray painting & glueing	Spray booth		P		Full Shift			17	ppm	0.13	Maizlish *et al*, 1987
	2. Car parts manufacture											
	Spray painting & glueing	Spray booth		P	acetone, MEK, Naptha, toluene, xylene, ethylbenzene	Full Shift			12	ppm	0.09	
	3. Offset printing Printing			P	hexane	Full Shift			302	ppm	1.7	
Paint manufacture	Paint production 1985	LEV/dilution	78	P	Mixed solvents (xylene, toluene acetone, MEK isobutanol, MIBK white spirit, etc)	6-8hrs		0.59	0.13	CONC/ OEL		ICI, 1991 (private communication)
	Paint production 1990	LEV/dilution	35	P		6-8hrs		0.99	0.21	CONC/ OEL		

1 Total samples = 112

TABLE A-8. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (NOT SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint & Glue	Spray application	Spray booth	35	P	Mixed solvents	90-180					0.13	Whitehead *et al*, 1984
	Spray application	Spray booth	24	P	Mixed solvents	90-180					0.21	
	Spray application	Spray booth	30	P	Mixed solvents	90-180					0.15	
	Solvent wiping	General Vent	13	P	Mixed solvents	90-180					0.15	
	Paint mixing	General Vent	6	P	Mixed solvents	90-180					0.20	
Paint & Degreasers	Spray painting	Spray booth	243		Mixed solvents						0.24	Elofsson *et al*, 1980
	Grinding, filling etc		61		Mixed solvents						0.12	
	Colour mixing, degreasing cleaning		136		Mixed solvents						0.24	
Paint (1986/87: before and after remedial work on LEV system)	Curtain painting (before)	LEV	24	P	Mixed solvents	<3hrs			69	mg/m^3	0.18	Rosen *et al*, 1990
		LEV	16	P	Mixed solvents	<3hrs			47	mg/m^3	0.11	
			2	P	Mixed solvents	<3hrs			423	mg/m^3	1.10	
			1	P	Mixed solvents	<3hrs			697	mg/m^3	0.93	
	Curtain painting (after)	LEV	15	P	Mixed solvents	<3hrs			38	mg/m^3	0.08	
		LEV	13	P	Mixed solvents	<3hrs			24	mg/m^3	0.07	
			1	P	Mixed solvents	<3hrs			232	mg/m^3	0.49	
			1	P	Mixed solvents	<3hrs			163	mg/m^3	0.38	
	Spray painting (before)		47	P	Mixed solvents	<3hrs			75	mg/m^3	0.17	
	Spray painting (after)		18	P	Mixed solvents	<3hrs			68	mg/m^3	0.15	

TABLE A-8. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (NOT SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint Degreasers Glue	Spray painting		27 21 24	P P P	Mixed solvents	<20 <20 <20					<0.25 -1.0 >1.0	Seedorff *et al*, 1990
	Manual chemical cleaning		21 19 26	P P P	Mixed solvents	<20 <20 <20					<0.25 -1.0 >1.0	
	Mechanical chemical cleaning		8 4 4	P P P	Mixed solvents	<20 <20 <20					<0.25 -1.0 >1.0	
	Glueing		8 5 3	P P P	Mixed solvents	<20 <20 <20					<0.25 -1.0 >1.0	
Paint (Spray application to furniture)	Painter	Spray booth	10 10	P P	Mixed solvents Mixed solvents	Shift 15		0.5 1.28	0.2 0.46	Conc/ OEL		Alexandersson and Hedenstierna, 1987
	Assistant painter		3 3	P P	Mixed solvents Mixed solvents	Shift 15		0.38 1.72	0.23 0.79	Conc/ OEL		
	All exposed		38 38	P P	Mixed solvents Mixed solvents	Shift 15		0.52 1.72	0.15 0.41	Conc/ OEL		
Paint (Spray application to vehicles)	Spray booth Spray booth	LEV off LEV on	3 8	P P	Mixed solvents Mixed solvents		1.50 0.10	4.70 0.40		Conc/ OEL		Jaycock and Levine, 1984
	Work bay Work bay	LEV off LEV on	1 6	P P	Mixed solvents Mixed solvents		 0.10	2.90 1.30		Conc/ OEL		
Paint (Paint manufacture)	Charging solvents Pigment dispersion Tinting, thinning Can filling, paints Can filling, thinners Manual cleaning		33 18 14 39 14 51	P P P P P P	Mixed solvents Mixed solvents Mixed solvents Mixed solvents Mixed solvents Mixed solvents	4-43 9-66 15-32 11-32 9-20 3-28	0.20 0.20 0.10 0.02 0.10 0.50	16.00 4.40 2.00 6.60 7.40 30.00	2.00 1.50 0.90 1.30 1.80 5.70	Conc/ OEL Conc/ OEL Conc/ OEL		Ulfvarson, 1977 IARC, 1989

TABLE A-8. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (NOT SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint (Paint manufacture)	Manufacturing 1950 - 1969				Mixed solvents						2.00	Lundberg, 1986 [1]
	Manufacturing 1970 - 1974				Mixed solvents						1.50	
	Manufacturing 1975 - 1979				Mixed solvents						0.70	
	Manufacturing 1979 -				Mixed solvents						0.30	
	Cleaning tasks (up to late 70s)				Mixed solvents						5-10	
Paint (Paint manufacture)							-1969		1970-75		1976-	Orbaek *et al*, 1985[2]
	Mixing				Mixed solvents		2		1.3		0.70	
	Grinding				Mixed solvents		3		1.8		0.90	
	Tinting				Mixed solvents		2.2		1.5		0.60	
	Tapping				Mixed solvents		2.2		1.2		0.60	
	Cleaning				Mixed solvents		4.5		3		1.50	
	Filler manufacturing				Mixed solvents		0.2		0.15		0.10	
	Storage				Mixed solvents		0.2		0.15		0.10	
	Laboratory				Mixed solvents		0.7-2.0		0.4-1.0		0.15-0.4	
Paint	House painting				Mixed solvents				34[3]	Conc/ OEL		Molhave and Lajer, 1976; IARC, 1989
			44		Benzene				55	ppm		
			33		Trichloroethylene				91	ppm		

1 Figures based on measurements,and when available on estimates of exposure

2 Estimated exposures based on limited data

3 5 of 11 maximal values exceeded 1.0

TABLE A-8. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (NOT SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint (Vehicle refinishing, 1975-1977)	Spray painting Grinding, filling Colour mixing, degreasing	Spray booth	106 218 137		Mixed solvents Mixed solvents Mixed solvents						0.30 0.15 0.28	Elofsson *et al*, 1980
	Simulated vehicle refinishing (1955)				Mixed solvents						0.40	
	Spray painting, Colour mixing, degreasing				Mixed solvents						0.25	
Paint	Vehicle painting		100		Mixed solvents, mainly aromatic						<0.32	Lidstrom, 1981
Paint (Vehicle refinishing)	35 Spray booths not complying with T35-003	Spray booth	44	P (?)	Mixed solvents	4-56	0.03	1.90		Conc/ OEL	0.28	Delfoss and Laureillard, 1990
	17 Spray booths complying with T35-003	Spray booth	18	P (?)	Mixed solvents	6-95	0.01	0.23		Conc/ OEL	0.05	
Paint (Paint manufacture)	Paint production 1987	LEV/Dilution	57	P	Mixed solvents	8hrs	0.00	1.10		Conc/ OEL	0.16	BASF, 1990[1]
	Paint production 1984	LEV/Dilution	8	P	Mixed solvents	8hrs	0.00	0.41		Conc/ OEL	0.12	
	Paint production 1981	LEV/Dilution	62	P	Mixed solvents	8hrs	0.00	1.96		Conc/ OEL	0.19	
	Cleaning 1987		14	P	Mixed solvents	10-90	0.00	2.79		Conc/ OEL	0.93	

1 Results calculated in accordance with TRGS 403

TABLE A-8. SOLVENT EXPOSURE DATA: MIXED SOLVENTS (NOT SPECIFIED)

EXPOSURE SOURCE	TASK DESCRIPTION	VENTILATION	NO. SAMPLES	SAMPLE TYPE	SOLVENTS MONITORED	SAMPLE TIME	RESULTS			UNITS	CONC/ OEL	REFERENCE
							RANGE		MEAN			
							(min)	(max)				
Paint (Paint manufacture)	Paint production 1990	LEV/Dilution	14	P	Mixed solvents	60-120	<0.1	1.85		)	0.37	Herberts, 1990[1]
		LEV/Dilution	29	P	Mixed solvents	90-120	<0.1	1.42		)	0.30	
		LEV/Dilution	23	P	Mixed solvents	30-120	<0.1	1.35		)	0.36	
		LEV/Dilution	24	P	Mixed solvents	120	<0.1	1.75		)	0.24	
		LEV/Dilution	2	P	Mixed solvents	90-120	<0.1	0.71		Conc/	0.69	
		LEV/Dilution	10	P	Mixed solvents	12-120	<0.1	0.71		OEL	0.28	
		LEV/Dilution	5	P	Mixed solvents	60-120	<0.1	<1.00		)	0.23	
		LEV/Dilution	11	P	Mixed solvents	45-135	<0.1	0.55		)	0.23	
		LEV/Dilution	4	S	Mixed solvents	60-240	<0.1	0.46		)	0.21	
	Cleaning		5	P	Mixed solvents	120	0.11	0.94		)	0.51	
			5	P	Mixed solvents	120	0.12	0.47		)	0.26	
			22	P	Mixed solvents	30-120	<0.10	3.5		Conc/	0.63	
			4	P	Mixed solvents	120	<0.10	0.92		OEL	0.44	
			2	P	Mixed solvents	120	<0.10	<0.10		)	0.10	
			1	P	Mixed solvents	120				)	0.19	
			5	P	Mixed solvents	20-120	<0.10	<1.00		)	0.48	
Paint (Decorative paint trials)	Roller/brush application to wall boards, doors ceiling & floor	Special ventilation system	22 trials	P/F	Mixed Solvents	Cont.		300		ppm		Bygghalsan, 1975
	Spraying						500	700		ppm		

1 Results calculated in accordance with TRGS 403.

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APPENDIX B. 1,1,1-TRICHLOROETHANE (METHYLCHLOROFORM)

ANIMAL NEUROTOXICITY DATA

Appendix B. 1,1,1-TRICHLOROETHANE (METHYLCHLOROFORM)

General toxicity

Clinical signs of CNS depression are frequently reported to occur both during and for short periods following acute, subacute or chronic exposures to 1,1,1-trichloroethane in a wide range of species but at non-lethal dose levels growth, general appearance, behaviour, haematology, organ weights, gross and microscopic pathology have been reported to be unchanged in rats (Torkelson *et al*, 1958; Prendergast *et al*, 1967; Schwetz *et al*, 1975; York *et al*, 1982), mice (Schwetz *et al*, 1975; Quast *et al*, 1988), guinea-pigs and rabbits (Torkelson *et al*, 1958; Prendergast *et al*, 1967), gerbils (Rosengren *et al*, 1985; Karlsson *et al*, 1987), dogs (Prendergast *et al*, 1967) and monkeys (Torkelson *et al*, 1958). Decreased bodyweight was observed in female, but not male, rats exposed at 1,500 ppm and slight microscopic hepatic effects were also observed in both males and females at this dose level (Quast *et al*, 1988). Minor lesions of the liver of guinea-pigs were observed following exposure at 2,000 ppm for 0.5 h/d or 1,000 ppm for 1 h/d, 5 d/w for 3 months (Torkelson *et al*, 1958).

Behaviour

The majority of studies in which specific behavioural effects have been examined are acute studies and measurements have been performed either during and/or immediately after exposure. Where effects have been reported these have often been shown to reverse within a short time. Thus, in rats effects in a behavioural screen or conditioned avoidance task occurred during acute exposures of 1,750 ppm and above but reversed within minutes (Mullin and Krivanek, 1982); in mice decreased activity in a 'behavioural despair' swimming test, activity monitor, motor performance task, fixed-ratio responding task or a drug discrimination task effects were only observed during or immediately following acute exposures of greater than 1,000 ppm (De Ceaurriz *et al*, 1983; Hougaard *et al*, 1984; Kjellstrand *et al*, 1985; Moser and Balster, 1985, 1986; Rees *et al*, 1987); in the baboon a reduction in the number of trials attempted in a match-to-sample discrimination task reversed immediately following exposure (Geller *et al*, 1982). In the latter study the accuracy of responding was not affected by exposure to doses as high as 2,100 ppm acutely or 1,200 ppm continuously for 7 days suggesting that the decreased response attempts reflected CNS depression or general toxicity rather than any effect on 'cognitive function'.

In subacute studies the behaviour of rats in an open-field was reported to be unaffected by exposure to 1,1,1-trichloroethane (Savolainen *et al*, 1977b) and although acute effects (during exposure) were observed in mice on a fixed ratio task the effects had reversed by 23 hours following each exposure (Moser *et al*, 1985).

Motor activity levels were increased when measured immediately following exposure to 4,000 ppm 6h/d for 4 days (Albee *et al*, 1990b). However, in a comprehensive neurotoxicity study no effects on behaviour, except a minor decrease in forelimb grip strength in female rats only, were observed following 13 weeks of exposure at levels up to 2,000 ppm, 6h/d, 5d/w (Mattsson *et al*, 1991).

It may be concluded that there is no evidence for long-lasting behavioural effects following acute, subacute or chronic exposures.

Neurophysiology

In a specific and comprehensive neurotoxicity study of 1,1,1-trichloroethane a battery of electrophysiological measurements was conducted. Visual, auditory, somatosensory and caudal nerve evoked potentials were measured following 13 weeks exposure at 200, 630 or 2,000 ppm 1,1,1-trichloroethane for 6h/d, 5d/w (Mattsson *et al*, 1991). No treatment related findings were discovered, although in a preliminary study it was demonstrated that flash evoked potentials occurred during exposure (Albee *et al*, 1990a). This demonstrates that effects occurring during exposure are rapidly reversible.

Neuropathology

The brain, spinal cord and peripheral nerve of mice exposed up to 1,500 ppm for 2 years were examined by Quast *et al* (1988) using conventional histopathological techniques and no abnormalities were observed.

In the specific neurotoxicity study for rats exposed up to 2,000 ppm for 13 weeks conducted by Mattsson *et al* (1991) a comprehensive neuropathological examination of the brain, spinal cord, peripheral nerves and limb muscles was conducted. Perfusion fixation and special techniques revealed no abnormalities.

Neurochemistry

Effects of inhalation exposure on brain lipid, amino acid and/or protein levels/activity have been investigated in rats, mice and gerbils in an attempt to find a mechanism of neurotoxicity. In only one of these studies were specific behavioural measurements conducted concurrently and this showed no effect on open-field behaviour (Savolainen *et al*, 1977b). The biological significance of such small changes in brain chemistry, therefore, remain unclear. The effects reported do not provide a consistent picture of specific brain lesions; acute exposures (50 to 4,910 ppm for up to 4 hours) produced changes in cAMP, cGMP and guanylate cyclase activity in various regions of mouse brain

which reversed within 1 hour of cessation of dosing (Nilsson, 1986a,b); no changes in rat cerebral cortex lipid or fatty-acid composition occurred following continuous exposure to 320 ppm for 30 days (Kyrklund *et al*, 1988) but slight decreases in brain RNA content were recorded after exposure to 500 ppm, 6 h/d for 4-5 days (Savolainen *et al*, 1977b); in gerbils exposed continuously to 70 ppm for 3 months followed by 4 months recovery slight decreases in DNA but not glial fibrillary acidic protein or S-100 protein were seen in three brain regions, and at doses of 210 and 1,000 ppm increases in glial fibrillary acidic protein levels only were seen in cerebral sensorimotor cortex (Rosengren *et al*, 1985; Karlsson *et al*, 1987). As no clinical, behavioural or pathological assessment was performed and as there is no evidence in the literature to suggest that such changes are associated with abnormal behaviour the significance of the reported effects remain unclear.

TABLE B-1. REPEATED (SUBCHRONIC OR CHRONIC) INHALATION EXPOSURES USING 1,1,1 TRICHLOROETHANE OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	500 ppm	26w (5d/w, 7h/d)	No effects on growth, general appearence, mortality, haematology, gross and microscopic pathology, organ weights	Torkelson *et al* (1958)
Rat	150 ppm 500 ppm 1,500 ppm	2y (5d/w, 6h/d) 516 exposures 2y (5d/w, 6h/d) 516 exposures 2y (5d/w, 6h/d) 516 exposures	) No effects on mortality, clinical signs of toxicity, haematology, urinalysis,) clinical chemistry, body weight, organ weight, gross or microscopic pathology.)) Decreased bodyweight in females. Slight microscopic pathology of liver. No effects on mortality, clinical signs of toxicity, haematology, urinalysis, body or organ weights.	Quast *et al* (1988)
Rat	200 ppm 630 ppm 2,000 ppm	13w (6h/d, 5d/w) 13w (6h/d, 5d/w) 13w (6h/d, 5d/w)	) No treatment related effects on clinical, electrophysiological or) histopathological examination. Minor decreases in forelimb gripstrength in females) only.	attsson *et al* (1991)
Mice	150 ppm 500 ppm 1,500 ppm	2y (5d/w,6h/d) (516 exposures) 2y (5d/w, 6h/d) 2y (5d/w, 6h/d)	) No effects on mortality, clinical signs of toxicity, haematology, clinical) chemistry, body weight, organ weight, gross or microscopic pathology.)))	Quast *et al* (1988)
Guinea-pig	500 ppm 2,000 ppm 1,000 ppm 2,000 ppm	26w (5d/w, 7h/d)) 13w (5d/w, 0.05h/d) 13w (5d/w, 0.1h/d) 13w (5d/w, 0.2h/d) 13w (5d/w, 0.5h/d) 13w (5d/w, 0.3h/d) 13w (5d/w, 0.6h/d) 13w (5d/w, 1.2h/d) 13w (5d/w, 3.0h/d)	) No effects on growth, general appearance, mortality, haematology, organ weights) or gross and microscopic pathology.) Normal except for inflammation of lungs. Normal except for lung irritation and fatty changes in liver.) No effects on growth, general appearance, Organ weights, gross or) microscopic pathology. No effects on growth, general appearance or organ weights. Inflammation of lungs. Decreased acticvity and muscle tone. Retarded growth, but no effect on final bodyweight. Inflammation of lungs, fatty changes in liver and increased liver weight.	Torkelson *et al* (1958)
Rabbit	500 ppm	26w (5d/w, 7h/d)	No effects on growth, general appearance, mortality, haematology, organ weights or gross and microscopic pathology.	Torkelson *et al* (1958)
Monkey	500 ppm	26w (5d/w, 7h/d)	No effects on growth, general appearance, mortality, haematology, organ weights or gross and microscopic pathology.	Torkelson *et al* (1958)

TABLE B-2. OTHER RELEVANT STUDIES USING 1,1,1-TRICHLOROETHANE

Species	Exposure Route	Concentration or Dose	Duration (Days/weeks/ months/years)	Observations and Remarks	Reference
Rat	Inhalation	10,000 ppm 10,000 ppm 10,000 ppm 10.000 ppm 10,000 ppm	3m (5d/w, 0.05h/d) 3m (5d/w, 0.1h/d) 3m (5d/w, 0.2 h/d) 3m (5d/w, 0.5 h/d) 3m (5d/w, 1.0 h/d)	} No effects on growth, mortality, gross pathology, micropathology, or) organ weights.)) Anaesthesia and/or ataxia during exposure. No effects on growth, mortality, gross or microscopic pathology. Slight increase in liver weight	Torkelson *et al* (1958)
Rat	Inhalation	2,170 ppm 370 ppm 136 ppm	6w (5d/w, 8h/d) 13w (7d/w, 24h/d) 13w (7d/w, 24h/d)	No visible signs of toxicity, no deaths, no gross or microscopic abnormalities in brain or other organs, no effects on bodyweight gain or haematology As above No compound related effects recorded. Infection in some animals	Prendergast *et al* (1967)
Rat	Inhalation	1,750 ppm 3,080 ppm 6,100 ppm 11,550 ppm	4h 4h 4h 4h	No effects on general behavioural screen either during or following exposure Behavioural effects observed during exposure but begin to recover within 5 to 10 min and normal 18 h after exposure. No significant effect on conditioned avoidance task performed during and after exposure Clinical signs of CNS depression and effects on behavioural screen and conditioned avoidance task observed during exposure - recovered within 18 h. Significant decrease in body temperature. Clinical signs of CNS depression and death in 33% of animals. Surviving animals recovered within 18 h. Significant decease in body temperature during exposure.	Mulin and Krivanek (1982)
Rat	Inhalation	3,500 ppm 6,000 ppm 7,800 ppm	0.5 - 2.0h as above	No effects on behaviour, local cerebral blood flow or glucose consumption) Decreased mobility and exploratory behaviour. Increased cerebral) blood flow and glucose consumption during exposure.	Hougaard *et al* (1984)
Rat	Inhalation	320 ppm	4w (7d/w, 24h/d)	) No changes in brain of body weigt or in crebral cortex lipid or fatty acid) composition.	Kyrklund *et al* (1988)
Rat	Inhalation	1,000 ppm 2,000 ppm	4d 4d	) Changes in flash evoked potentials and EEG during exposure)	Albee *et al* (1990a)
Rat	Inhalation	4,000 ppm	4d	Increased motor activity immediately following exposure	Albee *et al* (1990b)
Rat	Gavage	705 mg/kg/d	4d	Changes in flash evoked potentials and EEG immediately following exposure.	Spencer *et al* (1990)

TABLE B-2. OTHER RELEVANT STUDIES USING 1,1,1-TRICHLOROETHANE

Species	Exposure Route	Concentration or Dose	Duration (Days/weeks/ months/years)	Observations and Remarks	Reference
Rat (male)	Inhalation	500 ppm	4-5d, 6h/d	No effects on behaviour in open-field test. Slight decrease in brain RNA content	Savolainen *et al* (1977b)
Rat (female)	Inhalation	875 ppm	9d (days 6-15 of gestation) 7d/w, 7h/d	No significant toxicity (no effect on bodyweight, food consumption. Slight increase in liver weight).	Schwetz *et al* (1975)
Rat (female)	Inhalation	2,100 ppm	2 - 5 w (premating and/or gestation, 5-7d/w, 6h/d	No signs of toxicity, no effects upon organ weight, clinical chemistry, no adverse effect upon bodyweight.	York *et al* (1982)
Mouse	Inhalation	872 ppm	9d (days 6-15 of gestation, 7d/w, 7h/d)	No effects on organ or bodyweight. No evidence of toxicity.	Schwetz *et al* (1975)
Mouse	Inhalation	3,000 - 35,000 ppm	10-60mins	Initial CNS stimulation followed by depression and death at high concentration. Up to 11,000ppm tested on motor performance test. Animals showed decreased ability but recovered within 30 minutes of exposure.	Moser and Balster (1985)
Mouse (male)	Inhalation	2,064-3,569 ppm	4h	No clinical signs reported. Decreased immobility in a 'behavioural despair' swimming test immediately after exposure.	De Ceaurriz *et al* (1983)
Mouse (male)	Inhalation	890, 1,300, 2,000, 4,000 ppm	1h	No clinical signs reported. Minor effect on motor activity during exposure at doses above 890ppm.	Kjellstrand *et al* (1985)
Mouse (male)	Inhalation	6,000 ppm plus increasing concentration (8mins x 1,000 ppm, 8mins x 2,000 ppm, 8mins x 4,000 ppm & 8mins x 8,000 ppm) 1d/w.	4w (4d/w, 20 min/d)	Fixed ratio responding was decreased during exposure but recovered within 23 hours.	Moser *et al* (1985)
Mouse (male)	Inhalation	1,800, 3,600, 7,200, 10,800 ppm	30 mins	Effects on fixed-interval responding during exposure but recovered within 15 minutes.	Moser and Balster (1986)
Mouse (male)	Inhalation	50 - 4,910 ppm	0.5-4h	No effects on behaviour. Reversible (within 1h) changes in cAMP, cGMP and guanylate cyclase activity of various brain regions.	Nilsson (1986a,b)
Mouse (male)	Inhalation	125 - 14,000 ppm	20 mins	Dose related effects on a drug discrimination procedure performed immediately after exposure.	Rees *et al* (1987)
Gerbil	Inhalation	70 ppm 210 ppm 1,000 ppm	3m (7d/w, 24h/d) + 4m "recovery" period	Clinical observations not reported. No deaths, no effects on bodyweight. Increase in glial fibrilllary acidic protein in cerebral senssorimotor cortex only following exposure to 210 and 1,000ppm. No effects on S-100 protein.	Rosengren *et al* (1985)
Gerbil	Inhalation	70 ppm	3m (7d/w, 24h/d) + 4m "recovery" period	No clinical observations reported. No deaths, no effects on brain or body weight. Slight decrease in DNA concentration of three brain regions.	Karlsson *et al* (1987)

TABLE B-2. OTHER RELEVANT STUDIES USING 1,1,1-TRICHLOROETHANE

Species	Exposure Route	Concentration or Dose	Duration (Days/weeks/ months/years)	Observations and Remarks	Reference
Guinea-pig	Inhalation	136 ppm 370 ppm 2,170 ppm	13w (7d/w, 24h/d) 13w (7d/w, 24h/d) 6w (5d/w, 8h/d)	No compound related effects but some evidence of infection.) No deaths, visible signs of toxicity, effects on bodyweight, gross or) macroscopic pathology or serum urea nitrogen.)	Prendergast *et al* (1967)
Rabbit	Inhalation	136 ppm 370 ppm 2,170 ppm	13w (7d/w, 24h/d) 13w (7d/w, 24h/d) 13w (7d/w, 24h/d)	No compound related effects recorded, but evidence of lung infection (and 1 death).) No deaths, no visdible signs of toxicity, gross or) microscopic pathology. Decreased body weight gain.)	Prendergast *et al* (1967)
Dog	Inhalation	136 ppm 370 ppm 2,170 ppm	13w (7d/w, 24h/d) 13w (7d/w, 24h/d) 6w (5d/w, 8h/d)	No compound related effects recorded, but evidence of lung infection.) No deaths, no visdible signs of toxicity, gross or) microscopic pathology. Decreased body weight gain.)	Prendergast *et al* (1967)
Baboon	Inhalation	700 ppm 1,400 ppm 1,800 ppm 2,100 ppm 1,200 ppm	4w (1d/w, 4h/d) 4w (1d/w, 4h/d) 4w (1d/w, 4h/d) 4w (1d/w, 4h/d) 4w (7d/w, 24h/d)	) All animals were exposed to all concentrations. Subchronic study) performed 3 months after acute studies.)) No effects on accuracy of responding of match-to-sample discrimination test conducted during exposure, but fewer trials attempted. Recovery following cessation of exposure.	Geller *et al* (1982)

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APPENDIX C: 1,12-TRICHLORO-1,2,2-TRIFLUOROETHANE (FREON 113)

ANIMAL NEUROTOXICITY DATA

Appendix C. 1,1,2-TRICHLORO-1,2,2-TRIFLUOROETHANE (FREON 113)

Very few animal studies have been reported which detail neurological signs and of these the longest duration was 4 weeks.

General Toxicity

Steinberg *et al* (1969) performed acute and subacute/subchronic studies in rats, dogs and guinea-pigs using a repeated exposure to 5,100 ppm for 6 h/d, 5 d/w for 4 weeks. Assessments included clinical observations, general pathology, and haematological analysis (dogs). No significant changes occurred.

Carter *et al* (1970) exposed mice, rats, dogs and monkeys to 1,000 ppm Freon 113 vapour continuously for 14 days. Evaluations included haematology, clinical chemistry, electro-encephalography and organ and body weights. No effects attributable to exposure were observed.

Behaviour

Steinberg *et al* (1969) exposed rats and dogs to 11,000 - 13,000 ppm Freon 113 vapour for 6 h and found central nervous system effects consisting of restlessness followed by lethargy and/or tremors. Effects were quickly reversed following termination of exposure. Specific behavioural activity was measured after exposure at 5,100 ppm for 6h/d, 5d/w for 4 weeks. No effects were seen at either testing point of 1 day or 4 weeks. Assessments included rotobar test and activity wheels.

Neurophysiology

No reports included neurophysiological techniques.

Neuropathology

No reports including neuropathological examination have been found.

Neurochemistry

Neurochemical measures have not been made following subchronic exposures. Savolainen and Pfaffli (1980a) measured brain RNA, glutathione azoreductase, glutathione peroxide and NADPH-diaphorase in rats exposed to 200, 1,000 or 2,000 ppm Freon 113 6 h/d, 5 d/w for 2 weeks. Transient effects were reported which reversed during the exposure period or after a 7 day withdrawal period

except that brain RNA at the highest exposure remained slightly below the control range. The biological significance of such a small change remains unclear.

TABLE C-1. REPEATED (SUBCHRONIC OR CHRONIC) INHALATION EXPOSURES USING 1,1,2-TRICHLORO-1,2,2-TRIFLUOROETHANE (FREON 113) OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or Dose	Duration	Observations and Remarks	Reference
No relevant studies				

TABLE C-2. OTHER RELEVANT STUDIES USING 1,1,2-TRICHLORO-1,2,2-TRIFLUOROETHANE (FREON 113)

Species	Exposure Route	Concentration or Dose	Duration (days/weeks/ months/years)	Observations and Remarks	Reference
Rat	Inhalation	5,100 ppm	4w (5d/w, 6h/d)	No signs of toxicity or changes in growth rate. No effect on performance in rotobar test or in activity wheels. No general pathology. Neuropathology not performed.	Steinberg *et al* (1969)
Rat	Inhalation	11,400 ppm 13,000 ppm	1d (6h/d) 1d (6h/d)	No signs and no effect on performmance in "rotobar" test. Restlessness followed by decreased activity. No effect on performance in rotobar.	Steinberg *et al* (1969)
Rat	Inhalation	1,000 ppm	14d (24h/d)	No effects on haematology, clinical chemistry, electroencephalography, body weights or organ weights.	Carter *et al* (1970)
Rat	Inhalation	200 ppm 1,000 ppm 2,000 ppm	2w (5d/w, 6h/d)	) Dose-dependent accumulation of compound in perirenal fat and brain.) Reversible changes in neurochemical activity observed.)	Savolainen and Pfaffli (1980a)
Rat	Inhalation	500 ppm	single exposure (18h)	No effect on brain synaptosome Ca-uptake	Edelfors and Ravn-Jonsen (1985)
Mouse	Inhalation	1,000 ppm	14d (24h/d)	No effects on haematology, clinical chemistry, electroencephalography, body weights or organ weights.	Carter *et al* (1970)
Guinea-pig	Inhalation	5,100 ppm	4w (5d/w, 6h/d)	No signs of toxicity or changes in growth rate. No general pathology. Neuropathology not performed	Steinberg *et al* (1969)
Dog	Inhalation	5,100 ppm	4w (5d/w, 6h/d)	No neurological changes, no changes in haematological parameters, no general pathology. Neuropathology not performed.	Steinberg *et al* (1969)
Dog	Inhalation	11,400 ppm 13,000 ppm	1d (6h/d) 1d (6h/d)	Vomiting, lethargy, nervousness, stupor and tremors during exposure. No signs 15 mins after termination of exposure. As above plus trembling and ataxia during exposure.	Steinberg *et al* (1969)
Dog	Inhalation	1,000 ppm	14d (24h/d)	No effects on haematology, clinical chemistry, electroencephalography, body weights or organ weights.	Carter *et al* (1970)
Monkey	Inhalation	1,000 ppm	14d (24h/d)	No effect on haematology, clinical chemistry, electroencephalography, body weights or organ weights.	Carter *et al* (1970)

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APPENDIX D, N-HEXANE

ANIMAL NEUROTOXICITY DATA

Appendix D N-HEXANE

The neurological dysfunction of sensorimotor or motor nerves caused by n-hexane exposure is well documented in man and is reproducible in animal studies (Spencer and Schaumburg, 1985). N-hexane metabolizes to 2,5-hexanedione, a substantially more neurotoxic compound than the parent alkane, in both animals and man. It has been demonstrated clearly in experimental studies that the duration of inhalation exposure is more important than exposure concentration on the severity and speed of onset of peripheral neuropathy. Cessation of exposure normally leads to partial or complete recovery. Concurrent exposure to methyl ethyl ketone may substantially potentiate effects caused by n-hexane. Relatively little research has been conducted to study CNS effects quantified by behavioral, neurophysiological, neuropathological or neurochemical methods.

General Toxicity

Acute exposure to n-hexane is reported to result in light narcosis, anaesthesia, loss of reflexes, respiratory arrest and death in a number of species following increasing exposure (8,000 - 64,000 ppm) (Spencer and Schaumburg, 1980). Effects on body weight gain have been noted using exposure regimes that produce peripheral neuropathy (Rebert and Sorenson, 1983; Ikeda *et al*, 1986). Non-neurotoxic exposures have minor or no effect on body weight even at exposures as high as 10,000 ppm (Cavender *et al*, 1984).

Behaviour

The importance of exposure schedule on the neurotoxicity caused by n-hexane was investigated (Pryor *et al*, 1982). Besides effects on limb grip strength, an exposure of 1,000 ppm 24 h/d, 5 d/wk for 11 weeks caused severe impairment of performance of a multisensory conditioned avoidance response and transient decreases in undifferentiated motor activity in male F-344 rats. In comparison, other rats were only slightly affected by 10 minute exposures, 6 to 12 times/d, 5 d/wk for 18 weeks at extremely high concentrations of 24,000 or 48,000 ppm. When the frequency of the 48,000 ppm exposure was increased to 24 times/d, for an additional 4 weeks, more severe effects appeared.

N-hexane exposure at 3,000 ppm for 6 h/d, 5 d/wk, for 13 weeks to pigeons (Ponecorvo *et al*, 1985) did not alter matching accuracy or reaction time, but did produce a trend towards reduced accuracy in the sensory-motor task. In another 13 week study (Dunnick *et al*, 1989) male and female B6C3F1 mice were exposed by inhalation to concentrations of n-hexane at 0, 500, 1,000, 4,000, and 10,000 ppm 6 h/d, 5 d/wk, and at 1,000 ppm for 22 h/d, 5 d/wk (1000C group). The only neurobehavorial parameter affected was a decrease in locomotor activity in female mice in the 1000C and 10,000 ppm

groups.

No effects were observed in detailed animal observations on neurological functions in rats exposed to 0, 3,000, 6,500, or 10,000 ppm n-hexane vapour 6h/d, 5d/w for 13 weeks (Cavender *et al*, 1984).

Neurophysiology

Rebert et al (1982) examined brainstem evoked auditory responses and caudal nerve action potential in rats exposed to hexane either continuously (1,000 ppm, 24 h/d, 5 d/w, 11 w) or intermittently (24,000 or 48,000 ppm, 6 - 24 times 10min/d, 22 w). Changes in auditory evoked responses and caudal nerve action potential (increased latency) seen at 1,000 ppm exposure did not completely recover within 22 weeks of termination of exposure. Intermittent exposures levels of 24,000 or 48,000 ppm produced less severe responses which, generally, recovered with 5 weeks of exposure termination.

Rebert and Sorenson (1983) studied sensory evoked responses in male F-344 rats exposed to 0, 500, 1,000, or 1,500 ppm n-hexane for 24 h/d, 5 d/wk for 11 weeks. Concentration-related increased latencies of the ventral caudal nerve action potential and components of the somatosensory, visual and auditory evoked responses were seen.

Neuropathology

In a 13 week study (Cavender *et al*, 1984) with emphasis on neurotoxic effects, male and female F-344 rats were exposed to 0, 3,000, 6,500, or 10,000 ppm n-hexane vapours 6 h/d, 5 d/wk. In a single male rat of the 10,000 ppm group isolated, greatly enlarged axons were observed in cross sections taken from the dorsal surface of the medulla.

In the study of Dunnick *et al* (1989) no neuropathological effects were observed. Schaumburg (1982) reported on the giant axonal changes that could be observed in the anterior cerebellar vermis, lateral geniculate body, fornix, mammillary bodies, superior colliculi, corpus callosum, and in the radial fibers of the frontal cortex of cats and rats after repeated exposure to n-hexane or its metabolite, 2,5-hexanediol. At the same symposium, Spencer (1982) reported that rats inhaling 500 ppm n-hexane for 22 h/d, 7 d/wk, showed CNS giant axonal degeneration after two months. On the other hand, 125 ppm n-hexane under a similar exposure regime for six months failed to produce any specific effects.

Neurochemistry

Male Wistar rats were exposed for 18 hours to an atmosphere of 500 ppm vapourised n-hexane

(Edelfors and Ravn-Jonsen, 1985). Brain synaptosome preparations were obtained from exposed and control animals. Calcium uptake was measured in the synaptosomes using unstimulated or potassium-stimulated preparations. In the potassium-stimulated experiment there was no effect on Ca-uptake even at an exposure concentration 5X the Danish OEL and with an 18 hour continuous exposure. Norepinephrine (NE) and dopamine (DA) levels in male Wistar rat brain were measured after exposure to 200 or 400 ppm n-hexane continuously for 30 days (Ikeda *et al*, 1986). In the rats exposed at 200 ppm, no significant change was observed in either NE or DA levels in any brain region. In the animals exposed to 400 ppm NE levels were significantly elevated in several regions of the brain, and DA levels were significantly decreased in two other regions of the brain.

TABLE D-1. REPEATED SUBCHRONIC OR CHRONIC INHALATION EXPOSURE USING n-HEXANE OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	3,000 ppm 6,500 ppm 10,000 ppm	13w (5d/w, 6h/d) 13w (5d/w, 6h/d) 13w (5d/w, 6h/d)	No significant neurotoxic or toxicologic effects. No significant neurotoxic or toxicologic effects. Lower body wt. gain and slightly lower brain wts. in males only.	Cavender *et al* (1984)
Mouse	500 ppm 1,000 ppm 4,000 ppm 10,000 ppm 1,000 ppm	13w (5d/w, 6h/d) 13w (5d/w, 6h/d) 13w (5d/w, 6h/d) 13w (5d/w, 6h/d) 13w (5d/w, 22h/d)	No significant neuropathologic, neurobehaviour or toxicologic effects. " " Decrease in locomotor activity in females only. Decrease in locomotor activity in females only.	Dunnick *et al* (1989)
Pigeon	3,000 ppm	13w (5d/w, 6h/d)	Did not alter matching accuracy or reaction time, but trend towards reduced accuracy in sensory motor task.	Ponecorvo *et al* (1985)

TABLE D-2. OTHER RELEVANT STUDIES USING n-HEXANE

Species	Exposure Route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	1,000 ppm	11w (5d/w, 24h/d)	Severe impairment of performance of a multi-sensory conditioned avoidance response; transient decrease in motor activity.	Pryor *et al* (1982)
Rat	Inhalation	24,000 ppm 48,000 ppm 48,000 ppm	18w (5d/w, with repeated 10m exp) 18w (5d/w, with repeated 10m exp) 22w (5d/w,with repeated 10m exp)	) Slightly affected neurobehaviour. Decreased grip strength.))) More severe neurobehavioral signs.	Pryor *et al* (1982)
Rat	Inhalation	500 ppm 125 ppm	9w (7d/w, 22h/d) 26w (7d/w, 22h/d)	CNS giant axonal degeneration. Failed to produce any specific effects.	Spencer (1982)
Rat	Inhalation	1,000 ppm 24,000 ppm 48,000 ppm	11w (5d/w, 24h/d) 22w (5d/w, with repeated 10min exp 6-24/d) 22w (5d/w,with repeated 10min exp 6-24/d)	Irreversible changes in auditory-evoked response and peripheral nerve conduction velocity.) Minor changes in auditory evoked responses. Reversible)) Changes in periipheral nerve conduction veleocity.	Rebert *et al* (1982)
Rat	Inhalation	500 ppm 1,000 ppm 1,500 ppm	11w (5d/w, 24h/d) 11w (5d/w, 24h/d) 11w (5d/w, 24h/d)	) Concentration-related decrease of body wt. gain; concentration) -related increased latencies of peripheral nerve action potential and) sensory evoked responses.	Rebert and Sorenson (1983)
Rat	Inhalation	500 ppm	single exposure (18h)	No effect on brain synaptosome Ca-uptake	Edelfors and Ravn-Jonsen (1985)
Rat	Inhalation	200 ppm 400 ppm	30d (7d/w, 24h/d) 30d (7d/w, 24h/d)	Body wt. gain significantly decreased Body wt. gain significantly decreased; norepinephrine elevated and dopamine decreased in the brain.	Ikeda *et al* (1986)

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APPENDIX E: METHYL N-BUTYL KETONE

ANIMAL NEUROTOXICITY DATA

Appendix E. METHYL N-BUTYL KETONE (MnBK)

General Toxicity

Methyl n-butyl ketone causes an identical pattern of peripheral neurological damage as n-hexane with chronic inhalation exposures (Spencer *et al*, 1980). Both compounds undergo metabolism through a common metabolite, 2,5-hexanedione, which is a substantially more neurotoxic compound than either parent molecule (O'Donoghue and Krasavage, 1980). Both n-hexane and MnBK are able to potentiate the neurotoxic potency of MnBK.

The most common systemic effect observed following inhalation exposure is weight loss or reduced weight ain in developing animals. For example Srague Dawley rats exposed to MnBK by inhalation to 1,000 ppm (25w, 6h/d, 5d/w) showed a progressive body weight loss (Johnson *et al*, 1977a,b). Monkeys (*Macaca fascicularis*) exposed by inhalation to 1,000 pmm (25w, 6h/d, 5d/w) also showed a progressive decline in boby weight (Johnson *et al*, 1977a,b). No effects were seen in either species at 100 ppm for 29 (rats) or 41 (monkeys) weeks (Johnson *et al,* 1977a,b).

Behaviour

In the above study by Johnson *et al* (1977a,b) no significant effects were seen on operant behavior (bar pressing task) in rats exposed to 100 ppm when tested for the first 19 weeks of exposure. The rats in the 1,000 ppm dose group were also tested for effects on operant behavior during the first 10 weeks of their exposure. The reduction in response rate in the 1,000 ppm group developed by the second week of exposure and continued during the 10 weeks of measurement.

Neurophysiology

In the study conducted on monkeys reported above, electroencephalograms were recorded monthly, but they did not reveal any abnormal patterns for either exposure group. In the 1,000 ppm exposure group, there was evidence of exposure-induced effects on averaged visual evoked potentials, with latencies for certain components being increased starting at 4 months of exposure. No effects on these latencies occurred in the 100 ppm exposure group (Johnson *et al*, 1977a,b).

Decreased motor nerve conduction velocities were seen in both rats and monkeys exposed to 100 ppm (after 9 months) or 1,000 ppm (after 3-4 months) 6h/d, 5d/w (Johnson *et al*, 1977a,b). Recovery, as measured by nerve conduction velocity was found to occur 6 months and 2 months after termination of the 1,000 ppm and 100 ppm exposures respectively (Johnson *et al*, 1977a,b).

Neuropathology

Peripheral and central nervous system damage consistent with dying back axon neuropathy has been observed in a number of studies in rats following oral or inhalation exposures (Duckett *et al*, 1974; Spencer *et al*, 1975; Krassavage *et al*, 1980). CNS damage has not been shown to occur in the absence of peripheral nerve damage.

Neurochemistry

No studies examining neurochemistry were found.

TABLE E-1. REPEATED (SUBCHRONIC OR CHRONIC) INHALATION EXPOSURE USING METHYL N-BUTYL KETONE (MnBK) OF RELEVANCE TO OCCUPATIONAL EXPOSURE.

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	1,300 ppm	4m (5d/w, 6h/d)	Narcosis and incorination during exposure. Reduced weight gain. Fore and hind limb weakness after approximately 3m. Peripheral and CNS abnormalities consistent with dying back axonal degeneration.	Spencer *et al*, 1975
Rat	100 ppm 1,000 ppm	23w (5d/w,6h/d) 25w (5d/w.6h/d)	No effects on operant behaviour. Decrease in rate of response for operant behaviour. Progressive loss in body weight.	Johnson *et al*, 1977a,b)
Monkey	100 ppm 1,000 ppm	41w (5d/w, 6h/d) 25w (5d/w, 6h/d)	No effect on EEGs No effect on EEGs. Evidence of effects on averaged visual evoked potentials.	Johnson *et al*, 1977a,b)

TABLE E-2. OTHER RELEVANT STUDIES USING METHYL N-BUTYL KETONE

Species	Exposure Route	Concentration or Dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	200 ppm	6w (5d/w, 8h/d)	Muscular weakness immediately after each exposure. Histological evidence of peripheral neuropathy.	Duckett *et al*, 1974
Rat	Oral	6.6 mmol/kg	approx 8 w (5d/w) (until paralysis)	Decreased body weight gain and food consumption. Hind limb paralysiis after approx 7-8 wks. Giant axonal neuropathy.	Krasavage *et al*, 1980.

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APPENDIX F: METHYL CHLORIDE (CHLOROMETHANE)

ANIMAL NEUROTOXICITY DATA

Appendix F. METHYL CHLORIDE (CHLOROMETHANE)

The neurotoxicity of methyl chloride has been reviewed by Repko and Lasley (1979) and Repko (1981). These reviews, and more recent papers of animal toxicology are summarised below.

General Toxicity

Clinical signs of disturbance of the central nervous system, following experimental exposure to methyl chloride, have been reported in dogs and monkeys (Smith and Van Oettingen, 1947), guinea pigs (Kolkmann and Volk, 1975), mice (Morgan *et al*, 1982; Landry *et al*, 1985; Jiang *et al*, 1985) and rats (Morgan *et al*, 1982). In general, the clinical signs were limited to incoordination and other abnormalities of gait and only occurred at acutely toxic dose levels.

Decreases in food consumption and/or body weight gain have also been reported in rats exposed during pregnancy (Wolkowski-tyl *et al*, 1983) and in mice exposed at perilethal dose levels (Landry *et al*, 1985).

Kidney, liver, testicular and adrenal abnormalities have been recorded in mice chronically exposed to methyl chloride at or below dose levels which produce signs of neurotoxicity (Morgan *et al*, 1982).

Behaviour

Specific behavioural or 'performance' measures were used in only one of the studies. Landry *et al* (1985) used a rotating rod to assess performance of mice exposed to a range of concentrations of methyl chloride under one of two exposure patterns (continuous or intermittent). Performance was consistent with signs of general toxicity and thus was seen to be diminished at dose levels which also produced general systemic toxicity and/or death (150, 200 and 400 ppm for 22 h/d or 1,600 and 2,600 ppm for 5.5 h/d). Slight, reversible effects on performance were seen in the absence of clinical signs at a dose of 800 ppm for 5.5 h/d.

Neurophysiology

No references to studies involving neurophysiological measures were found.

Neuropathology

Neuropathological changes are limited to the CNS and have been reported in the cerebellar granule layer of mice (Landry *et al*, 1985; Jiang *et al*, 1985; Morgan *et al*, 1982; Wolkowski-tyl *et al*, 1983),

rats (Morgan *et al*, 1982) and guinea pigs (Kolkmann and Volk, 1975). The lesions observed are essentially similar, consisting of coagulative necrosis of cerebellar granule cells, although specific species, strain and sex differences in the severity of the lesions were observed. Rats were more resistant to methyl chloride toxicity than mice and brain lesions were more severe in female C57BL/6 mice (Morgan *et al*, 1982).

Neurochemistry

No references to specific neurochemistry studies were found.

TABLE F-1 REPEATED (SUBCHRONIC OR CHRONIC) INHALATION EXPOSURE USING METHYL CHLORIDE (CHLOROMETHANE) OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	300 ppm 500 ppm 1,000 ppm 2,000 ppm 3,000 ppm 4,000 ppm	up to 64w,(6d/w, 6h/d) up to 64w,(6d/w, 6h/d) up to 64w(6d/w, 6h/d) up to 43d(6d/w, 6h/d) up to 6d (6d/w, 6h/d) up to 4d (6d/w, 6h/d)	) No effects)) Lethality observed at all dose levels. No description of behavioural effects.)))	Smith and Von Oettingen (1947)
Mouse	300 ppm 500 ppm 1,000 ppm 2,000 ppm 3,000 ppm	up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d) up to 64w (6d/w,6h/d)	No effects) Lethality at all dose levels. No description of behavioural signs.)))	Smith and Van Oettingen (1947)
Guinea-pig	300 ppm 500 ppm 1,000 ppm 2,000 ppm 3,000 ppm	up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d) up to 84d (6d/w, 6h/d) up to 5d (6d/w, 6h/d) up to 2d (6d/w, 6h/d)	No effects.) Lethality at all dose levels. No description of behavioural signs.)))	Smith and Van Oettingen (1947)
Cat, goat, chicken	2,000 ppm	up to 64w (6d/w, 6h/d)	No behavioural effects.	Smith and Von Oettingen (1947)
Rabbit, dog	300 ppm 500 ppm 1,000 ppm 2,000 ppm 3,000 ppm	up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d) up to 64w (6d/w, 6h/d)	) Lethality at all dose levels above 300 ppm. At 300 ppm signs of CNS depression) in monkeys & dogs, no behavioural effects described for other species.)))	Smith and Van Oettingen (1947)
Monkey	300 ppm 2,000 ppm	up to 64w (6d/w, 6h/d)	No behavioural effects.	Smith and Van Oettingen (1947)

TABLE F-2. OTHER RELEVANT STUDIES USING METHYL CHLORIDE (CHLOROMETHANE)

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	2,000 ppm	12d (7d/w, 6h/d)	Signs of toxicity not reported. No CNS lesion. Testicular, hepatocellular and renal tubule degeneration.	Morgan *et al* (1982)
		3,500 ppm	12d(7d/w/ 6h/d)	Two females killed in extremis day 11. Slight general toxicity in four animals. No CNS lesion. Testicular, hepatocellular renal tubule and adrenal fatty degeneration.	
		5,000 ppm	12d (7d/w, 6h/d)	Incoordination of forelimbs day 3. Approximately 50% animals killed in extremis day 5. Minimal CNS lesion. Testicular, hepatocellular, renal tubule and adrenal fatty degeneration.	
Rat (female)	Inhalation	100 ppm 500 ppm	12d (gestation days 7-19)	) No evidence of toxicity.)	Wolkowski-Tyl *et al* (1983)
		1,500 ppm	(7d/w, 6h/d)	) Decreased body weight gain, feed consumption. No) behavioural effects	
Mouse B6C3F1	Inhalation	500 ppm	12d (7d/w, 6h/d)	Signs or toxicity not reported. No CNS damage. Minimal basophilia in renal tubules of one male.	Morgan *et al* (1982)
		1,000 ppm	12d (7d/w, 6h/d)	Haematuria in all females day 8. No CNS damage. Mild to moderate basophilia in renal tubules.	
		2,000ppm	12d (7d/w, 6h/d)	All males dead or moribund by day 2, females by day 5. Minimal CNS damage. Hepatocellular and renal tubular degeneration.	
Mouse C3H	Inhalation	500 ppm	12d (7d/w, 6h/d)	Signs of toxicity not reported. No CNS damage. Hepatocellular degeneration in males.	Morgan *et al* (1982)
		1,000 ppm	12d (7d/w, 6h/d)	One male died day 11. All females haematuria by day 8. No CNS damage. Degeneration and necrosis of proximal convoluted tubules and/or basophilic renal tubules.	
		2,000 ppm	12d (7d/w, 6h/d)	All animals moribund by day 5. No CNS damage. Degeneration and necrosis of proximal convoluted tubules and/or basophilic renal tubules. Hepatocellular degeneration in males.	

TABLE F-2. OTHER RELEVANT STUDIES USING METHYL CHLORIDE (CHLOROMETHANE)

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Mouse C57BL/6	Inhalation	500 ppm	12d (7d/w, 6h/d)	Signs of toxicity not reported. No CNS damage. Slight hepatocellular degeneration	Morgan *et al* (1982)
		1,000 ppm	12d (7d/w, 6h/d)	Haematuria in all females on day 8. Mild to moderate cerebellar degeneration, hepatocellular degeneration and basophilic renal tubules.	
		2,000 ppm	12d (7d/w, 6h/d)	All animals dead or moribund by day 5. Severe brain lesions in females, hepatocellular degeneration in males. Moderate degeneration and necrosis of proximal convoluted tubules and/or basic renal tubules.	
Mouse C57BL/6 (female)	Inhalation	100 ppm 500 ppm	12d (gestation days 7-19) (7d/w, 22h/d)	) No evidence of toxicity)	Wolkowski-Tyl *et al* (1983)
		1,500 ppm	12d (gestation days 7-19) (7d/w, 22h/d)	Severe toxicity. All animals killed in extremis after 6 - 9 days pf exposure. Cerebellar granule layer.	
Mouse C57BL/6 (female)	Inhalation	1,500 ppm	2w (5d/w, 6h/d)	Lethal in 20% of animals. Motor incoordination in some animals. All animals had focal and diffuse malacia of cerebellar granule layer.	Jiang *et al* (1985)
Mouse C57BL/6 (female)	Inhalation	15 ppm 50 ppm	11d (7d/w, 22h/d) 11d (7d/w, 22h/d)	) No evidence of toxicity.)	Landry *et al* (1985)
		100 ppm	11d (7d/w, 22h/d)	No clinical signs of toxicity, slight cerebellar lesions.	
		150 ppm	11d (7d/w, 22h/d)	Severe toxicity after 4 days and decreased rotarod performance. Animals moribund in 10 days. Moderate degeneration of cerebellar granule layer.	
		200 ppm 400 ppm	11d (7d/w, 22h/d) 11d (7d/w, 22h/d)	) Lethal in 4/5 days. Severe degeneration of cerebellar granule layer.)	
		150 ppm	11d (7d/w, 5.5h/d)	No evidence of toxicity.	
		400 ppm	11d (7d/w, 5.5h/d)	No clinical signs of toxicity. Slight cerebellar lesion.	
		800 ppm	11d (7d/w, 5.5h/d)	No clinical signs of toxicity but slight performance decrement on day 4 only. Slight cerebellar lesion.	
		1,600 ppm	11d (7d/w, 5.5h/d)	Signs of slight systemic toxicity. Performance deficits on day 4 only. Slight cerebellar lesion.	
		2,400 ppm	11d (7d/w, 5.5h/d)	Severe toxicity, animals incapacitated by day 8. Slight to moderate cerebellar lesions.	
Guinea-pig	Inhalation	2,000 ppm	up to 70d (6d/w, 10min/d)	Staggering gait, atactic head movements decreased activity in approximately 50% of animals from 17 days. Necrosic of cerebellar cortex (granule cell layer).	Kolkmann and Volk (1975)

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APPENDIX G: METHYLENE CHLORIDE (DICHLOROMETHANE)

ANIMAL NEUROTOXICITY DATA

Appendix G. METHYLENE CHLORIDE (DICHLOROMETHANE)

The neurotoxicity of methylene chloride was reviewed by Winneke (1981).

General Toxicity

High acute doses of methylene chloride are narcotic and methylene chloride was used as a general anaesthetic for many years. Methylene chloride is metabolised to carbon monoxide, a process probably mediated by an activation of a cytochrome P450-dependent mixed function oxidase system in the liver (Ahmed *et al*, 1977, Norpoth *et al*, 1974). Thus, the neurotoxicity of methylene chloride depends both on a direct, non specific narcotic action on the central nervous system as well as an equally non specific carbon monoxide induced hypoxic effect.

Chronic toxicity studies of methylene chloride exposed animals have shown it to be of low toxicity but changes in liver and mammary tissue pathology have been reported in rats, guinea-pigs and dogs (Heppel *et al*, 1944; Burek *et al*, 1984; US-NTP, 1986; Nitschke *et al*, 1988). No evidence of toxicity and no liver damage was observed in rabbits or monkeys at dose levels up to 10,000 ppm (Heppel *et al*, 1944).

Behaviour

In a specific neurotoxicity study animals were exposed to a range of dose levels up to 2,000 ppm methylene chloride 6 h/d, 5 d/w for 13 weeks. No behavioural effects were noted during the daily observations and in a detailed functional observational battery conducted 2 to 3 days after the end of the 13 week exposure period no behavioural abnormalities and no effects on grip-strength were observed (Mattsson *et al*, 1988a). In other subchronic or chronic inhalation studies no evidence of irreversible behavioural changes have been seen (Heppel *et al*, 1944; Heppel and Neal, 1944).

In a variety of other studies specific behavioural changes have been observed to occur immediately after or during exposure to methylene chloride and in all cases were reversible in 16-24 hours. Thus, increased preening frequency and time was observed in rats exposed to 500 ppm methylene chloride for 4 to 5 days when examined immediately after exposure but not observed 17 hours after exposure (Savolainen *et al*, 1977a); running wheel activity in the rat was depressed during exposure to 5,000 or 10,000 ppm but partially recovered 30 minutes after exposure (Heppel and Neal, 1944); after exposure to 48,000 ppm until unconsciousness (approximately 20 seconds) no effects on locomotor behaviour or analgesia were observed in mice but the ability to learn a passive avoidance task was decreased when tested one hour after exposure (Alexeff and Kilgore, 1983); mice exposed to dose levels between 750 and 2,500 ppm show changes in activity during and for up to 2 hours following

exposure but no effects were observed at lower dose levels (Kjellstrand *et al*, 1985).

Neurophysiology

A detailed electrophysiological examination of rats following exposure to 2,000 ppm methylene chloride for 13 weeks was conducted by Mattsson *et al* (1988a, 1989a). A variety of evoked potentials (flash evoked potential, cortical flicker fusion, auditory brain stem responses, somatosensory evoked potentials) and peripheral nerve conduction velocity measurements did not demonstrate any difference between exposed and control animals although a previous study showed that effects occurred during exposure (Mattsson *et al*, 1988b).

Single, high concentrations of methylene chloride (5,000, 10,000 and 15,000 ppm) has been shown to affect a number of electrophysiological parameters during the exposure period (Rebert *et al*, 1989). These dose levels are representative of the exposures seen in solvent abuse and, consequently, not directly relevant to occupational exposure. Long lasting effects, following termination of exposure, were not examined.

Neuropathology

The brain was examined in the study by Nitschke *et al*, 1988 following 2-years exposure upto 500 ppm. No abnormalities were detected. In the only study in which specific neuropathological assessment was performed, no neuropathological changes were observed in the central or peripheral nervous system of rats exposed to 2,000 ppm for 13 weeks (Mattsson *et al*, 1988a, 1989a).

Neurochemistry

A number of papers have reported studies investigating specific effects on brain neurotransmitter, enzyme and/or protein levels or activity. Only two of the studies have used subchronic or chronic exposures and in both cases exposure was for 24 hours a day. Following three months exposure plus four months 'recovery' the only effect in gerbils at non-lethal dose levels was a decrease in DNA concentrations in hippocampus (Rosengren *et al*, 1986a; Karlsson *et al*, 1987). Using short-term exposure patterns a variety of effects have been reported but no consistent picture has emerged so far. Effects reported include: decreases in succinate dehydrogenase activity in cerebellum of rats and reversible increases in acid proteinase activity in cerebrum following exposure at 1,000 ppm for 2 weeks (Savolainen *et al*, 1981); changes in catecholamine levels and turnover in various areas of the CNS of rats (Fuxe *et al*, 1984); an inhibition of 3^{H}-clonidine binding to 2-adrenoceptors when mouse cerebral cortex membranes were dosed with 3 - 200 mol/l methylene chloride *in vitro* (Wikberg *et al*, 1987).

TABLE G-1. REPEATED (CHRONIC OR SUBCHRONIC) INHALATION EXPOSURE METHYLENE CHLORIDE (DICHLOROMETHANE) OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	500 ppm	up to 26w (5d/w, 7h/d)	Decreased running wheel activity 1 hour after exposure. Partial recovery in post exposure period. No effect on growth, appetite, general appearance or fertility.	Heppel and Neal (1944)
Rat	5,000 ppm 10,000 ppm	up to 26w (5d/w, 7h/d) 7w (5d/w, 4h/d)	No evidence of toxicity but 1 death. No effects on bodyweight gain, food consumption or gross and microscopic pathology. Gait effects followed by severe CNS depression/prostration during exposure, recovery within one hour. 2 deaths. No significant pathology in surviving animals.	Heppel *et al* (1944)
Rat	2,000 ppm	13w (5d/w, 6h/d)	No effects in functional observational battery, grip-strength measure or evoked potentials. No neuropathological changes.	Mattsson *et al* (1988a, 1989a)
Rat	50 ppm 200 ppm 500 ppm	2y (5d/w, 6h/d) 2y (5d/w, 6h/d) 2y (5d/w, 6h/d)	) No mortality, no effects on body weight or clinical condition. No gross or) histopatholgical changes. No mortality, no effects on body weight or clinical condition. Histopatholgical lesions in liver and mammary tissue.	Nitschke et al (1988)
Guinea-pig	5,000 ppm 10,000 ppm	up to 6m (5d/w, 7h/d) 7w (5d/w, 7h/d)	Decreased bodyweight gain. Only pathological change was pneumonia and centrilobular fatty degeneration of liver. Increasing somnolance and incoordination during exposure. Slight to moderate fatty degeneration of liver.	Heppel *et al* (1944)
Rabbit	5,000 ppm 10,000 ppm	up to 6m (5d/w, 4h/d) 7w (5d/w, 4h/d)	No evidence of toxicity. No effects on bodyweight gain, haematology, gross or microscopic pathology. Excitement followed by CNS depression during exposure. 60% deaths. No pathological lesions in surviving animals.	Heppel *et al* (1944)
Dog	5,000 ppm	up to 6m (5d/w, 7h/d)	No evidence of toxicity. No effects on bodyweight gain, haematology, gross or microscopic pathology.	Heppel *et al* (1944)
Monkey	10,000 ppm	7w (5d/w, 4h/d)	Incoordination and prostration during exposure. No effect on food consumption on bodyweight gain. No compound related pathology.	Heppel *et al* (1944)

TABLE G-2. OTHER RELEVANT STUDIES

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	500 ppm 1,000 ppm 100 ppm	2w (5d/w, 6h/d)	) Clinical or behavioural effects not reported. Decreased succinate) dehydrogenase activity in cerebellum at 1,000ppm and 100 (twa)) ppm (irreversible) and reversible increase in acid proteinase activity) at 1,000ppm in cerebrum.	Savolainen *et al* (1981)
Rat	Inhalation	2,000 ppm 4,000 ppm	4d (6h/d) 4d (6h/d)	) Changes in somatosensory evoked potentials and EEG during) exposure.	Mattsson *et al* (1988b)
Rat (male)	Inhalation	70 ppm 300 ppm 1,000 ppm	3d (6h/d)	) Clinical or behavioural effects not reported. Changes in) catecholamine levels and turnover in various areas of CNS and in) secretion of anterior pituitary hormones.	Fuxe *et al* (1984)
Rat (male)	Inhalation	5,000 ppm 10,000 ppm 15,000 ppm	1d (1h/d)	) Changes in electrophysiological parameters (electroencephalogram) and sensory evoked potentials during exposure.)	Rebert *et al* (1989)
Rat (female)	Inhalation	1,250 ppm	9d (day 6-15 of gestation) (7d/w, 7h/d)	No signs of toxicity reported, no effects on bodyweight gain or food consumption. Significant increase in carboxyhaemoglobin during exposure - reversible in 24 hours.	Schwetz *et al* (1975)
Rat (female)	Inhalation	500 ppm	4-5d (6h/d)	Increased preening frequency and time immediately after exposure. No effects on brain protein, RNA or glutathione content. Increased acid proteinase activity. Slight increases in liver microsomal cytochrome P450 content.	Savolainen *et al* (1977a)
Mouse	Inhalation	1,250 ppm	9d (day 6-15 of gestation) (7d/w, 7h/d)	No signs of toxicity reported. No effects on bodyweight. Significant increase in carboxyhaemoglobin during exposure - reversible in 24 hours.	Schwetz *et al* (1975)
Mouse	*In vitro*	3-200 mmol/l		Inhibited the binding of ^{3}H-clonidine to 2-adrenoceptors in mouse cerebral cortex membranes	Wikberg *et al* (1987)
Mouse (male)	Inhalation	168 mg/l (48,000 ppm)	Until loss of consciousness (approx. 20 sec)	Animals aged 3, 5 or 8 weeks of age tested for learning ability using a passive-avoidance task. Decreased learning ability observed - worse in younger animals. No effects on locomotor behaviour or analgesia. Decreased bodyweight gain in 8 week old animals.	Alexeff and Kilgore (1983)
Mouse (male)	Inhalation	400 ppm 550 ppm 600 ppm 750 ppm 850 ppm 1,100 ppm 2,200 ppm 2,500 ppm	1d (1h/d)	) No effects on motor activity during or after exposure.))) Initial increase in activity during exposure. Decrease in activity for) up to 2 hours following exposure.)))	Kjellstrand *et al* (1985)

TABLE G-2. OTHER RELEVANT STUDIES

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Gerbil	Inhalation	210 ppm	3m (7d/w,24h/d) + 4m "recovery" period	No effects on body weight gain during exposure. 1 death. Decreased DNA concentration in hippocampus after 4 months recovery period.	Rosengren (1986a)
		350 ppm	10w (7d/w, 24h/d)	Lethal in 50% of animals. No effect on body weight. Increased Brain weight after 4 month recovery period. Increased concentration of astroglial prooteins in frontal cortex, decreased concentration of DNA in hippocampus and cerebellar hemisphere.	
		700 ppm	7w (7d/w,24h/d)	100% lethality.	
Gerbil	Inhalation	210 ppm	3m (7d/w, 24h/d) + 4m "recovery" period	No deaths, no effects on body weight or brain weight. No changes in protein content of brain. Very slight decrease in DNA concentration in hippocampus.	
Dog	Inhalation	10,000 ppm	6d (4h/d)	Incoordination followed by excitement during exposure. Centrilobular congestion and moderate fatty degeneration of liver.	Heppel *et al* (1944)

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APPENDIX H: METHYL ETHYL KETONE (MEK)

ANIMAL NEUROTOXICITY DATA

Appendix H. METHYL ETHYL KETONE (MEK)

General Toxicity

Male and female Fischer 344 rats were exposed to 0, 1,250, 2,500, or 5,000 ppm MEK vapours 6 h/d, 5 d/wk for 90 days. No evidence of adverse effects were observed on the clinical health or growth of male or female rats, except for a depression of mean body weight in the 5,000 ppm exposure group, and slight but significant increases in liver weight, liver weight/body ratio, and liver weight/brain weight ratio. There were some changes in serum chemistry values, but these were inconsistent in their relationship to dose (Cavendar *et al*, 1983).

Behaviour

No neurological signs were observed in rats following exposure to MEK at a lethal dose level (6,000 ppm, 7 wks, 7d/w, 6h/d) (Altenkirch *et al*, 1978).

Neurophysiology

No studies examining neurophysiology were found.

Neuropathology

Rats were exposed continuously (i.e., 24 h/d) to MEK at 1,125 ppm for 16, 25, 53 and 55 days. At termination nerve tissue was collected for microscopic examination and quantitative histological studies were performed (Saida *et al*, 1976). No peripheral nerve toxicity was seen with MEK alone. In addition it was reported that further studies were carried out for as long as five months without evidence of abnormality.

MEK was administered at 150 mg/kg/d to cats by subcutaneous injection twice daily, 5 d/wk for up to 8.5 months. Selected tissues were removed and examined by light and electron microscopy (Spencer and Schaumberg, 1976). Chronic intoxication produced no clinical or pathologic evidence of neuropathy.

Altenkirch *et al* (1978) exposed rats for 8 h/d, 7 d/wk to MEK for 7 weeks (planed for 15 weeks). MEK was initially presented at 10,000 ppm, but this level was reduced to 6,000 ppm after several days because of severe irritation of the upper respiratory tract. The animals were killed, perfused with fixative and sections of nerve tissue were examined microscopically. Rats exposed to MEK did not develop any obvious motor impairment until the 7th week when all animals died without neurological

symptoms. Pathological and histological examinations revealed severe signs of bronchopneumonia in all animals. There was no evidence of histological alterations in the nerve tissue. Thus MEK was found to be without neurotoxic potential.

Rats exposed by inhalation 22 h/d for 6 months to 500 ppm MEK did not develop any indication of polyneuropathy (Egan *et al*, 1980).

The study reported above by Cavendar *et al* (1983) is the only report of significance for occupational exposure. It included special neuropathological as well as routine pathological examination; it demonstrated that repeated exposure of rats up to 5,000 ppm (6 h/d, 5 d/wk, 13 wk) produced no neuropathological changes. Thus earlier observations that MEK was not neurotoxic, even following repeated exposure at relatively high levels, were confirmed.

Neurochemistry

No studies examining neurochemistry were found.

TABLE H-1. REPEATED (SUBCHRONIC AND CHRONIC) INHALATION EXPOSURE USING METHYL ETHYL KETONE (MEK) OF RELEVANCE FOR OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	235 ppm	12w (5d/w, 7h/d)	No significant gross or microscopic pathalogical changes	LaBelle and Brieger (1955)
Rat	1,254 ppm 2,518 ppm 5,041 ppm	90d (5d/w, 6h/d) 90d (5d/w, 6h/d) 90d (5d/w, 6h/d)	) No effects on eyes, nervous system; No morphological changes in CNS or PNS.))	Toxigenics (1981)
Rat	1,250 ppm 2,500 ppm 5,000 ppm	13w (5d/w, 6h/d) 13w (5d/w, 6h/d) 13w (5d/w, 6h/d)	) Special neuropathological and routine pathological studies did not reveal any) treatment related lesions. Increased liver weight (M+F), increased spllen weight) (F) and smaller brain (F) at 5,000ppm.	Cavendar *et al* (1983)
Guinea-Pig	235 ppm	12w (5d/w, 7h/d)	No significant effects	LaBelle and Brieger (1955)

TABLE H-2. OTHER RELEVANT STUDIES USING METHYL ETHYL KETONE (MEK)

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	1,125 ppm	up to 55d (24h/d)	No peripheral neurotoxicity from histological evaluation. CNS not examined.	Saida *et al* (1976)
Rat	Inhalation	6,000 ppm	7w (7d/w, 8h/d)	Failed to produce any CNS or PNS damage.	Altenkirch *et al* (1978)
Rat	Inhalation	500 ppm	26w (7d/w, 22h/d)	Failed to produce any CNS or PNS damage.	Egan *et al* (1980)
Mouse	Tissue Culture	100 µg/ml	4-6w (7d/w, 24h/d)	Organotypic CNS-PNS-muscle culture free of neurotoxic changes.	Spencer, 1982
Cat	SC injection	150 mg/kg/d	8.5m	MEK produced no clinical or pathological evidence of neuropathy. CNS not examined.	Spencer & Schaumberg (1976)
Baboon	Inhalation	100 ppm	7d (24h/d)	No impairment in behaviour test	Geller *et al* (1979)

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APPENDIX I: STYRENE

ANIMAL NEUROTOXICITY DATA

Appendix I. STYRENE

General Toxicity

Wolf (1956) conducted studies in rats, rabbits, guinea pigs and Rhesus monkeys. Exposures were 7 h/d, 5 d/wk for between 5 and 12 months at concentrations ranging from 650 to 2,000 ppm. The results of these studies can be summarised as follows. At repeated exposures to 650 ppm: no effect in guinea pigs. At repeated exposures to 1,300 ppm: eye and nasal irritation in rats; no effect in rabbits; eye and nasal irritation, and slight growth depression in guinea pigs; and no effect in Rhesus monkeys. At repeated exposures to 2,000 ppm: no effect in rabbits; and eye and nasal irritation, and moderate growth depression in rats and guinea pigs. In 3 chronic inhalation studies growth depression was seen but with no evidence of neurotoxicity (Conti *et al*, 1988; Jersey *et al*, 1978; Maltoni *et al*, 1982).

Behaviour

Oral administration of styrene at 100 - 200 mg/kg/d for 14 consecutive days improved acquisition of a conditioned avoidance pole climbing response, but had no effect on spontaneous locomotor activity (Husain *et al*, 1985); in a chronic inhalation study, there was also a lack of styrene-induced changes in motor activity (Savolainen *et al*, 1980). Weanling rats exposed to greater than 800 ppm styrene for several weeks showed changes in a conditional avoidance task which was due to a high-frequency hearing loss (Pryor *et al*, 1987).

In order to investigate the neurobehavioral consequences of styrene exposure, Kulig (1989a) conducted a chronic inhalation study with rats exposed to 0, 350, 700, or 1,400 ppm for 16 h/d, 5 d/wk for 18 weeks (6 week post exposure recovery period followed). Several times during the study, animals were evaluated for spontaneous activity, grip-strength, performance on a discrete-trial two-choice visual discrimination task, and peripheral nerve conduction velocity. Compared to controls, treated rats showed a mild and inconsistent reduction in activity and grip strength; no effect on coordinated movement; no treatment-related deficits in discrimination performance could be detected during the last weeks of exposure and in the post exposure recovery period, although early in the exposure phase of the study there were deficits in discrimination performance.

Albee *et al* (1992a,b) conducted an ototoxic and neurotoxicological evaluation of styrene. Male rats were exposed at 50, 200 or 800 ppm for 6h/d, 5d/w for 13 weeks. Examinations included a functional observational battery for signs of neurotoxicity. No exposure-related behavioural changes occurred.

Neurophysiology

Pryor *et al* (1987) conducted an electrophyiological assessment (auditory evoked potential) in rats following exposures to 800, 1,000 or 1,200 ppm, 14h/d, 7d/w for 3 wks and demonstrated hearing deficits.

In addition to the behavioural aspects Kulig (1989a) measured peripheral nerve conduction velocity and observed no effects. Albee *et al* (1992a) confirmed the absence of any toxicologically significant changes in peripheral nerve conduction velocity. However, in their comprehensive electrophysiological examination of the nervous system (evoked potential recording of the visual, auditory and somatosensory systems) specific hearing defects were observed in rats exposed to 800 ppm styrene. The deficit was revealed by increased auditory brainstem response thresholds.

Neuropathology

A thorough examination of the nervous system using specialist neuropathology techniques was conducted by Albee *et al* (1992a) on rats exposed to 50-800 ppm for 13 weeks. No treatment related lesions were noted except cochlear hair cell lesions in rats exposed to 800 ppm.

Neurochemistry

Male rats were exposed by inhalation to 300 ppm styrene for 2-11 weeks, 6 h/d, 5 d/wk (Savolainen and Pfaffli, 1977). Although the exposures caused a marked accumulation of styrene in brain and perinephric fat up to the 4th week of the study, thereafter the body styrene content decreased until at the end of study it was about 50% of the level of the 4th week. Metabolic adaptation as determined by serum enzyme measurements was observed. Minor alterations in spinal cord axonal proteins were detected, while protein composition in the cerebellum did not change. The authors concluded "that the current (in 1977) threshold limit value for styrene is relatively safe in order to prevent neurotoxic complication".

Male rabbits were exposed to styrene at 750 ppm 12 h/d for 7 days to determine whether brain dopamine was affected (Mutti *et al*, 1988). Styrene caused a significant depletion of striatal (SDA) and tubero-infundibular (TIDA) dopamine. In separate experiments rabbits were dosed with one of several acid metabolites to determine the effect on brain dopamine. There were significant depletions again of SDA and TIDA with mandelic and phenylglyoxylic acids, but not hippuric, methylhippuric, or 7-methylmandelic acids. The authors conclude that the results indicate that dopamine is a target for styrene because it is biotransformed into α-keto acids. The *in vitro* studies reported in this paper suggest that dopamine condenses non enzymatically with reactive carbonylic groups of these α-keto

acids based on experiments with glyoxylic acid and phenylglyoxylic acid, thus causing it to become ineffective as a neurotransmitter. The authors suggest that the mechanism described might account for some neurobehavioral effects observed in workers occupationally exposed to styrene, at least for reversible impairments and changes in mood.

TABLE I-1. REPEATED (SUBCHRONIC AND CHRONIC) INHALATION EXPOSURE USING STYRENE OF RELEVANCE TO OCCUPATIONAL EXPOSURE.

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	1,300 ppm 2,000 ppm	7m (5d/w, 7h/d) 5m (5d/w, 7h/d)	Eye and nasal irritation. Eye and nasal irritation, and moderate growth depression.	Wolf *et al* (1956)
Rat	300 ppm	2-11w (5d/w, 6h/d)	Enzymatic adaptive changes.	Savolainen and Pfäffli (1977)
Rat	600 ppm 1,200 ppm	18-20m(5d/w, 6h/d)	) High dose reduced to 1,000 ppm due to decreased weight gains. Possible) increase in mammary adeocarcinomas at 600 ppm.	Jersey *et al*, 1978
Rat	300 ppm	17w (5d/w, 6h/d)	No effects on body weight, cerebral glial cells, behaviour or motor activity.	Savolainen *et al*, 1980
Rat	25 ppm 50 ppm 100 ppm 200 ppm 300 ppm	52w (5d/w, 4h/d)	) No evidence of increased incidence of brain tumours.))))	Maltoni *et al*, 1982
Rat	25 ppm 50 ppm 100 ppm 200 ppm 300 ppm	52 w (5d/w, 4h/d)	) Higher incidence of total malignant tumours at 100 ppm. Higher incidence of) mammary tumours in all exposed females.)))	Conti *et al*, 1988
Rat	50 ppm 200 ppm 800 ppm	13w (6h/d, 5d/w) 13w (6h/d, 5d/w) 13w (6h/d, 5d/w)	) No treatment related effects on body weight, functional observation battery,) electrophysiology or neuropathology. Effects on auditory brainstem response and lesions in cochlear hair cells demonstrating hearing deficits.	Albee *et al* (1992a)
Guinea-pig	650 ppm 1,300 ppm 2,000 ppm	6m (5d/w, 7h/d) 7m (5d/w, 7h/d) 5m (5d/w, 7h/d)	No effect. Eye and nasal irritation, slight growth depression. Eye and nasal irritation, moderate growth depression.	Wolf *et al* (1956)
Rabbit	1,300 ppm 2,000 ppm	12m (5d/w, 7h/d) 5m (5d/w, 7h/d)	No effect. No effect.	Wolf *et al* (1956)
Monkey	1,300 ppm	12m (5d/w, 7h/d)	No effect.	Wolf *et al* (1956)

TABLE I-2 OTHER RELEVANT STUDIES USING STYRENE

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	800 ppm 1,000 ppm 1,200 ppm	3w (7d/w, 14h/d)	) Marked hearing loss as evaluated by behavioural (conditioned) avoidance) and electrophysiological (brain stem auditory-evoked) response) techniques.	Pryor *et al* (1987)
Rat	Inhalation	350 ppm 700 ppm 1,400 ppm	18w (5d/w, 16h/d) 18w (5d/w, 16h/d) 18w (5d/w, 16h,d)	) Speed performance of learned behaviour affected; marked tolerance) of repeated exposure; no evidence of carry-over of effects into the) recovery period (6) -weeks) post exposure.	Kulig (1989a)
Rat	Oral	100 mg/kg/d 200 mg/kg/d	14d	) No neurological deficits or effects on spontaneous locomotion or) regional brain catecholamines; Increases in brain serotonin; effect) on learning (increased avoidance reactions).	Husain *et al* (1985)
Rabbit	Inhalation	750 ppm	7d (12h/d)	Significant depletion of brain dopamine.	Mutti *et al* (1988)

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APPENDIX J: TETRACHLOROETHYLENE (PERCHLORETHYLENE)

ANIMAL NEUROTOXICITY DATA

Appendix J. TETRACHLOROETHYLENE (PERCHLORETHYLENE)

General Toxicity

Tetrachloroethylene is narcotic in high acute doses and clinical signs of CNS depression, often leading to death, have been observed in a number of animal species (Rowe *et al*, 1952; Goldberg *et al*, 1964a). Signs of general systemic toxicity including decreased body weight gain and food consumption have also been reported in subacute and/or chronic studies on rats (Rowe *et al*, 1952; Nelson *et al*, 1980), mice (Schwetz *et al*, 1975) and guinea-pigs (Rowe *et al*, 1952) at doses as low as 200 ppm (7 h/d, 5 d/w for 220 days). In contrast, no adverse effects on behaviour, general condition, growth, clinical chemistry, or pathology were observed in subacute studies involving rats, rabbits and monkeys at an exposure of 400 ppm 7 h/d, 5 d/w for 183-250 days (Rowe *et al*, 1952) or rats exposed 70 to 7,000 ppm, 8 h/d, 5 d/w for up to 7 months (Carpenter, 1937).

Tetrachloroethylene is hepatotoxic and degenerative changes of the liver have been observed in rats, guinea-pigs and rabbits at exposures which do not produce neurotoxicity (Rowe *et al*, 1952).

Behaviour

Specific behavioural effects have been observed during and for short periods following inhalation exposures. No studies have described long-lasting effects following either acute, subacute or chronic inhalation exposure.

Motor activity was recorded using a Doppler radar unit during inhalation exposure of mice to 90 - 3,600 ppm tetrachloroethylene for one hour. Activity was increased during exposure but recovered within 3 hours (Kjellstrand *et al*, 1985). Using a `behavioural despair' swimming test mice showed decreased duration of immobility immediately following 4 hours inhalation exposure to 596 - 820 ppm. Animals were not tested at later time periods (DeCeaurriz *et al*, 1983).

In rats activity in the open field was increased immediately, but not 17 hours, following exposure to 200 ppm, 6 h/d for 4 to 5 days (Savolainen *et al*, 1977a); no effects on the ability to perform a conditioned avoidance task were observed following exposures to 1,150 ppm, 4 h/d, 5 d/w for 2 weeks (Goldberg *et al*, 1964a). In the latter study, a single 4 hour exposure to 2,300 ppm caused ataxia and hence inability to perform the task although the effect disappeared after further inhalation exposures.

A functional observation battery was included in the specific neurotoxicity study performed by Albee *et al* (1992b). Rats were exposed to 50, 200 or 800 ppm tetrachloroethylene for 6h/d, 5d/w for 13

weeks. No treatment related behavioural effects were seen.

Neurophysiology

Following exposure to 50, 200 and 800 ppm tetrachloroethylene for 13 weeks a systematic electrophysiological examination comprising evoked potential testing of visual, auditory and somatosensory systems and conduction velocity evaluation of caudal nerves was conducted (Albee *et al*, 1992b). No toxicologically significant changes were noted in any of the parameters measured. The results did not support a diagnosis of neurotoxicity.

Neuropathology

Specific neuropathological examination of the eye, optic nerve, optic tract, brain (multiple sections), spinal cord, peripheral nerves and limb muscles was performed in the study of Albee *et al* (1992b). No treatment related lesions were observed.

Neurochemistry

A large number of papers have investigated neurotransmitter, amino acid, protein and/or DNA levels in various regions of the brain in order to elucidate the mechanism of neurotoxicity of tetrachloroethylene. In all of these studies exposure was continuous (24 h/d, 7 d/w) and, thus, exposure via routes other than inhalation cannot be excluded (e.g. through contamination of food and water, grooming etc) and the relevance of the findings to occupational exposure is unknown. No consistent pattern of changes has been found. Changes observed have included increased amino acids levels of rat mid-brain, decreased acetycholine content in striatum and small changes in brain lipid and fatty-acid composition of rats exposed continuously to 320 - 800 ppm for a month (Honma *et al*, 1980a,b; Kyrklund *et al*, 1988). No effects on calcium uptake in rat brain synaptosomes was observed following a single 18 hour exposure to 30 ppm (Edelfors and Ravn-Jonsen, 1985). In the gerbil exposure to 50 to 320 ppm continuously for 3 months to 1 year has been reported to cause slight decreases in DNA content of frontal cortex (Rosengren *et al*, 1986b; Karlsson *et al*, 1987), changes in levels of S-100 protein (Rosengren *et al*, 1986b), altered lipid composition and fatty acid pattern (Kyrklund *et al*, 1984a; 1987a), and changes in taurine and glutamate levels in hippocampus (Briving *et al*, 1986). The reversibility of the reported changes has often not been examined and/or no behavioural or pathological assessment was performed. The functional significance of such changes, therefore, is unknown.

TABLE J-1. REPEATED (SUB-CHRONIC OR CHRONIC) INHALATION EXPOSURE USING TETRACHLOROETHYLENE (PERCHLORETHYLENE) OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	70 ppm 230 ppm 470 ppm	7m (5d/w, 8h/d)	) No deaths, no effects on bodyweight food consumption, clinical chemistry,) haematology, gross or microscopic pathology (except liver and spleen).)	Carpenter (1937)
	7,000 ppm	50d (5d/w, 8h/d)	Slight unsteadiness when removed from exposure - reversible in minutes. Pathological changes in liver and kidney, other organs including nerve tissue, normal.	
Rat	400 ppm	183d (5d/w, 7h/d)	No adverse effects on general behaviour, mortality, growth, haematological examination, organ weights.	Rowe *et al* (1952)
Rat	50 ppm 200 ppm 800 ppm	13w (6h/d, 5d/w) 13w (6h/d, 5d/w) 13w (6h/d, 5d/w)	) No toxicologically significant changes in a functional observation battery,) electrophysiology or neuropathology.)	Albee *et al* (1992b)
Guinea-pig	100 ppm	185d (5d/w, 7h/d)	No adverse effects on general appearance or behaviour, mortality, growth or body weight. Increased liver weight. Only pathological change was slight vacuolation of liver.	Rowe *et al* (1952)
	200 ppm	220d (5d/w, 7h/d)	No adverse effects on general appearance, mortality or clinical chemistry. Decreased body weight gain and increase in liver weight. Only pathological change was fatty degeneration of liver.	
	400 ppm	236d (5d/w, 7h/d)	As above.	
	1,600 ppm	10d (5d/w, 7h/d)	No deaths but significant decrease in body weight. Increased liver weight with moderate fatty degeneration of liver and degeneration of testes.	
	2,500 ppm	24d (5d/w, 7h/d)	Loss of equilibrium, strength and coordination during exposure. Bodyweight loss reversible in 20 day recovery period. Increased liver weight with fatty degeneration.	
Rabbit	400 ppm	222d (5d/w, 7h/d)	No adverse effects on general appearance or behaviour, growth, clinical chemistry, organ weight or gross and microscopic pathology.	Rowe *et al* (1952)
	2,500 ppm	39d (5d/w, 7h/d)	Marked CNS depression during exposure. Slight degeneration of liver.	
Monkey	400 ppm	250d (5d/w, 7h/d)	No adverse effects on general appearance, behaviour, growth, haematological examination, clinical chemistry, and gross and microscopic pathology.	Rowe *et al* (1952)

TABLE J-2. OTHER RELEVANT STUDIES USING TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	2,000 -20,000 ppm	0.2-14h	CNS depression (stupor, unconsciousness) leading to respiratory failure and death. No deaths at 2,000 ppm. Deaths occurred at all dose levels of 3,000 ppm and above within 5 hours of starting exposure. Unconsciousness occurring within a few minutes at concentrations of 6,000 ppm or more. In surviving animals no pathological changes, except minor liver changes, were observed.	Rowe *et al* (1952)
		2,500 ppm	18d (5d/w, 7h/d)	Lethal in 80% of animals. All animals showed CNS depression. No histopathological abnormalities except in liver.	
		1,600 ppm	25d (5d/w, 7h/d)	No deaths. CNS depression during exposures in first week, increased activity during exposures of following weeks. Decreased body weight. No pathological changes.	
Rat (male)	Inhalation	200 ppm	4-5d (6h/d)	Increased activity in open field 1 hour following exposure, reversible by 17 hours. No consistent changes in brain protein seen.	Savolainen *et al* (1977a)
Rat (Male)	Inhalation	200 ppm	1m (7d/w, 24h/d)	) No clinical observations reported. Significant increases in) glutamine/threonine/serine levels of mid brain in 400 and 800ppm) group.))	Honma *et al* (1980a)
		400 ppm	1m (7d/w, 24h/d)		
		800 ppm	1m (7d/w, 24h/d)		
Rat (Male)	Inhalation	200 ppm	1m (7d/w, 24h/d)	) No clinical observations reported. No significant effects on) dopamine, noradrenaline of 5HT content of various brain regions.) Decrease in acetylcholine content of striatum in 800 ppm group only.))	Honma *et al* (1980b)
		400 ppm	1m (7d/w, 24h/d)		
		800 ppm	1m (7d/w, 24h/d)		
Rat (male)	Inhalation	300 ppm	18h/d	No effect on calcium uptake in brain synaptosomes.	Edelfors and Ravn-Jonson (1985)
Rat (male)	Inhalation	320 ppm	30d (7d/w, 24h/d)	No clinical observations reported. Small changes in brain lipid and acid composition.	Kyrklund *et al* (1988)
Rate (female)	Inhalation	1,150 ppm	2w (5d/w, 4h/d)	) No effects on behaviour in conditioned avoidance test. Decrease in) bodyweight gain. Single 4 hour exposure caused ataxia which) disappeared despite further exposure. No other effects on behaviour) in avoidance task.	Goldberg *et al* (1964a)
		2,300 ppm			
Rat (female)	Inhalation	900 ppm	7d (day 7-13 of gestation) (7h/d)	Decreased food consumption and bodyweight gain.	Nelson *et al* (1980)
		900 ppm	7d (day 14-20 of gestation) (7h/d)	Decreased food consumption and bodyweight gain.	
		100 ppm	7d (day 14-20 of gestation) (7h/d)	No effects observed.	

TABLE J-2. OTHER RELEVANT STUDIES USING TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Mouse (male)	Inhalation	596, 649, 484, 820 ppm	4h/d	) Decreased duration of immobility in a "behavioural despair") swimming test performed immediately after exposure.	DeCeaurriz *et al* (1983)
Mouse (male)	Inhalation	90, 320, 400, 600, 800, 1200, 1,800 and 3,600 ppm	1h/d	) Increased motor activity at all dose levels during exposure.) Recovered within 3 hours.)	Kjellstrand *et al* (1985)
Mouse (female)	Inhalation	300 ppm	9d (day 6-15 of gestation) (7h/d)	Small but significant reduction in body weight. No effect on food consumption.	Schwetz *et al* (1975)
Gerbil	Inhalation	120 ppm	12m (7d/w, 24h/d)	No clinical observations recorded. No changes in body or brain weight. Small changes in fatty acid and pattern of phospholipids of various brain regions.	Kyrklund *et al* (1984a)
Gerbil	Inhalation	60 ppm 320 ppm	3m (7d/w, 24h/d) + 4m 'recovery' period	) No clinical observations reported. No effects on brain or body) weight. Minor changes in concentrations of S-100 protein and DNA) in various brain regions.	Rosengren *et al* (1986b)
Gerbil	Inhalation	50 ppm 120 ppm	12m (7d/w, 24h/d) 12m (7d/w, 24h/d)	) No clinical observations recorded. No changes in body or brain) weight. No effects on uptake of glutamate or GABA, no changes in) amino acids or glutathione except decreased taurine levels in) hippocampus and cerebellar vermis and increased glutamate in) hippocampus of 120 ppm group.	Briving *et al* (1986)
Gerbil	Inhalation	60 ppm	3m (7d/w, 24h/d) + 4m 'recovery' period	No clinical observations reported. No changes in body weights, brain weights or protein concentrations in brain. Slight decrease in DNA content in frontal cerebral cortex.	Karlsson *et al* (1987)
Gerbil	Inhalation	320 ppm	3m (7d/w, 24h/d)	No clinical observations reported. No changes in bodyweight. Minor decrease in brain weight and minor changes in lipid composition and fatty acid pattern of various brain regions.	Kyrklund *et al* (1987a)

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APPENDIX K: TOLUENE

ANIMAL NEUROTOXICITY DATA

Appendix K. TOLUENE

General Toxicity

Huff (1990) exposed rats to 0, 600, or 1,200 ppm toluene vapour 6.5 h/d, 5 d/wk for 103 weeks and mice under the same schedule at concentrations of 0, 120, 600, or 1,200 ppm. The results showed low-levels of chronic toxicity with no evidence of carcinogenic activity or neurotoxicity.

Typically no or minimal signs of toxicity and no changes in body weight have been reported in a variety of studies in rats using occupational type exposures at concentrations as high as 2,000 ppm for 12 weeks (Maeda, 1970; Rhudi *et al*, 1978, Shigata *et al*, 1978). Higher exposure concentrations or abuse type exposure patterns are reported to produce decreases in body weight in the absence of significant toxicity (Bruchner and Peterson, 1978, 1981; Stumph *et al*, 1985). Exposures at 4,000 ppm for 2h/d for 60 days had no effect on body weight (Ikeda *et al*, 1978).

In a model of solvent abuse, Bruckner and Peterson (1978; 1981) examined the effects of 7 consecutive cycles of 10 min exposure to 1,200 ppm toluene followed by 20 min exposure to air 5 d/wk for 8 weeks. This protocol caused lowered body weights as compared to controls, as well as lowered kidney, lung, liver and brain weights, however, organ/body weight ratios were actually increased. There were no treatment related histopathological effects to the examined organs. The only other statistically significant effects were elevated serum AST and increased susceptibility to infection.

Behaviour

No effects on psychomotor performance (rotorod, tilting plane test) were seen in male Sprague-Dawley rats (only 5-8 per group) exposed to 0 or 1,000 ppm toluene 8 h/d, 7 d/wk for 13 weeks (Tahti *et al*, 1983).

Male rats exposed to either 0 or 2,500 ppm 3 h/d, 5 d/wk for 1 day, or 1, 2 or 3 weeks (Stumph *et al*, 1985) showed behavioural changes during exposure. This effect was reversible within 30 minutes.

Rats exposed to 1,500 ppm toluene, 6 h/d, 5 d/wk for up to 26 weeks showed uncoordinated movement, laboured breathing, dry rales and excessive salivation (API, 1980; Lewis and Holdsworth, 1982). The first 7 exposures, at 2,000 ppm, caused CNS depression in the rats.

Recent studies using multisensory conditioned avoidance response (CAR) have demonstrated that repeated inhalation exposure of young adult rats to > 900 ppm toluene can cause significant,

irreversible high frequency hearing loss in as little as 2 weeks. However, young adult rats exposed to 700 ppm, 14 h/d for 16 weeks did not have significantly affected hearing as assessed by CAR (Pryor *et al*, 1983a,b; 1984a,b, 1987). Other studies in weanling rats indicated that they were more severely effected than young adult rats under the same conditions of inhalation exposure to toluene (Pryor *et al*, 1984a).

The effects of toluene on operant behaviour were studied using the Sidman avoidance test, with weekly measurements conducted immediately following exposures. Rats were exposed to either 0, 800 or 2,000 ppm 7 h/d, 5 d/wk (+ 3 h/d, 1 d/wk) for 12 weeks (Shigeta *et al*, 1978). Slight changes in behavioural patterns were observed after 4 weeks exposure to 2,000 ppm, but there was no effect on behaviour at 800 ppm.

Behavioural performance and extinction of a conditioned response were evaluated in rats exposed to 0 or 2,000 ppm toluene 8 h/d for 52 days (Maeda, 1970). The exposed group was more excitable than controls, but there was no effect on learning performance. However, extinction of the conditioned response was significantly worse in the exposed group.

Ikeda and Miyake (1978) exposed rats to 4,000 ppm toluene, 2 h/d for 60 days. Animals for the study were selected on the basis of their performance in a battery of behavioural tests: acquisition of the differential reinforcement of low rate of responding (DRL 12sec) schedule, memory (in the continuous reinforcement (CRF) schedule), and extinction of the fixed ratio 30 (FR30) schedule; and also and "emotionality". There were no effects on the CRF schedule, FR30 schedule, activity and emotionality. DRL 12sec schedule was impaired, and impaired acquisition was still apparent 80 days after termination of exposure.

The effects of toluene exposure on the circadian rhythm was studied in rats by exposing them to 1,000 ppm, 6 h/d, 6 d/wk for 4 weeks (no control group). There was a disturbance characterised by a significant increase in the activity during the light period (12 h light/dark periods). Thus repeated exposure to toluene appears to influence the circadian rhythm in rats (Ikeda *et al*, 1981).

A test battery of activity tests consisting of FR1, FR30, and DRL 12sec, wheel running activity, and an open field test was used to determine the effect of long term toluene exposure on learning behaviour (Miyake *et al*, 1983). Rats were exposed by inhalation to 0, 1,000, 4,000, or 7,000 ppm toluene 1 h/d, 6 d/wk for 6.5 months with behavioural observations made during exposures and the testing battery was conducted following termination of the exposure period. Toluene had no effect on the activity test battery, except slow acquisition of the timing behaviour of the DRL 12sec schedule was revealed. The authors concluded, "It is not clear from our experiment whether this brain dysfunction is an irreversible behavioural effect". The effect of subacute inhalation exposure to toluene on the sleep

cycle and EEG was studied in rats exposed to 0 or 4,000 ppm, 4 h/d, 7 d/wk for 4 weeks (Hisanaga and Takeuchi, 1983). On completion of the exposure period, the percentage time awake increased significantly and the time in slow wave and paradoxical sleep decreased significantly. Some of the effects seen on the sleep cycle and CNS electrophysiology persisted for at least one exposure-free week.

Mice were exposed to 6,000 ppm toluene 30 min/d, 7 d/wk for 7 weeks to study the effect on operant behaviour (Moser and Balster, 1981). Activity remained low during the exposure phase of the study and no tolerance was evident. Three days after the last exposure, response rate and reinforcement rate had returned to baseline levels. This indicated that there was no residual or permanent effect of toluene.

Locomotor activity was not affected in rats following exposure to 4,000 ppm 2h/d,60 days (Ikeda and Miyake, 1978) or in mice exposed to 0, 100, 1,000, or 3,000 ppm toluene 5 h/d, 5 d/wk for 12 weeks (Bushnell *et al*, 1985). Reversible effects on locomotor activity occurred during the first 6 weeks of exposure to 900 or 2,400 ppm toluene (14h/d, 7d/w, 14 weeks) (Pryor *et al*, 1983a).

Pryor *et al* (1983a) conducted a study exposing weanling rats to 0, 900, or 1,400 ppm toluene 14 h/d, 7 d/wk for 14 weeks to determine cognitive deficits and high frequency hearing loss. Acquisition of the multisensory CAR was significantly impaired in the exposed groups, although this was probably due to hearing loss rather than a cognitive effect.

Ladefoged *et al* (1991) examined a number of behavioural endpoints in rats two months following exposure at 6h/d, 5d/w for 6 months. No effects on motor activity, passive avoidance, activity and motivation in a Morris water maze, or performance in a radial arm maze were observed. The authors concluded there was no evidence of overt neurotoxicity.

Neurophysiology

Naaslund (1985; 1986) exposed rats to 500 ppm toluene, at either 8 h/d or 16 h/d, 5 d/wk for 12 weeks in a study of the effects of toluene on EEG and neurochemical parameters. EEG measurements during the exposure phase were performed immediately before exposure after the 2 day weekend break, and were continued for a one month post exposure recovery phase. Exposure to 500 ppm caused an irreversible loss in the frequency of theta wave activity, first becoming significant in the 8 h/d group after 10 days exposure, and in the 16 h/d group after 40 days exposure. Qualitative changes in theta wave activity occurred as well. Frequency of theta wave activity did not increase during the one month postexposure recovery period. Minor changes in activity of some neurochemicals was shown for a couple regions of the brain, but permanent changes were not

demonstrated.

The effect of subacute inhalation exposure to toluene on the sleep cycle and EEG was studied in rats exposed to 0 or 4,000 ppm, 4 h/d, 7 d/wk for 4 weeks (Hisanaga and Takeuchi, 1983). On completion of the exposure period, the percentage time awake increased significantly and the time in slow wave and paradoxical sleep decreased significantly. Some of the effects seen on the sleep cycle and CNS electrophysiology (Ponecorvo *et al*, 1985) did not alter matching accuracy or reaction time, but did produce a trend towards reduced accuracy in the sensory-motor task.

Neurophysiological effects (brain flash evoked potentials, FEP; pentylene-tetrazol induced seizures, PTZ) were measured following the exposure phase, in which rats were exposed to 0 or 1,000 ppm toluene 6 h/d, 5 d/wk for 30 days (Dyer *et al*, 1984). Toluene had no effect on the FEP for the first of paired flashes, but there was an altered recoverability of the nervous system demonstrated by significant latency shifts in the response to the second of the paired flashes. FEPs were determined 18 hours after the last toluene exposure. There was no significant effect on PTZ induced seizures.

In the studies of Pryor and coworkers (Pryor *et al*, 1983a,b, 1984a,b, 1987; Rebert *et al*, 1983) brain stem evoked auditory potentials were recorded and produced evidence of high frequency hearing loss following repeated exposures to concentrations of 900 ppm and above. No effects were seen at 700 ppm (16 w, 14h/d, 5d/w).

Following 13 weeks exposure at 8,000 ppm toluene vapour in an "abuse" paradigm (multiple, short [15-25 minute] exposures) clear effects on evoked potentials, particularly brainstem auditory evoked potentials, were observed (Mattsson *et al*, 1989c).

Neuropathology

No changes in brain tissue were observed after exposure using histological (Ikeda and Miyake, 1978; Miyake *et al*, 1983; Stumph *et al*, 1985; Huff, 1980; Ladefoged *et al*, 1991) or electron microscopic (Alho *et al*, 1986) techniques. Likewise there were no observed effects on the peripheral nervous system (API, 1980; Lewis and Holligsworth, 1982) following toluene exposure.

A specific neuropathological examination was performed on rats following 13 weeks exposure in an "abuse" paradigm (Mattsson *et al*, 1989c). No changes were detected.

Histolopathological evidence of cochlear abnormalities was seen in rats that had been exposed as weanlings to 1,200 ppm toluene (5w, 14h/d) (Pryor *et al*, 1984a).

Neurochemistry

Male rabbits were exposed to toluene at 750 ppm 12 h/d for 7 days to determine whether brain dopamine was affected (Mutti *et al*, 1988); exposed animals were not significantly different from controls.

Male rats were exposed by inhalation to toluene at 0, 200, 400 or 800 ppm, 8 h/d for 30 days (Honma *et al*, 1983). After exposure ceased changes in dopamine, norepinephrine, serotonin, acetylcholine (ACH), cyclic AMP, cyclic GMP, GABA, glutamic acid, glutamine, aspartic acid, taurine, glycine, and alanine content of different areas of the brain were studied. ACH was reduced in a dose related manner in the striatum and in whole brain, reaching statistically significance for the 800 ppm exposure group. According to the authors, ACH is thought to regulate fine motor function, memory maintenance, sleep and other important brain functions. There were no other significant differences seen for the other neurotransmitters and amino acids measured.

Male Sprague-Dawley rats were exposed continuously to vapours of toluene at 0 or 320 ppm for 30 days (Kyrklund *et al*, 1987b). Following this subchronic exposure, different regions of the brains of the rats were examined for lipid contents and ethanolamine phosphoglyceride fatty acid patterns. Whole brain and cerebral cortex weight were reduced. Phospolipid concentrations were reduced in the cerebral cortex. There was no change in the fatty acid content of the cerebral cortex.

Norepinephrine (NE) and dopamine (DA) levels in male Wistar rat brain were looked at after exposure to 200 or 400 ppm toluene continuously for 30 days (Ikeda *et al*, 1986). In the rats exposed at 200 ppm, no significant change was observed in either NE or DA levels in any brain region. In the animals exposed to 400 ppm NE levels were reduced in the olfactory cortex and DA levels in the striatum.

Male, Sprague-Dawley rats were exposed to either 0 or 1,000 ppm toluene 8 h/d for 3 months to investigate the effect on catecholamine contents in sympathetic neurons using a formaldehyde-induced-fluorescence technique (Alho *et al*, 1986). No change in catecholamine level could be shown in either sympathetic ganglion or adrenal medulla.

In the study by Ladefoged *et al* (1991) irreversible changes in regional amine content was seen following exposure at 500 or 1,500 ppm, 6h/d, 5d/w for 6 months which were unaccompanied by effects on behaviour or neuropathology.

TABLE K-1. REPEATED (SUBCHRONIC AND CHRONIC) INHALATION EXPOSURE USING TOLUENE OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	100 ppm 300 ppm 1,000 ppm	13w (5d/w, 6h/d)	) Only significant effect reduced final body weight for 1,000 ppm males group.))	Rhudy *et al* (1978)
Rat	100 ppm 1,500 ppm 2,000 ppm	26w (5d/w, 6h/d) 26w (5d/w, 6h/d) 26w (7d/w, 6h/d)	) No effects reported.)) When examined one week after 8, 17 or 26 weeks exposure, or a 2 week post-exposure reversibility phase, no histopathological effects were seen in CNS or PNS tissues examined. All rats showed in-coordination and some showed laboured breathing, dry tales, excessive salivation, and ano-genital fur staining.	API (1980); Lewis and Holdsworth (1982)
Rat	500 ppm 500 ppm	12w (5d/w, 8h/d) 12w (5d/w, 16h/d)	) Irreversible loss in the frequency of theta wave activity (1 month recovery period).)	Naaslund (1985, 1986)
Rat	600 ppm 1,200 ppm	13w (5d/w, 6.5h/d)	) Degeneration (15 mo.) and erosion (2 yr.) of tissues of the nasal cavity. No) evidence of carcinogenicity. Histopathological examination of the brain showed) no effects.	Huff (1990)
Rat	500 ppm 1,500 ppm	6m (6h/d, 5d/w) 6m (6h/d, 5d/w)	) No treatment related effects on bodyweight, passive avoidance acivity and) motivation in a Morris Maze, or performance in a radial arm maze. No loss of) cerebral cortical neurones. Increase in perikaryal and nuclear size at 500 ppm.) Irreversible changes in regional amine content.	Ladefoged *et al* (1991)
Rat (male)	800 ppm 2,000 ppm	12w (5d/w, 7h/d) + 12w (1d/w, 3h/d) 12w (5d/w, 7h/d) + 12w (1d/w, 3h/d)	No effect on behaviour. Slight changes in behaviour patterns after 4 weeks exposure, apparently caused by individual differences in sensitivity.	Shigeta *et al* (1978)
Rat (male)	1,000 ppm	13w (7d/w, 8h/d)	No effects on psychomotor performance (rotorod, tilting plane), haematology or clinical chemistry. Only 5-8 rats/group.	Tahti *et al* (1983)
Mouse	100 ppm 1,000 ppm 3,000 ppm	12w (5d/w, 5h/d)	CO_2 production significantly reduced only at week 1; locomotor activity not affected.	Bushnell *et al* (1985)
Mouse	120 ppm 600 ppm 1,200 ppm	103w (5d/w, 6.5h/d)	No toxic effects. No evidence of carcinogenicity. Histopathological examination of the brain showed no effects.	Huff (1990)
Pigeon	100 ppm 1,000 ppm 3,000 ppm	13w (5d/w,6h/d)	) No adverse effects on delayed match to sample test for working memory.) Reduced accuracy and increased response times in delayed match to sample test. Effects persisted for several days after exposure terminatioon.	Ponecorvo *et al*, 1985

TABLE K-2. OTHER RELEVANT STUDIES USING TOLUENE

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	2,000 ppm	52d (8h/d)	No effect on learning performance. Extinction of conditioned response significantly worse as compared to controls.	Maeda (1970)
Rat	Inhalation	4,000 ppm	60d (2h/d)	Acquisition was impaired during exposure phase and even 80 d. after termination of exposure. Other behavioural parameters were uneffected; no microscopic lesions were observed in brain sections.	Ikeda *et al* (1978)
Rat	Inhalation	1,000 ppm	4w (6d/w, 6h/d)	Functional disturbance of the circadian rhythm after repeated exposure.	Ikeda *et al* (1981)
Rat	Inhalation	4,000 ppm	4w (7d/w, 4h/d)	Effects on the sleep cycle and CNS electro-physiology. Some effects persisted for at least one-week after last exposure.	Hisanaga & Takeuchi (1983)
Rat	Inhalation	200 ppm 400 ppm 800 ppm	30d (8h/d)	) Brain acetylcholine levels decreased in a dose related fashion;) statistically significant at 800ppm.)	Honma *et al* (1983)
Rat	Inhalation	1,000 ppm 4,000 ppm 7,000 ppm	154d (6d/w, 1h/d)	) During recovery phase acquisitioin of timing behaviour was slowed :) not clear if this is an irreversible effect. No lesions were observed in) histology of CNS.	Miyake *et al* (1983)
Rat	Inhalation	900 ppm 1,400 ppm	14w (7d/w, 14h/d)	) Altered motor activity and acquisition of a conditioned avoidance) response, thus limited evidence of a CNS effect	Pryor *et al* (1983a)
Rat	Inhalation	1,200 ppm 1,400 ppm	5w (7d/w, 14h/d) 5w (7d/w, 14h/d)	) High frequency hearing loss demonstrated by performance in) condition-avoidance task.	Pryor *et al* (1983b)
Rat	Inhalation	1,200 ppm 1,400ppm	5w (7d/w, 14h/d) 5w (7d/w, 14h/d)	) High frequency hearing loss demonstrated by electrophysiological) abnormalities.	Rebert *et al* (1983a)
Rat	Inhalation	1,000 ppm	6w (5d/w, 6h/d)	Residual dysfunction resulting in an altered recovery of the CNS, as determined by brain flash evoked potentials.	Dyer *et al* (1984)
Rat	Inhalation	1,000 ppm 400 ppm 700 ppm 1,500 ppm 2,000 ppm 2,000 ppm 4,000 ppm 3,000 ppm 3,000 ppm	2w (7d/w, 14h/d) 16w (7d/w, 14h/d) 16w (7d/w, 14h/d) 3d (14h/d) 3d (14h/d) 1d (8h/d) 1d (8h/d) 2w (intermittent, 30m/h for 8h) 9w (intermittent, 30m/h for 8h)	High frequency hearing loss.) No evidence of ototoxicity.)) High frequency hearing loss.)) No evidence of ototoxicity.) High frequency hearing loss. No evidence of ototoxicity.	Pryor *et al* (1984b)

TABLE K-2. OTHER RELEVANT STUDIES USING TOLUENE

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	1,000 ppm	3m (7d/w, 8h/d)	No statistically significant effect on catecholamine levels of sympathetic neurons.	Alho *et al* (1986)
Rat	Inhalation	200 ppm 400 ppm	30d (24h/d)	No effect on dopamine (DA) or noradrenaline (NA) in any region of the brain. NA levels reduced in olfactory cortex and DA levels in striatum.	Ikeda *et al* (1986)
Rat	Inhalation	320 ppm	30d (24h/d)	Brain and cerebral cortex weights reduced. Phospholipid concentrations were reduced in the cerebral cortex.	Kyrkland *et al* (1987b)
Rat	Inhalation	8,000 ppm	single	Effects on evoked potentials and EEG.	Mattsson *et al* (1989b)
Rat	Inhalation	8,000 ppm	multiple 15-25min exposures over 13w, abuse paradigm	Decreased bodyweight. Effects on visual, auditory and somatosensory evoked potentials.	Mattsson *et al* (1989c)
Rat (male)	Inhalation	1,200 ppm	8w (5d/w) (7 consecutive cycles of 10 min. exposure followed by 20 min. air)	Increased susceptibility to infection. Reduced bodyweight. Serum AST significantly elevated. Kidney, lung, liver and brain weights were lower, but organ/bodyweight were increased. No treatment related histopathological changes.	Bruckner & Peterson (1978, 1981)
Rat (male)	Inhalation	2,500 ppm	Up to 3w (5d/w, 3h/d)	Mean body weight significantly reduced; no effect on brain weight. Behavioural changes during exposures, which were reversible within 30 min. of exposure cessation. Blood triglyceride levels were lower after 1 and 2 weeks, but no effect at 1 day and 3 weeks.	Stumph *et al* (1985)
Mouse	Inhalation	6,000 ppm	7w (7d/w, 0.5h/d)	Behavioural activity affected, however, no evidence of tolerance or residual effects.	Moser and Balster (1981)
Rabbit	Inhalation	750 ppm	7d (12h/d)	No effect on brain dopamine.	Mutti *et al* (1988)

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APPENDIX L: TRICHLOROETHYLENE

ANIMAL NEUROTOXICTY DATA

Appendix L. TRICHLOROETHYLENE

The toxicity, including neurotoxicity, of trichloroethylene has been reviewed by Defalque (1961), Waters *et al* (1977) and Annau (1981).

General Toxicity

Trichloroethylene is anaesthetic in high acute doses and has been used as an inhalation analgesic and anaesthetic. Clinical signs indicative of CNS depression have been observed in both acute and chronic studies which are quickly reversible if animals are removed from the exposure but lead to coma and death at high dose levels and/or prolonged exposure (ATDSR, 1989).

Behaviour

A variety of experimental models has been used in the study of trichloroethylene neurotoxicity and a variety of effects have been reported.

In rats, Grandjean (1960) found trichloroethylene had no effect on a conditioned food motivated response following acute exposure for 3 hours at 200 or 800 ppm whereas Kishi *et al* (1986) reported decreased performance in a similar task when animals were exposed to 250 - 4,000 ppm for 4 hours. In another acute study motor activity and swimming performance were decreased during and following exposures at dose levels of 400, 800 or 1,600 ppm for 5 or 6 hours (Grandjean, 1963). The effects reversed within 1 hour. However, in a drinking water study in which rats received an average daily load of 5.5 mg for 4 weeks and then 8.5 mg for an additional 2 weeks (separated by a 2-week interval) increased performance in a spatial navigational task was observed. No increase in performance was observed in rats exposed to an average daily load of 5.5 mg for 4 weeks only (Isaacson *et al*, 1990). Ataxia was noted during exposure to 4,000 ppm (Wilmer *et al*, 1992).

In subacute or chronic studies effects on swimming performance (Battig and Grandjean, 1963), escape response in a conditioned avoidance task (Goldberg *et al*, 1964a), social activity (Silverman and Williams, 1975), ambulation, preening and rearing behaviour in an open field (Savolainen *et al*, 1977b) and responding in a two-choice visual discrimination task (Kulig, 1987) have been reported when animals were examined either during or immediately following exposure. In all cases these effects were reversible within 2 weeks of terminating exposure. The reversibility of any effects in a short time following exposure is supported by the studies of Ikeda *et al* (1980) who saw no effects on a variety of spontaneous or learned behaviours when animals were examined 2 weeks after exposure and demonstrated very elegantly by Kulig (1987) who showed effects on a number of parameters during the exposure period and their reversal within 2 days of ending the exposures. At very high

dose levels (4,380 ppm, 4h/d, 5 d/w for 2 weeks or 8,000 ppm, 0.5h/d, 6 d/w for 80 days) an inability to learn or relearn avoidance tasks or fixed-ratio tasks has been reported (Goldberg *et al*, 1964a; Ikeda *et al*, 1980). In both of these studies acute, CNS depressant effects were observed during the exposures, and testing was performed at no longer than two weeks following exposures and so the reversibility of such effects is unknown.

In the mouse, the only behavioural effects which have been recorded are changes in motor activity occurring during single exposures (Kjellstrand *et al*, 1985).

Memory tests following trichloroethylene exposure have been conducted in the gerbil. Following continuous exposure at 320 ppm for 9 months no effects on spatial memory, tested in a radial arm maze, was observed (Kjellstrand *et al*, 1980) but when animals were observed following 71 or 106 days exposure at 150 ppm decreases in the correct number of arm choices and seeds eaten whilst in the maze were recorded (Kjellstrand *et al*, 1981). A further group of animals exposed at 150 ppm for 150 days and allowed to 'recover' for 40 days showed an increase in seeds eaten. In view of the results from the first study when no effects were observed after a much higher exposure then the latter 'effects' must be treated with some caution. The authors themselves suggest that the effects reflect changes in 'emotionality' rather than memory.

Neurophysiology

Peripheral nerve function was assessed electrophysiologically in rats after 18 weeks of exposure to 500, 1,000, or 1,500 ppm trichloroethylene for 16 h/d and 6 weeks post exposure (Kulig, 1987) and following 12 weeks of exposure, 12 h/d at 1,600 or 3,200 ppm (Rebert *et al*, 1991). No effects on nerve conduction velocity were observed. Rebert *et al* (1991) also examined a number of other electrophysiological parameters (auditory, visual and somatosensory evoked potentials) in the same animals. The only effect observed was on auditory evoked potentials indicating a high frequency hearing loss in the 3,200 ppm exposure group only. The effect was confirmed in a different strain of rat (Fischer 344, original study in Long-Evans rat) at exposure levels of 2,000 and 3,200 ppm for 2 weeks (Rebert *et al*, 1991). Changes in electophysiological parameters have also been observed during exposures at 2,000 or 4,000 ppm (Wilmer *et al*, 1992).

In an acute exposure study using intravenous injections 24-85 mg/kg of trichloroethylene in the rabbit changes in electroretinogram components were observed (Blain *et al*, 1990). The relevance of the finding to occupational exposures is unclear.

Neuropathology

In four studies which involved specific neuropathological examination different species as well as different exposure routes have been used. In the first report, dogs were exposed to concentrations varying from 500 to 3,000 ppm daily for 2-8 hours 5 d/w. At the highest exposure the animals showed signs of severe intoxication and pathological changes occurred which were most pronounced in the cerebellum which showed selective destruction of the Purkinje cell layer (Baker, 1958). In the second study, rabbits were treated acutely or chronically with intramuscular injections twice or three times a week. The animals did not develop neurologic deficits but were reported to have moderately diffuse neuronal damage in the majority of cranial nerve nuclei and the cerebellum. The similarity of the changes to artifactual ischaemic damage or encephalitis due to infection makes interpretation of the results difficult (Bartonicek and Brun, 1970).

In the third study gerbils were exposed continuously to 60 or 320 ppm for 3 months followed by 4 months 'recovery'. No light microscopic changes could be detected but ultrastructural examination of cerebellum revealed decreased amounts of microtubules and increased content of lysosomes and myelin bodies (Haglid *et al*, 1981). The relevance of such subtle changes in the absence of any behavioural effects or effects at the end of the exposure period must be questioned.

The fourth study showed a decreased amount of myelin in one layer of the hippocampus, the stratum lacunosum-moleculare, following exposure to a total load of 154 or 273 mg trichloroethylene in the drinking water for 4 or 6 weeks. At the higher dose level the effect was associated with an increased level of performance in a spatial learning task (Isaacson *et al*, 1990).

Neurochemistry

Biochemical studies to investigate the mechanism of neurotoxicity of trichloroethylene have been conducted in rats, mice and gerbils and a variety of effects have been reported.

Levels of gerbil brain total protein were unchanged after exposure at 50 - 320 ppm continuously for up to a year (Haglid *et al*, 1981; Kyrklund *et al*, 1983) but soluble protein levels were reported to be decreased in cerebral cortex, brainstem and hippocampus, to be increased or decreased in the cerebellar vermis and sensory-motor cortex, to be increased in frontal and visual cortex and to be unchanged in cerebellar hemispheres (Haglid *et al*, 1980, 1981; Kyrklund *et al*, 1983). Levels of S-100 protein, which is believed to indicate astrogliosis, have been reported to be increased in hippocampus, brainstem and anterior hemispheres of cerebellum but to be unchanged in posterior hemispheres of cerebellum and cerebellar vermis of the gerbil (Kyrklund *et al*, 1984b; Haglid *et al*, 1981). A variety of studies in which amino acids and neurotransmitter levels have been measured

have shown there to be no effects on taurine, aspartate, alanine, dopamine, noradrenaline or serotonin (Honma *et al*, 1980b; Briving *et al*, 1986); glutamate and glutamine/threonine/serine levels were reported to be decreased and glycine levels to be increased in the rat (Honma *et al*, 1980a) whereas these parameters were unchanged in the gerbil although glutathione levels were increased in hippocampus (Briving *et al*, 1986). However GABA and glutamate uptake was reported to be increased in cerebellar vermis but unchanged in hippocampus of gerbil (Briving *et al*, 1986).

Brain fatty acid, phosphatase and lipid levels have been variously, and conflictingly, reported to be affected following exposures lasting from 1 month (Kjellstrand *et al*, 1982; Kyrklund *et al*, 1983, 1984a, 1986). DNA content of brain has also been reported to be increased in the cerebellar vermis and sensory motor cortex (Haglid *et al*, 1981) but RNA content to be decreased (Savolainen *et al*, 1977b).

Many of the effects reported have been shown to occur immediately following exposure and in those studies where later time points have been examined most of them reverse within 30 days. In very few of the studies have any behavioural or neuropathological measures been undertaken and very few descriptions of clinical condition are reported. Thus the functional significance of any of these often very minor changes is unclear, as is the possibility that such changes may induce the types of memory loss or behavioural deficits reported in 'painters syndrome'.

TABLE L-1. REPEATED (SUBCHRONIC OR CHRONIC) INHALATION EXPOSURES USING TRICHLOROETHYLENE OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	400 ppm	10m (5d/w, 8h/d)	No general behavioural abnormalities recorded. No effect on body weight gain. Swimming performance was decreased and exploratory behaviour was increased. No effect on learning behaviour. All animals had recovered by 2 weeks after termination of exposure.	Batting and Grandjean (1963)
Rat	1,600 ppm 3,200 ppm	12w (6-7d/w, 12h/d) 12w (6-7d/w, 12h/d)	No effects on bodyweight or in an electrophysiological multisensory test battery. Electrophysiological changes indicative of high frequency hearing loss.	Rebert *et al* (1991)
Rat (male)	100 ppm 200 ppm 500 ppm 1,000 ppm 100 ppm	Approx. 5w (5d/w, 6-7h/d) 12½w (5dw, 6-7h/d)	) Reduction in total activity observed 5 minutes after exposure (from Day 1 at) 1,000ppm, from 1½ to 8½ weeks at lower doses).) Reduced social activity at all) dose levels immediately after exposure.)))	Silverman and Williams (1975)

TABLE L-2. OTHER RELEVANT STUDIES USING TRICHLOROETHYLENE.

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	200 ppm 800 ppm	3h/d	) No effect on a conditioned food motivated response conducted) immediately after exposure.	Grandjean (1960)
Rat	Inhalation	400 ppm 800 ppm 400 ppm 800 ppm 1,600 ppm	6h/d 5h/d	) Decreased swimming performance immediately after exposure,) recovered within 1 hour.) Motor activity decreased during and for 1 hour following exposure) (only significant at 1,600 ppm).)	Grandjean (1963)
Rat	Inhalation	200 ppm 560 ppm 1,568 ppm 4,380 ppm	2w (5d/w, 4h/d)	) Ataxia at dose levels of 1,568 and 4,380 ppm during first few days of) exposures which recovered despite further exposures. Decreased) bodyweight gain at 1,568 and 4,380 ppm. Inhibition of performance) in a conditioned-avoidance and/or escape response when) conducted immediately after exposure which recovered within 2 days) of termination of exposure. Decreased ability to learn avoidance) task at 4,380 ppm.	Goldberg *et al* (1964a)
Rat	Inhalation	125 ppm	5w (5d/w, 4h/d)	No effects on bodyweight. Effects on discrete avoidance behaviour during exposure which reversed within 2 weeks.	Goldberg *et al* (1964b)
Rat	Inhalation	699 ppm 34.5 ppm	6w (5d/w, 8h/d) 90d (7d/w, 24h/d)	No mortalities, signs of toxicity, or pathological lesions. No mortalities, signs of toxicity or pathological lesions.	Prendergast *et al* (1967)
Rat	Inhalation	1,800 ppm	Up to 6w (5-7d/w, 6h/d) Prior to and/or during mating & pregnancy)	No treatment related toxicity, no effects on body or organ weight.	Dorfmuller *et al* (1979)
Rat	Inhalation	2,600 ppm 5,000 ppm 8,000 ppm	80d (6d/w, 0.5h/d)	) No effects on bodyweight, spontaneous activity (activity wheel, open) field test) or retention of learned tasks, 2 weeks after exposure.) Decreased ability to relearn fixed-ratio task. No pathological) changes.	Ikeda *et al* (1980)
Rat	Inhalation	9,000 - 16,000 ppm Abuse pattern	1 d	Concentration of 14,000 ppm and above rapidly produced loss of righting reflex but recovered rapidly following cessation of exposure. No evidence of liver or kidney damage.	Utesch *et al* (1981)
Rat	Inhalation	150 ppm	30d (7d/w, 24h/d)	No mortalities. No effects on body weight but increased liver weight. No effects on brain weight or brain acid phosphatase.	Kjellstrand *et al* (1982)
Rat	Inhalation	250-4,000 ppm	4h	Performance in a signalled bar press shock avoidance task decreased during and for at least 2 hours following exposure.	Kishi *et al* (1986)
Rat	Inhalation	320 ppm	5d (24h/d) 30d (7d/w, 24h/d) 90d (7d/w, 24h/d)	) No effects on body or brain weight. No effects on lipid class) composition of brain or saturated fatty acid profile. Alterations of) brain ethanolamine phosphoglycerides during exposure which was) partially reversible in 30 day exposure free period.	Kyrklund *et al* (1986)

TABLE L-2. OTHER RELEVANT STUDIES USING TRICHLOROETHYLENE.

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	500 ppm 1,000 ppm 1,500 ppm	18w (5d/w, 16h/d)	) No effects on open field behaviour, gripstrength, coordinated) movement or peripheral nerve conduction velocity. Changes in) responding in a two-choice visual discrimination task during study) period, recovered within 2 days of termination of exposure.	Kulig (1987)
Rat	Inhalation	2,000 ppm 3,200 ppm	3w (7d/w,12h/d) 3w (7d/w,12h/d)	) Electrophysiological changes indicative of high frequency hearing) loss.	Rebert *et al* (1991)
Rat	Inhalation	2,000 ppm 4,000 ppm	4d (6h/d) 4d (6h/d)	) Changes in somatosensory and flash evoked potentials and EEG) during exposure. Ataxia at 4,000 ppm.	Wilmer *et al* (1992)
Rat (male)	Inhalation	200 ppm	4 - 5d (6h/d)	Increased ambulation, preening frequency and duration and rearing frequency 1 hour after exposure (reversible in 17 hours). No effects on brain protein content. Decreased brain RNA content.	Savolainen *et al* (1977b)
Rat (male)	Inhalation	200 ppm 400 ppm 800 ppm	1m (7d/w, 24h/d)	) Clinical condition not recorded. Minor changes in amino acid content) of mid-brain at 800 ppm when measured immediately after exposure.)	Honma *et al* (1980a)
Rat (male)	Inhalation	200 ppm 400 ppm 800 ppm	1m (7d/w, 24h/d)	) Clinical condition not reported. No significant effects on dopamine,) noradrenaline or 5HT content of brain. Reduction in striatal) acetylcholine content at 800 ppm when measured immediately after) exposure.	Honma *et al* (1980b)
Rat (male)	Inhalation	150 ppm	18h/d	No effects on calcium uptake of brain synaptosomes.	Edelfors & Ravn-Jonsen (1985)
Rat (female)	Inhalation	300 ppm	9d (days 6 - 15 of gestation) (7h/d)	Decreased bodyweight gain. No effects on food consumption or organ weight. Clinical condition not reported.	Schwetz *et al* (1975)
Rat (female)	Inhalation	300 ppm	4 or 24d (7d/w, 24h/d)	Slight decrease in regeneration of sciatic nerve 4 days following crush injury in rats exposed for 20 days prior to and 4 days following crush. No effect in animals only exposed post-crush. No effect on liver weight.	Kjellstrand *et al* (1987)
Rat	Oral	312 mg/l in drinking water. (Total dose = 825 mg in 61d)	61d (during mating, pregnancy & suckling).	No mortalities. No effects on bodyweight or food consumption. Decreased water consumption.	Noland-Gerbec *et al* (1986)
Rat	Oral (drinking water)	5.5 mg/d 5.5 mg/d plus 8.5 mg/d following 2 week exposure free period	4w (7d/w) 4w (7d/w) plus 2w(7d/w,12h/d))	No effects on performance in a spatial learning task but decreased myelin in one layer of hippocampus. Increased level of performance in a spatial learning task and decreased myelin in one layer of hippocampus.	Isaacson *et al* (1990)

TABLE L-2. OTHER RELEVANT STUDIES USING TRICHLOROETHYLENE.

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat (female)	Oral	1,000 kg/d	Up to 1y (5d/w)	No effects on brain or bodyweight. No signs of overt toxicity but decreased activity. Changes in phosphoinositides in brain from 2 hours after dosing.	Subramoniam *et al* (1989)
Mouse	Inhalation	300 ppm	9d (days 6-15 of gestation) (7h/d)	No effects on bodyweight or organ weights. Clinical condition not recorded.	Schwetz *et al* (1975)
Mouse	Inhalation	150 ppm	30d (7d/w, 24h/d)	No mortalities. Slight increase in bodyweight, increased liver weight (females only). No effect on brain weight. Small increase in brainstem acid phosphatase activity.	Kjellstrand *et al* (1982)
Mouse	Inhalation	380, 480, 570, 700, 900, 1,100, 1,200, 1,800, 2,300, 3,600 ppm	1h/d	) Changes in motor activity measured during exposure. High) concentrations (>900 ppm) caused initial) increases in activity. 700) ppm caused decreases in activity.	Kjellstrand *et al* (1985)
Mouse	Inhalation	150 ppm 300 ppm	4 or 24d (7d/w, 24h/d)	) Decreased regeneration of sciatic nerve 4 days following crush) injury. Animals exposed for 20 days prior to and/or 4 days following) crush. Increased liver weight.	Kjellstrand *et al* (1987)
Mouse	Oral	0.1-5.0 mg/ml in drinking water (app. 18-800 mg/kg/d)	4-6m	Decreased bodyweight gain at the highest dose, increased liver and kidney weights, changes in microsomal enzymes and changes in urine protein and ketone levels.	Tucker *et al* (1982)
Mouse	*In Vitro*	3 - 200 mmol		Inhibition of clonidine binding to adrenoceptors in cerebral cortex membranes.	Wikberg *et al* (1987)
Gerbil	Inhalation	320 ppm	2w (7d/w, 24h/d) 4w (7d/w, 24h/d) 8w (7d/w, 24h/d)	) No effects on body or brain weight or food consumption. Changes in) brain protein levels in various areas of the brain measured) immediately after exposure.	Haglid *et al* (1980)
Gerbil	Inhalation	320 ppm	9m (7d/w, 24h/d)	No effect on spatial memory (tested in a radial arm maze).	Kjellstrand *et al* (1980)
Gerbil	Inhalation	60 ppm 320 ppm	3m (7d/w, 24h/d) + 4 month 'recovery' period	) No effects on brain or bodyweight. No effects on brain total protein) levels. Changes in levels of soluble proteins, DNA and S-100) protein in various brain regions. No light microscopic changes.) Ultrastructure showed decreased amounts of microtubules and) increased content of lyposomes and myelin bodies.	Haglid *et al* (1981)
Gerbil	Inhalation	150 ppm	71d (7d/w, 24h/d) 106d (7d/w, 24h/d) 150d (7d/w, 24h/d)	) Fewer correct choices and fewer seeds eaten in 8 or 16 arm radial) arm maze when measured following 71 or 106 day exposure) periods. Animals exposed for 150 days and allowed to recover for) 40 days showed an increase in seeds eaten in the maze. Effects on) "emotionality" are hypothesised.	Kjellstrand *et al* (1981)
Gerbil	Inhalation	150 ppm	30d (7d/w, 24h/d)	No mortalities. No effects on body, liver or brain weights. Small increase in brainstem acid phosphatase activity.	Kjellstrand *et al* (1982)

TABLE L-2. OTHER RELEVANT STUDIES USING TRICHLOROETHYLENE.

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Gerbil	Inhalation	50 ppm 150 ppm	12m (7d/w, 24h/d)	) Clinical signs not reported. No effects on brain total protein,) phospholipids, cholesterol or plasmalogen. Cholesterol to) phospholipid ratio was decreased and changes in lipid and acyl) group.	Kyrklund *et al* (1983)
Gerbil	Inhalation	510 ppm 170 ppm	5m (7d/w, 8h/d) 5m (7d/w, 24h/d)	) Clinical signs not reported. No changes in cerebellar weight. Minor) changes in lipid composition or S-100 protein content of cerebellum.	Kyrklund *et al* (1984b)
Gerbil	Inhalation	50 ppm 150 ppm	12m (7d/w, 24h/d)	) Clinical signs not reported. No effects on body or brain weight.) Increased glutathione levels in hippocampus (150ppm) and) increased GABA and glutamate uptake in cerebellar dermis.	Briving *et al* (1986)
Guinea-pig	Inhalation	699 ppm 34.5 ppm	6w (5d/w, 8h/d) 90d (7d/w, 24h/d)	No mortalities, signs of toxicity or pathological lesions. As above.	Prendergast *et al* (1967)
Rabbit	Inhalation	699 ppm 34.5 ppm	6w (5d/w, 8h/d) 90d (7d/w, 24h/d)	No mortalities, signs of toxicity or pathological lesions. Decrease in bodyweight gain. No mortalities, signs of toxicity or pathology.	Prendergast *et al* (1967)
Rabbit	intra-muscular	2.92 g twice weekly 4.38 g three times weekly	41 to 247d 29d	No effect on bodyweight gain. Moderate neuropathological changes indicative of non-specific encephalitis. Decreased bodyweight and evidence of marked systemic toxicity. Mild neuropathological changes in the form of chronic ischaemic or toxic nerve cell damage.	Bartonicek & Brun (1970)
Rabbit	intravenous	24-85 mg/kg	Single exposure of three consecutive injections	Significant changes in components of electroretinogram.	Blain *et al* (1990)
Dog	Inhalation	30,000 ppm 500 - 3,000 ppm	single exposure 60 - 160 h of exposure (5d/w, 2 -8 h/d)	Unconsciousness and convulsion within 20 minutes. Death within 40 minutes. No neuropathological changes. Few clinical signs of toxicity below 3,000 ppm. At 3,000 ppm, tremors, ataxia, rigidity and convulsions which recovered within 5 minutes of cessation of exposure. Only 3 dogs survived the exposures. Pathological changes consisting of selective destruction of the Purkinje cell layer of the cerebellum.	Baker (1958)
Dog	Inhalation	699 ppm 34.5 ppm	6w (5d/w, 8h/d) 90d (7d/w, 24h/d)	Bodyweight loss. No mortalities, signs of toxicity or pathology. No mortalities, signs of toxicity or pathology.	Prendergast *et al* (1967)
Monkey	Inhalation	699 ppm 34.5 ppm	Dog	No mortalities, signs of toxicity or pathology. As above.	Prendergast *et al* (1988)

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APPENDIX M: WHITE SPIRIT

ANIMAL NEUROTOXICITY DATA

Appendix M. WHITE SPIRIT

White spirit is a generic name given to the commercially available solvents which are complex mixtures of predominantly C7-C12 hydrocarbons (paraffins, cycloparaffins, and aromatics) boiling in the range of 130-220^0 C. Examples of alternative names in general use are Stoddard Solvent, Mineral Turpentine, or Mineral Spirit. White Spirit typically have aromatic hydrocarbon contents of about 15-25% by volume, although in the past few years dearomatised white spirit (DAWS) have been introduced. These DAWS are solvents in which the aromatic components have been converted into cycloparaffins by catalytic hydrogenation. The DAWS solvents have aromatics contents below 0.5% by volume. Due to the variability in their composition there is no fixed conversion ratio from mg/m^3 to ppm and hence in the following paragraphs exposure concentrations are generally quoted as mg/m^3 unless the original authors reported their data in ppm.

General Toxicity

Rats, guinea pigs, rabbits, dogs, and monkeys were exposed to mineral spirit vapours (aromatic fraction between 13 and 19%) either continuously for 90 days, or repeatedly for 30 days (8h/d, 5d/w) to concentrations ranging from 114 to 1,353 mg/m^3 (Rector *et al*, 1966). None of the animals showed adverse effects during the in-life phase, except for the guinea pigs which had mortality rates from 27 to 79%. Haematological, biochemical, and pathologic (not stated whether nervous system tissue was examined) studies failed to reveal changes that could explain these deaths. The only other finding was that animals exposed continuously to 1,271 mg/m^3 had congested lungs.

Dogs exposed to 0, 84, 190, or 330 ppm vapours of Stoddard Solvent (6 h/d, 5 d/wk) for 13 weeks showed no deviance from controls for haematology, clinical chemistry or histopathology (Carpenter *et al*, 1975a).

Male rats exposed to the same regime showed slight pathological changes to the kidneys (Carpenter *et al*, 1975a). Distal tubular kidney disfunction in male rats chronically exposed to white spirit solvent was shown by Viau *et al* (1984). Phillips and Egan (1984) conducted a subchronic inhalation study exposing male and female Sprague-Dawley rats to either 0, 1,970, or 5,610 mg/m^3 dearomatised white spirit (DAWS) for up to 12 weeks. The most common finding was regenerative tubular epithelia and dilated tubules containing proteinaceous casts at the kidney corticomedullary junction.

C9 aromatic hydrocarbons can be a significant portion of regular white spirit, i.e., 10 - 15% by volume. Therefore, chronic inhalation toxicity of products such as high flash aromatic naphta (75% C9 isomers) can be of interest. Rats were exposed to to 0, 450, 900, or 1,800 mg/m^3 high flash aromatic solvent, 6 h/d, 5 d/wk for up to 12 months (Clark *et al*, 1989). The only observed effects

were increased liver and kidney weights seen in the high exposure males at 6 and 12 months and these were considered to be physiological adaptive responses, in the absence of histopathological changes.

Behaviour

Kulig (1989b, 1990) conducted acute and chronic inhalation neurotoxicity studies with white spirit, assessing in particular: visual discrimination performance, coordinated movement, spontaneous activity, grip strength, and peripheral nerve conduction time; and in the chronic study additionally evaluated food and water intake and neuropathology. A number of animals were also retained for a 3-week reversibility group. Male rats were exposed to either 0, 1,200, 2,400, or 4,800 mg/m^3 white spirit vapours. In the acute study, animals were exposed 8 h/d for 3 consecutive days with behavioural tests conducted immediately after exposures. In the chronic study, animals were exposed 8 h/d, 5 d/wk for 26 weeks with behavioural tests conducted weekly at least 10 hours after the last daily exposure (except week 17 when discrimination performance was assessed immediately post exposure). This study confirmed that white spirit exposure can cause transient behavioural effects following acute exposure, but no irreversible behavioural changes were demonstrated.

Male rats were exposed to 0, 101, 452, or 1,320 ppm C9 aromatic hydrocarbon vapours (which represent 10-15% by volume of white spirit) 6h/d, 5 d/wk for 13 weeks (API, 1988a). Neurotoxicity evaluations consisting of motor activity, startle response, forelimb and hindlimb grip strength, hindlimb splay distance, and thermal response were performed at 1, 2, and 3 months following initiation of exposures. No toxicologically significant effects were seen during the study other than body weight depression in the 1,320 ppm group. None of the specific neurobehavioural evaluations demonstrated signs of neurotoxicity that could be attributed to treatment.

Neurophysiology

Kulig (1989b) (see above) showed no effects on motor or sensory nerve conduction.

Neuropathology

Dogs exposed to 84, 190, or 330 ppm vapours of Stoddard Solvent (6 h/d, 5 d/wk) for 13 weeks were not different from controls with regard to haematology, clinical chemistry or histopathology (Carpenter *et al*, 1975a). Histopathological examination included sections from brain and sciatic nerve tissues.

Phillips and Egan (1984) conducted a subchronic inhalation study exposing male and female Sprague-Dawley rats to either 0, 1,970 (300 ppm), or 5,610 (900 ppm) mg/m^3 dearomatised white

spirit (DAWS) for up to 12 weeks. Brain weights were measured, and brain and cervical spinal cord were evaluated histopathologically. There were no effects reported for the nervous system tissues.

Kulig (1989b, 1990) conducted acute and chronic inhalation neurotoxicity studies with white spirit. Histopathological evaluation showed no compound-related changes in brain, spinal cord or sciatic nerve.

The chronic inhalation toxicity of products such as high flash aromatic naphta (75% C9 isomers) can be of interest. Rats were exposed to 0, 450, 900, or 1,800 mg/m^3 high flash aromatic solvent, 6 h/d, 5 d/wk for up to 12 months (Clark *et al*, 1989). Histopathological results for brain, spinal cord, sciatic nerve and posterior tibial nerve were not different from controls.

Male rats were exposed to 0, 101, 452, or 1,320 ppm C9 aromatic hydrocarbon vapours 6 h/d, 5 d/wk for 13 weeks (API, 1988b) in another study. Histopathologic examination following the last exposure was conducted on these nervous system tissues: sections of brain, spinal cord, L3 and L4 dorsal root ganglia, and sciatic and tibial peripheral nerves. In addition, teased nerve fibers from the lower tibial and sural nerves were examined. There were no exposure-related neuropathologic lesions or degenerative changes seen in any of the examined nervous system tissues.

Neurochemistry

No studies examining neurochemistry were found.

TABLE M-1. REPEATED (SUBCHRONIC AND CHRONIC) INHALATION EXPOSURE USING WHITE SPIRIT OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	84 ppm 190 ppm 330 ppm	13w (5d/w, 6h/d)	) Slight pathological changes to the kidneys. No effect seen in histopathological) examination of brain and sciatic nerve.)	Carpenter *et al* (1975a)
Rat	1,970 mg/m^3 (300 ppm) 5,610 mg/m^3 (900 ppm)	12 (5d/w, 6h/d)	) Mild male rat tubular nephrotoxocity. No effects on brain weights, or in) histopathological exam of brain and cervical spinal cord.))	Phillips & Egan (1984)
Rat	(high flash aromatic naphtha; 75% C^9 isomers) 90 ppm 180 ppm 360 ppm	12m (5d/w, 6h/d)	) Histopathological exam of brain, spinal cord, sciatic and tibial peripheral nerves) showed no effects. Also no effect on brain weights.))))	Clark *et al* (1989)
Rat (male)	6,500 mg/m^3 (1,200 ppm)	9 - 12 m (5d/w, 8h/d)	Distal tubular kidney dysfunction. Nervous system not examined.	Viau *et al* (1984)
Rat (male)	(C^9 aromatic hydrocarbons) 101 ppm 452 ppm 1,320 ppm	13m (5d/w, 6h/d)	) No demonstrable signs of neurotoxicity. Reversible, minimal toxicity (body weight) depression) was observed in the high concentration group.)))	API (1988a)
Rat (male)	(C^9 aromatic hydrocarbons) 101 ppm 452 ppm 1,320 ppm	13m (5d/w, 6h/d)	) No exposure related neuropathologic lesions in sections of brain, spinal cord, L3) and L4 dorsal root ganglia, and sciatic and tibial peripheral nerves.)))	API (1988b)
Rat (male)	1,200 mg/m^3 (200 ppm) 2,400 mg/m^3 (400 ppm) 4,800 mg/m^3 (800 ppm)	26 (5d/w, 8h/d)	) No effects on behavioural, or motor and peripheral nerve function. Microscopy) showed no exposure related changes in brain, spinal cord, sciatic nerve, or other) organs.)))	Kulig (1989b)
Dog	84 ppm 190 ppm 330 ppm	13w (5d/w, 6h/d)	) No significant differences compared to controls for haematology, clinical) chemistry, and histopathology (including sections from brain and sciatic nerve).)	Carpenter *et al* (1975a)

TABLE M-2. OTHER RELEVANT STUDIES USING WHITE SPIRIT

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	"various levels" 114 - 1,353 mg/m^3 (20 - 250 ppm)	30d (5d/w, 8h/d) or 90d (7d/w, 24h/d)	Gross observation of conjested lungs, substantiated by pathology in animals exposed continuously to 1,271 mg/m^3. Not clear if the nervous system tissues were examined.	Rector *et al* (1966)
Rat (male)	Inhalation	500 ppm	single exposure (18h)	Increased Ca-uptake in K stimulated synaptosomes; statistical significance not determined.	Edelfors & Ravn--Jonsen (1985)
Guinea pig	Inhalation	"various levels" 114 - 1,353 mg/m^3 (20 - 250 ppm)	30d (5d/w, 8h/d) or 90d (7d/w, 24h/d)	Animals exposed continuously for 90d showed mortality rates from 27 to 79%. Gross observation of conjested lungs confirmed by pathology in those animals exposed to 1,271 mg/m^3. Not clear if the nervous system tissues were examined.	Rector *et al* (1966)
Rabbit	Inhalation	"various levels" 114 - 1,353 mg/m^3 (20 - 250 ppm)	30d (5d/w, 8h/d) or 90d (7d/w, 24h/d)	Gross observation of conjested lungs, substantiated by pathology in animals exposed continuously to 1,271 mg/m^3. Not clear if the nervous system tissues were examined.	Rector *et al* (1966)
Dog	Inhalation	"various levels" 114 - 1,353 mg/m^3 (20 - 250 ppm)	"various levels" 114 - 1,353 mg/m^3 (20 - 250 ppm)	Gross observation of conjested lungs, substantiated by pathology in animals exposed continuously to 1,271 mg/m^3. Not clear if the nervous system tissues were examined.	Rector *et al* (1966)
Monkey	Inhalation	"various levels" 114 - 1,353 mg/m^3 (20 - 250 ppm)	"various levels" 114 - 1,353 mg/m^3 (20 - 250 ppm)	Gross observation of conjested lungs, substantiated by pathology in animals exposed continuously to 1,271 mg/m^3. Not clear if the nervous system tissues were examined.	Rector *et al* (1966)

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APPENDIX N: XYLENES

ANIMAL NEUROTOXICITY DATA

Appendix N. XYLENES

General Toxicity

In a US-NTP study (Hejtmancik *et al*, 1985) groups of male and female F-344 rats were administered mixed xylenes by oral gavage at dose levels of 0, 250, or 500 mg/kgbw/d, 5 d/wk for 103 weeks. Also groups of B6C3F1 mice were studied over the same time span, but at doses of 0, 500, or 1,000 mg/kgbw/d. It was reported that there was no evidence of systemic toxicity, except reduced body weights in the high dose groups of the 13 week studies.

Rats, guinea pigs, monkeys, and dogs were exposed to o-xylene at 0 ppm, or either 780 ppm 8 h/d, 5 d/wk for 30 days or 78 ppm continuously for 90 days (Jenkins *et al*, 1970). There were no significant changes in body weight or haematology data. The results of histopathological examination of the heart, lung, liver, spleen and kidney, and additionally (in monkeys and dogs) the brain and spinal cord, revealed no effects.

Groups of 25 male rats and 4 male dogs were exposed 6 h/d, 5 d/wk for (up to) 13 weeks to 0, 180, 460 and 810 ppm of mixed xylenes (Carpenter *et al*, 1975b). No significant effects were reported in body weight, haematology, blood chemistry, urinalysis, organ weights, or macroscopic and microscopic pathology of either species at any concentration tested.

Male rats were exposed to 0 or 3,500 ppm of o-xylene for 8 h/d for 6 weeks. A slight decrease in body weight gain was observed. Liver weight increased, but histology showed no evidence of liver pathology. Enzyme, histochemical and ultrastructural studies revealed slight hepato-cellular damage (Tatrai and Ungvary, 1980).

Rats were exposed to 690 ppm xylenes for up to 130 days, and rabbits to 1,200 ppm for up to 55 days (Fabre *et al*, 1960). In some animals the exposures caused paralysis of the hind legs and other signs of systemic toxicity, but because of a lack of experimental detail it is not possible to assess the significance of the findings in this study.

Behaviour

The effect of xylene on acquisition and extinction of an avoidance response was studied during exposure to 0 or 500 ppm xylene, 4 h/d, 5 d/wk for 3 weeks (Battig and Grandjean, 1964).

There were no effects on body weight gain or behaviour.

Neurophysiology

No studies examining neurophysiology were found.

Neuropathology

In the US-NTP study (Hetjtmancik *et al*, 1986) reported above the CNS was examined histopathologically at 2-3 sites in the highest dose groups tested with no adverse effects for rats or mice. Similarly no histopathological effects were seen in the brain and spinal cord of monkeys and dogs (Jenkins *et al*, 1970), or the brain and sciatic nerve of rats and dogs (Carpenter *et al*, 1975b).

Neurochemistry

Male Wistar rats were exposed to 0, 50, 400 or 750 ppm m-xylene 6 h/d, 5 d/wk for 2 weeks (Savolainen and Pfaffli, 1980b). Xylene concentrations were increased in brain during the second week of exposure in proportion to exposure concentrations. Statistically significant increases of brain NADPH-diaphorase and azoreductase activities were seen during week 2 at 400 and 750 ppm, while superoxide dismutase activity decreased in a dose-related fashion during the same time period. Cerebral glutathione concentration was decreased in all exposed animals. Biochemical analyses on rats after a 2 week recovery period indicated that neurochemical levels had returned to control value, but cerebral RNA was above the control value for the 2 higher exposure levels. The biological significance of these effects was not made clear by the authors. Male rabbits were exposed to xylene at 750 ppm 12 h/d for 7 days to determine whether brain dopamine was affected. No significant effects were observed (Mutti *et al*, 1988).

Inhalation exposure of male Sprague-Dawley rats 6 h/d for 3 days to 2,000 ppm of xylene, m-, o-, or p-xylene produced discrete increases of brain dopamine and noradrenaline levels and turnover in various parts of the hypothalamus and median eminence the day after the last exposure (Andersson *et al*, 1981). The authors suggested that the changes seen in dopamine and noradrenaline levels and turnover could "produce disturbances in catecholamine neurotransmission in the brain leading to disturbed brain function, e.g., in neuroendocrine, mental, and motor control". No overt behavioural signs were found during the experiments. It is not clear whether the relatively modest changes reported are in fact adverse effects; it is more likely that they are transient biochemical disturbances brought on by excessive exposure (2,000 ppm for 6 hr) to solvents.

Male Wistar rats exposed to 300 ppm xylene by inhalation, 6 h/d, 5 d/wk for 18 weeks showed a significant increase in cerebral microsomal superoxide dismutase activity (Savolainen *et al*, 1979). The was no effect on body weight gain, cerebral protein or RNA levels, acid proteinase, NADPH-

diaphorase, cytosolic glutathione peroxidase, or serum non specific cholinesterase activities.

Male rats were exposed by inhalation to xylene at 0, 200, 400 or 800 ppm continuously for 30 days (Honma *et al*, 1983). After exposure ceased changes in dopamine, norepinephrine, serotonin, acetylcholine (ACH), cyclic AMP, cyclic GMP, GABA, glutamic acid, glutamine, aspartic acid, taurine, glycine, and alanine content of different areas of the brain were studied. ACH was reduced in 400 and 800 ppm groups in the striatum, reaching statistically significance for the 800 ppm exposure group. ACH in the 200 ppm exposure group was actually slightly increased. According to the authors, ACH is thought to regulate fine motor function, memory maintenance, sleep and other important brain functions. Interestingly, in comparison to Andersson *et al* (1981) dopamine levels were unaffected.

Male Sprague-Dawley rats were exposed continuously to vapours of xylene at 0 or 320 ppm for either 30 or 90 days (Kyrklund *et al*, 1987b). Following these subchronic exposures, different regions of the brains of the rats were examined for lipid contents and ethanolamine phosphoglyceride fatty acid patterns. The group exposed for 30 days showed limited, transient changes consisting of an increase in the liver to body weight ratio and a decrease in linoleic acid of ethanolamine phosphoglyceride in the cerebral cortex. These minor changes were normalised for the group examined after 90 days exposure.

Male Wistar rats were exposed for 18 hours to an atmosphere of 500 ppm xylene (Edelfors and Ravn-Jonsen, 1985). Brain synaptosome preparations were obtained from exposed and control animals. Calcium uptake was measured in the synaptosomes using unstimulated or potassium stimulated preparations. In the potassium stimulated experiment there was an increased Ca-uptake, although statistical significance was not determined. The authors speculated that "an adaptation to a constantly high calcium uptake might account for the long-term toxicity of solvents". However, the authors failed to consider that the effect seen was not statistically significant even at an exposure concentration 5X the Danish OEL and with an 18 hour continuous exposure.

Female NMRI-BOM mice were exposed by inhalation 4 h/d, 5 d/wk for 7 weeks to 0 or 1,600 ppm m-xylene (Rank, 1985). The objective of the experiment was to determine whether there is a correlation between increased feeding and drinking response and alterations in α-adrenegic receptor binding in hypothalamus from m-xylene exposed mice. Food and water consumption were measured during 3 time intervals: during the 4 hour exposures, between the exposure periods, and on the weekends. Brains were taken from from all animals 20 hours after the last exposure, separated into the 4 parts to be investigated and were prepared for the 3^{H}-clonidine binding assay. The results showed that the binding was significantly decreased in the region of the hypothalamus, but unchanged in the other brain regions studied, i.e., diencephalon, cortex, and cerebellum. The induced eating and drinking

response observed in the m-xylene exposed animals as compared to controls led the author to hypothesize that there is a connection between this behaviour and the decrease in α-receptor binding in the hypothalamic region, however there was no statistical evidence that this was a direct or significant relationship.

Four male and 4 female gerbils per group were exposed to 0, 160, or 320 ppm xylene continuously (24 h/d, 7 d/wk) for 3 months (Rosengren *et al*, 1986a). A 4 month period of non-exposure followed, at the conclusion of which neurotoxicity was evaluated using 2 astroglial cell marker proteins and DNA. At the 3 and 7 month time points there were no deaths or significant differences in body weights or brain weights between control and exposed animals. At 7 months all animals were sacrificed for evaluation of selected brain neurochemicals. At 320 ppm there was a significant increase of measured glial fibrillary acidic (GFA) protein in the anterior cerebellar vermis, posterior cerebellar vermis and the frontal cerebral cortex; a significant increase of S-100 protein in the frontal cerebral cortex; and a significant increase of DNA in the posterior cerebellar vermis. No significant effects were seen in other areas of the brain. At 160 ppm there was a significant increase of measured glial fibrillary acidic (GFA) protein in the anterior cerebellar vermis, and a significant increase of DNA in the posterior cerebellar vermis. Although effects were seen in specific areas of the brain at 160 and 320 ppm, the only significant overall effect was the increased GFA determined at 320 ppm.

TABLE N-1. REPEATED (SUBCHRONIC AND CHRONIC) INHALATION EXPOSURE USING XYLENES OF RELEVANCE TO OCCUPATIONAL EXPOSURE

Species	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	180 ppm 460 ppm 810 ppm	13w (5d/w, 6h/d)	) No significant effects in body weight, haematology, blood chemistry, urinalysis,) organ weights, or macroscopic and microscopic pathology (including brain).)	Carpenter *et al* (1975b)
Rat	690 ppm	110-130d (6d/w, 8h/d)	Paralysis of hind legs. Other signs of toxicity observed, but no CNS neurotoxicity reported.	Fabre *et al* (1960)
Rat (male)	300 ppm	5-18w (5d/w, 6h/d)	Of a number of neurochemicals studied, only cerebral microsome superoxide dismutase activity was significantly increased by week 18.	Savolainen *et al* (1979)
Dog	180 ppm 460 ppm 810 ppm	13w (5d/w, 6h/d)	) No significant effects on body weight, haematology, blood biochemistry, urine) analysis, organs weights, or macroscopic and microscopic pathology (including) brain).	Carpenter *et al* (1975b)

TABLE N-2. OTHER RELEVANT STUDIES USING XYLENES

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Rat	Inhalation	78 ppm or 780 ppm	90d (continuous) 6w (5d/w, 8h/d)	) Results of histopathological exam of major organs, "essentially) negative".)	Jenkins *et al* (1970)
Rat	Inhalation	3,500 ppm	6w (7d/w, 8h/d)	Only investigated liver effects.	Tatrai and Ungvary (1980)
Rat	oral	250 mg/kgbw/d 500 mg/kgbw/d	103w (5d/w)	No evidence of systemic toxicity. No evidence of systemic toxicity or CNS damage.	Hejtmancik *et al* (1986)
Rat (male)	Inhalation	500 ppm	3w (5d/w, 4h/d)	No behavioural abnormalities. No effect on learning or performance.	Battig and Grandjean (1964)
Rat (male)	Inhalation (m-xyl)	50 ppm 400 ppm 750 ppm	2w (5d/w, 6h/d)	) Statistically significant changes in some neurochemicals; biological) significance unexplained.)	Savolainen and Pfäffli (1980b)
Rat (male)	Inhalation	2,000 ppm (0-,m-,p-xylene or xylenes)	3d (6h/d)	Produced discrete increases of dopamine and noradrenaline levels and turnover in various parts of the brain.	Andersson *et al* (1981)
Rat (male)	Inhalation	200 ppm 400 ppm 800 ppm	30d (7d/w, 24h/d)	No effect. No effect Acetylcholine decreased to statistically significant level in brain.	Honma *et al* (1983)
Rat (male)	Inhalation	500 ppm	single exposure (18h)	Increased Ca-uptake in k stimulated synaptosomes, but statistical significance not determined.	Edelfors and Ravn-Jonsen (1985)
Rat (male)	Inhalation	320 ppm 320 ppm	30d (7d/w, 24h/d) 90d (7d/w, 24h/d)	Minor, transient change, liver/body weight increased and fatty acid decrease in brain. Changes observed at 30d normalised.	Kyrklund *et al* (1987)
Rat (male)	Inhalation (p-xyl)	50 ppm 100 ppm 200 ppm 400 ppm 800 ppm 1,600 ppm	single expos (4h) single expos (4h) single expos (4h) single expos for ½, 1, 2, 4, 8h single expos (4h) single expos (4h)	) Inhalation of p-xylene at all concentrations caused a significant,) learned change in rats normal consumption of saccharin-flavoured) water, without affecting total fluid intake. Respiratory tract irritation,) rather than CNS dysfunction considered to be the likely cause of) conditioned flavour aversion.))	Bushnell and Peele (1988)
Mouse	Oral	500 mgkgbw/d 1,000 mg/kgbw/d	103w (5d/w)	No evidence of systemic toxicity No evidence of systemic toxicity or CNS damage.	Hejtmancik *et al* (1986)

TABLE N-2. OTHER RELEVANT STUDIES USING XYLENES

Species	Exposure route	Concentration or dose	Duration (days/weeks/ months/years)	Observations and remarks	Reference
Mouse (female)	Inhalation	1,600 ppm (m-xylene)	7w (5d/w, 4h/d)	Binding of 3H-clonidine was significantly decreased in the hypothalamus, but unaltered in the diencephalon, cortex and cerebellum. During exposure, m-xylene exposed mice ate and drank more than controls.	Rank (1985)
Gerbil	Inhalation	160 ppm 320ppm	3m (7d/w,24h/d) +4m recovery period 3m (7d/w, 24h/d) +4m recovery period	No deaths or significant differences in body weights or brain weights. Significant increase of GFA protein in anterior cerebellar vermis, and DNA in posterior cerebellar vermis. No deaths or significant differences in body weights or brain weights. Significant increase of GFA protein in anterior and posterior cerebellar vermis, and frontal cerebral cortex (only significant overall brain response). Significant increase on DNA in posterior cerebellar vermis.	Rosengren *et al* (1986)
Guinea-pig	Inhalation	78 ppm or 780 ppm	90d continuous 6w (5d/w, 8h/d)	) Results of histopathological exam of major organs, "essentially) negative".)	Jenkins *et al* (1970)
Dog	Inhalation	78 ppm or 780 ppm	90d (continuous) 6w (5d/w, 8h/d)	) Results of histopathological examination of major organs, including) brain and spinal cord, essentially negative.)	Jenkins *et al* (1970)
Monkey	Inhalation	78 ppm or 780 ppm	90d (continuous) 6w (5d/w, 8h/d)	) Results of histopathological examination of major organs, including) brain and spinal chord, essentially negative.)	Jenkins *et al* (1970)

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APPENDIX O. GLOSSARY

Acute:

short duration effects.

Acute exposure;

short-term exposure usually at high exposure levels.

Chronic:

long duration effects.

Chronic exposure:

long-term repeated exposure usually at low exposure levels.

Central Nervous System (CNS):

that part of the nervous system contained within the cranium and the vertebral column, i.e. the brain and the spinal cord.

Confounder:

variable factor which is of relevance to the endpoint under consideration.

Chronic Neurotoxicity:

neurotoxic (q.v.) effect which is present indefinitely or is irreversible.

Dementia:

progressive deficits in memory, cognitive function, mood and personality.

Encephalopathy:

a degenerative condition affecting the brain.

Maximale Arbeitzplatz Konzentration (MAK):

Maximum working place concentration.

Narcosis:

acute depression of the central nervous system inducing unconsciousness.

Narcotic:

a substance that suppress the function of the central nervous system and is capable of inducing unconsciousness.

Neuraesthenic syndrome:

"painter's syndrome.

Neurobehavioral:

behavioural systems controlled by the nervous system.

Neurological syndrome:

a collection of signs and symptoms associated with neurotoxicity.

Neurological dysfunction:

malfunctioning of the nervous system.

Neurological disorder:

change in personality due to altered function of the nervous system.

Neuronopathy:

degenerative process primarily affecting neurons.

Neurophysiology:

physiological (i.e. physical) functioning of the nervous system.

Neuropysychological:

q.v. neurobehavioural but applies to man.

Neurotoxicity:

adverse change in the structure or function of the nervous system.

Neurotoxin:

a substance which produces a neurotoxic effect.

Neurotoxic:

an adverse effect upon the structure and function of the nervous system.

Occupational Exposure Limit (OEL):

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.

Painters syndrome:

irreversible organic brain disease, characterised by personality change, impairment of memory, intellectual decline, causally related to long-term low-level exposure to organic solvents.

Pre-narcosis:

state of the CNS depression prior to unconsciousness.

Peripheral Nervous System (PNS):

that part of the nervous system outside the brain and the spinal cord, i.e. peripheral nerves and ganglia, including the autonomic nervous system.

(a) **Psycho-organic syndrome**:

study of psychiatric signs and symptoms associated with brain disease.

(the) **Psycho-organic syndrome**:

painters syndrome (q.v.).

Syndrome:

a collection of signs and symptoms.

Threshold limit values (TLV):

the level to which exposed workers may be exposed on a daily basis to airborne substances without adverse health effects.

Threshold Limit Value-Time Weighted Average (TLV-TWA):

time-weighted average concentration for a normal 8 hour work day and 40 hour work week, to which nearly all workers may be repeatedly exposed, day after day, without

adverse health effect.

Threshold Limit Value-Short Term Exposure Limit (TWA-STEL):

the concentration to which workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage or 3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue or materially reduce work efficiency, provided the daily TLV-TWA is not exceed. It is not a separate independent exposure limit; rather it supplements the time-weighted average (TWA) limit where there are recognised acute effects from a substance whose toxic effects are primarily of a chronic nature. STELs are recommended only where toxic effects have been reported from high short-term exposures in either humans or animals.

A STEL is defined as a 15-minute TWA exposure which should not be exceeded at any time during a working day even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than four times Per day. There should be at least 60 minutes between successive exposure in this range. An averaging period other than 15 minutes may be recommended when this is warranted by observed biological effects.

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