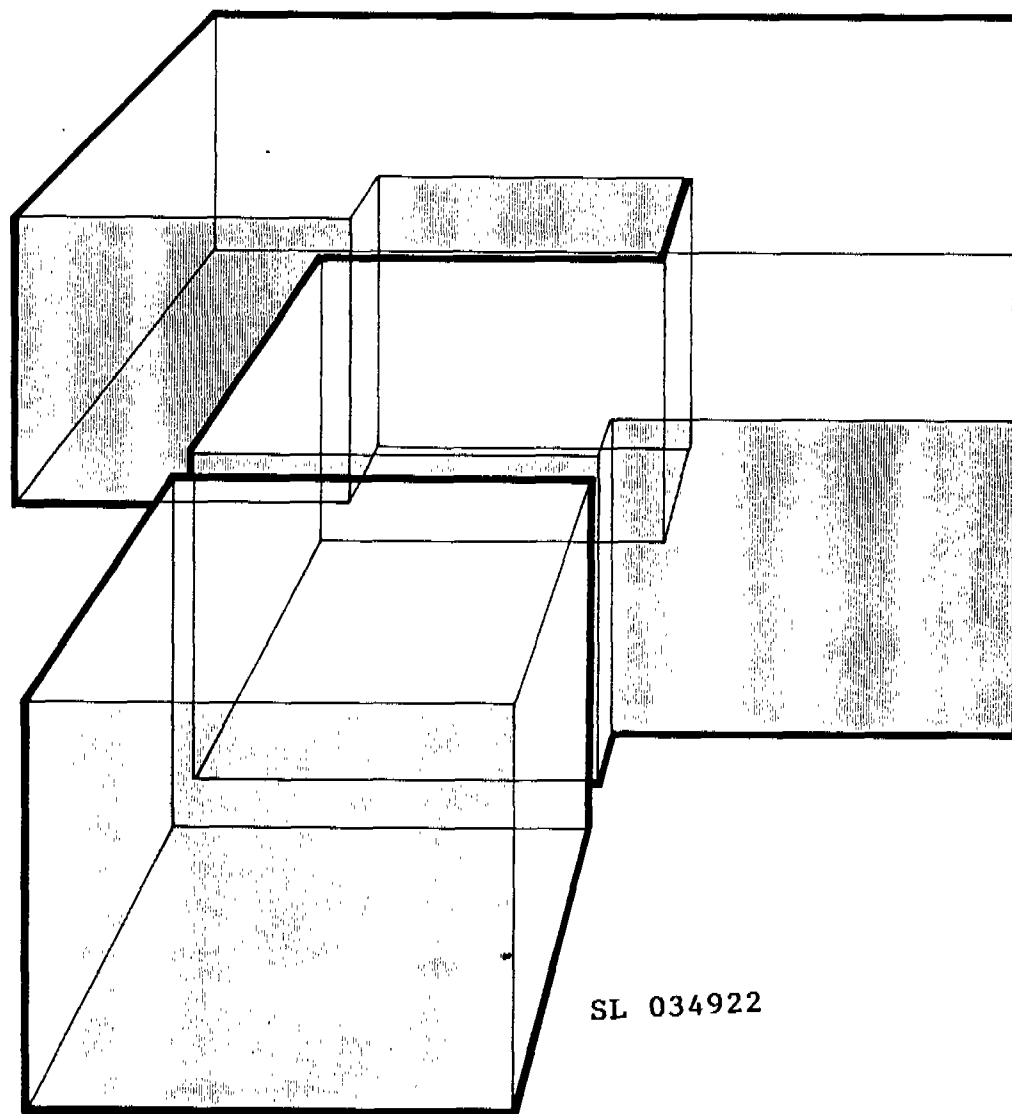


Toxicity review

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Trichloroethylene



SL 034922





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Toxicity review 6

Trichloroethylene

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These Toxicity Reviews set out the available scientific evidence on the biological impact of substances suspected of being hazardous to man. The papers have been prepared primarily for the Health and Safety Commission's Advisory Committee on Toxic Substances in order to assist its members in analysing the risks involved in working with such chemicals and in determining what controls of exposure may be appropriate. The Toxicity Reviews are critical summaries of the literature and, consequently, the opinions expressed in them are not necessarily those of the Health and Safety Executive. The Health and Safety Executive is publishing these papers in order to contribute information to scientific and public debate on the level of risk involved in exposure to such substances, on the acceptability of such risk and on the control measures that need to be adopted.

Titles already published

- TR1 Styrene
- TR2 Formaldehyde
- TR3 Carbon disulphide
- TR4 Benzene
- TR5 Pentachlorophenol

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Summary

Trichloroethylene is a colourless, volatile liquid. It is well absorbed orally and by inhalation and, from the limited data available, appears to be absorbed to some extent through the skin. The principal route of absorption in man is by inhalation. In man appreciable amounts (about 25%) of the absorbed material are excreted unchanged in the breath, but the majority is metabolised to trichloroacetic acid and trichloroethanol which are excreted predominantly unchanged (trichloroacetic acid) or as the glucuronide conjugate (trichloroethanol) in the urine. A similar metabolic profile has been shown in a number of animal species.

Toxicity to animals

Trichloroethylene has low acute toxicity to animals. Exposure of rats or mice to concentrations of the order of 10 000 ppm for four hours resulted in the death of 50% of the animals. The corresponding figure for a single oral dose was about 5 g/kg. In inhalation studies full anaesthesia was produced at concentrations of about 5000 ppm and above.

Trichloroethylene has also been shown to have low toxicity on repeated exposure. Inhalation studies, of up to seven months duration, have been carried out in a range of species. Some evidence of mild liver damage has occasionally been noted at concentrations of about 400–500 ppm and more frequently at near lethal concentrations (about 3000 ppm). Signs of disturbances in the central nervous system (CNS) were usually apparent at about 1000 ppm.

The mutagenicity of trichloroethylene has been investigated in a number of short-term tests. Positive results were obtained when trichloroethylene was tested using certain microorganisms (yeasts), indicating that the compound can produce point mutations. Positive results were also obtained when trichloroethylene was investigated using the micronucleus test, suggesting that the compound can produce chromosome abnormalities.

A number of long-term animal studies have been carried out to investigate the carcinogenicity of trichloroethylene, using both the inhalation and the oral route. No evidence of any significant carcinogenic effect was noted in the studies in rat and hamster. However the standard of this work was inadequate to base any conclusions on the negative result obtained. Technical trichloroethylene has been shown to be carcinogenic in mice when given orally, at high dose levels (1 g/kg and above); hepatocellular carcinoma was produced. The trichloroethylene used in these studies contained about 3000 ppm of epoxide stabilisers (epoxybutane and epichlorohydrin). These compounds are mutagenic and may have affected the results in the long-term animal studies, at the very high concentrations of trichloroethylene used.

No evidence of any teratogenic effects were noted when pregnant rats or mice were exposed to trichloroethylene by inhalation. Some fetotoxic effects, indicative of delayed development, were noted in rats, but only at a relatively high concentration (1800 ppm).

Toxicity to man

The principal effect after acute exposure to trichloroethylene is depression of the CNS, exposure to high concentrations (about 5000 ppm and above) producing narcosis and, in extreme cases, coma and death. Recovery from narcosis is usually uneventful, with no serious sequelae, and the compound has been used as an anaesthetic for short operations. Exposure of volunteers to 500–1000 ppm trichloroethylene under controlled conditions, resulted in some symptoms of CNS disturbance (dizziness, lightheadedness, lethargy) and some impairment in performance of a number of behavioural tests designed to measure visual-motor response. No signs of toxicity, nor any impairment in performance, were in general noted in subjects exposed to 300 ppm or less trichloroethylene.

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The most prevalent toxic effect noted in surveys of workers occupationally exposed to trichloroethylene involves the CNS. Symptoms of CNS disturbance (fatigue, headaches, dizziness, inability to concentrate) have frequently been noted in workers exposed to average levels of trichloroethylene estimated to be about 100–200 ppm. However these may have been due predominantly to excursions above the mean value as no symptoms were noted in volunteers repeatedly exposed to 100 ppm of trichloroethylene under controlled conditions. Furthermore no abnormalities in the electroencephalograph tracings were noted in such individuals. More severe 'pre-narcotic' symptoms (feelings of inebriation, visual disturbances) occurred in workers exposed to mean trichloroethylene levels of 200–300 ppm. Intolerance to alcohol (manifested by transient redness of the face and neck — ('trichloroethylene flush') and some impairment of performance in behavioural tests was noted at this level (but not at 100 ppm). There are limited data from audiometric tests to suggest that prolonged exposure to a level which produces toxic symptoms may also result in hearing defects. No significant adverse haematological effects were noted in surveys of workers exposed to mean trichloroethylene levels of up to about 300 ppm, but there was some evidence of mild liver dysfunction occurring in workers exposed to about 250 ppm and above.

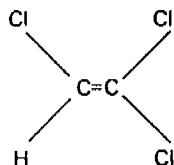
Experience in the use of trichloroethylene as an anaesthetic has shown that potentially serious ventricular arrhythmias may occur during anaesthesia, although cardiac arrest is rare. A number of studies have been carried out to investigate the effect of occupational exposure to trichloroethylene on the cardiovascular system, especially heart rhythm. The value of this work was in general very limited both by the lack of details regarding exposure levels, and the failure to use an adequate control group. There was some evidence, based on a very small number of subjects, that exposure to trichloroethylene levels of about 100 ppm produced ventricular arrhythmias in a small number of exposed persons. However insufficient data are available to assess the significance of this observation.

There is no evidence to suggest that exposure to trichloroethylene is associated with an increased incidence of cancer in man but this aspect has not been adequately investigated. Although a number of mortality studies have been carried out in workers potentially exposed to trichloroethylene, these all have serious limitations.

There is no evidence to indicate that exposure to trichloroethylene has produced any adverse effects in the offspring of women workers exposed to the material; this aspect has again not been investigated in detail. Although there are reports of an increased incidence of menstrual disorders in female workers, and of decreased libido in male workers, these occurred in persons exposed to levels of trichloroethylene sufficient to produce marked disturbances in the CNS. Insufficient information was available to assess the significance of these observations.

Identity

Trichloroethylene is a colourless, non-viscous liquid with the molecular formula C_2HCl_3 and a molecular weight of 131.4. It has the following structural formula:



The IUPAC and Chemical Abstracts Service (CAS) preferred name is trichloroethene, but trichloroethylene is the commonly used name. Its CAS registry number 79-01-6.

The pure compound has a boiling point of 87 °C, a melting point of -73 °C, and a density of 1.465 g/ml at 20 °C. It is only slightly miscible with water (0.1% w/v at 20 °C), but is miscible with acetone, ethanol, diethyl ether, chloroform and oils. Trichloroethylene is highly volatile, with a vapour pressure of 77 mm of mercury at 25 °C; the vapour being heavier than air

with a vapour density of 4.54. The chemical is non-flammable but is unstable in the presence of light and moisture, or high temperatures, producing phosgene, carbon monoxide, dichloroacetaldehyde and trichloroethylene epoxide.^{1, 2, 3}

Trichloroethylene has a sweetish odour resembling chloroform, with an odour threshold of around 20 ppm.^{1, 2, 3}

Commercial grades usually have a purity of greater than 99% and normally contain stabilisers such as amines (0.001–0.01% or more), or combinations of epoxides (e.g. epichlorohydrin, epoxybutane) and esters (0.2–2% total).^{1, 3}

Metabolism

Studies in animals

The metabolism of trichloroethylene has been studied in a number of species but primarily in the rat and mouse.

Trichloroethylene is readily absorbed through the lungs with 21–70% being retained in the rat and 40–54% in the mouse.^{4, 5} Increasing blood levels of trichloroethylene have been found in sheep and goats exposed to 0.5–1.5% trichloroethylene; these did not plateau within 30 minutes.⁶ It is also well absorbed orally. Studies in the rat and rabbit indicated a rapid and extensive absorption of trichloroethylene with less than 0.5% being excreted in the faeces and maximum blood levels being attained within two hours.^{7, 8} A less rapid dermal absorption was noted, 55 nmol/cm²/min of neat trichloroethylene being absorbed through mouse abdominal skin.⁹

Absorbed trichloroethylene is removed from the blood and rapidly distributed to the tissues; the volume of distribution in the rat was found to be in the range 110–190 ml.¹⁰ Studies in a range of species (rat, mouse, rabbit and dog) showed high levels of trichloroethylene in the brain and adipose tissue but also in the heart, lungs, liver, spleen and kidneys.^{5, 10, 11}

A similar distribution was seen in guinea-pigs where significant levels were also seen in the ovaries.¹² In sheep and goats a rapid transfer of trichloroethylene across the placental barrier was seen.⁶ As a result of this extensive tissue distribution plasma levels of trichloroethylene decreased in a bi- or multiphasic manner. After i.v. injection of low doses in the rat, plasma levels decreased in a biphasic manner characteristic of a two-compartment model. The first phase resulted in a rapid decrease in blood levels with a half-life ($t_{1/2}$) in the range 1.7–4.3 minutes, followed by a slower second phase with the $t_{1/2}$ in the range 18–29 minutes. At higher doses the elimination of trichloroethylene from the blood was best described by a three-compartment model with $t_{1/2}$ values of 1.3, 8.5 and 57 minutes for the first, second and third phases respectively.¹⁰ After oral dosing of rabbits only a single phase of elimination could be detected with a $t_{1/2}$ of 220 minutes.⁸ The rate of uptake and elimination of

trichloroethylene from adipose tissue was found to be linear with a $t_{1/2}$ of 215 minutes.¹⁰

Following inhalation of trichloroethylene in the mouse about 25% was found to be excreted unchanged in the breath. The elimination was in three phases with $t_{1/2}$ values of 14, 33 and 260 minutes for the first, second and third phases respectively.⁵ Oral dosing with ³⁶C1 labelled trichloroethylene resulted in 72–85% of the label being eliminated in the breath with a single $t_{1/2}$ of five hours.⁷ A much smaller quantity (3%) was, however, excreted unchanged in the breath following percutaneous absorption.⁹ The remainder of the trichloroethylene retained is metabolised, mainly in the liver, and the metabolites excreted in the urine or in the breath. The mouse appeared to possess a greater ability to metabolise high levels of trichloroethylene (1000 mg/kg orally) than the rat.¹³

The biotransformation of trichloroethylene is brought about by an initial conversion by the enzymes of the mixed function oxidase system to the transient metabolite trichloroethylene oxide. This epoxide undergoes intramolecular rearrangement to trichloroacetaldehyde which is then hydrolysed to chloral hydrate. This acts as a substrate for the enzymes alcohol dehydrogenase and chloral hydrate dehydrogenase producing trichloroethanol and trichloroacetic acid respectively, which are excreted in the urine, the former mainly as the glucuronide and the latter as the free acid.^{7, 14, 15, 16, 17, 18, 19, 20} Carbon dioxide, which may arise from the catabolism of chloral hydrate or trichloroacetic acid, is excreted in the breath.⁵ Other metabolites, excreted in much lower concentrations, have also been proposed. These include carbon monoxide, chloroform, monochloroacetic acid and dichloroacetic acid.^{8, 21, 22} The biotransformation of trichloroethylene has also been shown to occur in the lung tissue of the guinea-pig.²³ The involvement of cytochrome P-450 has been shown by demonstrating the effect of the inhibitor SKF 525A and the inducing agent phenobarbitone on the rate of metabolism of trichloroethylene and also circumstantially by the reciprocal metabolic inhibition by toluene.^{19, 24, 25} Quantitative differences have been observed between animal species and routes of administration.²⁶ A scheme depicting the major pathways of metabolism of trichloroethylene is shown in Figure 1.

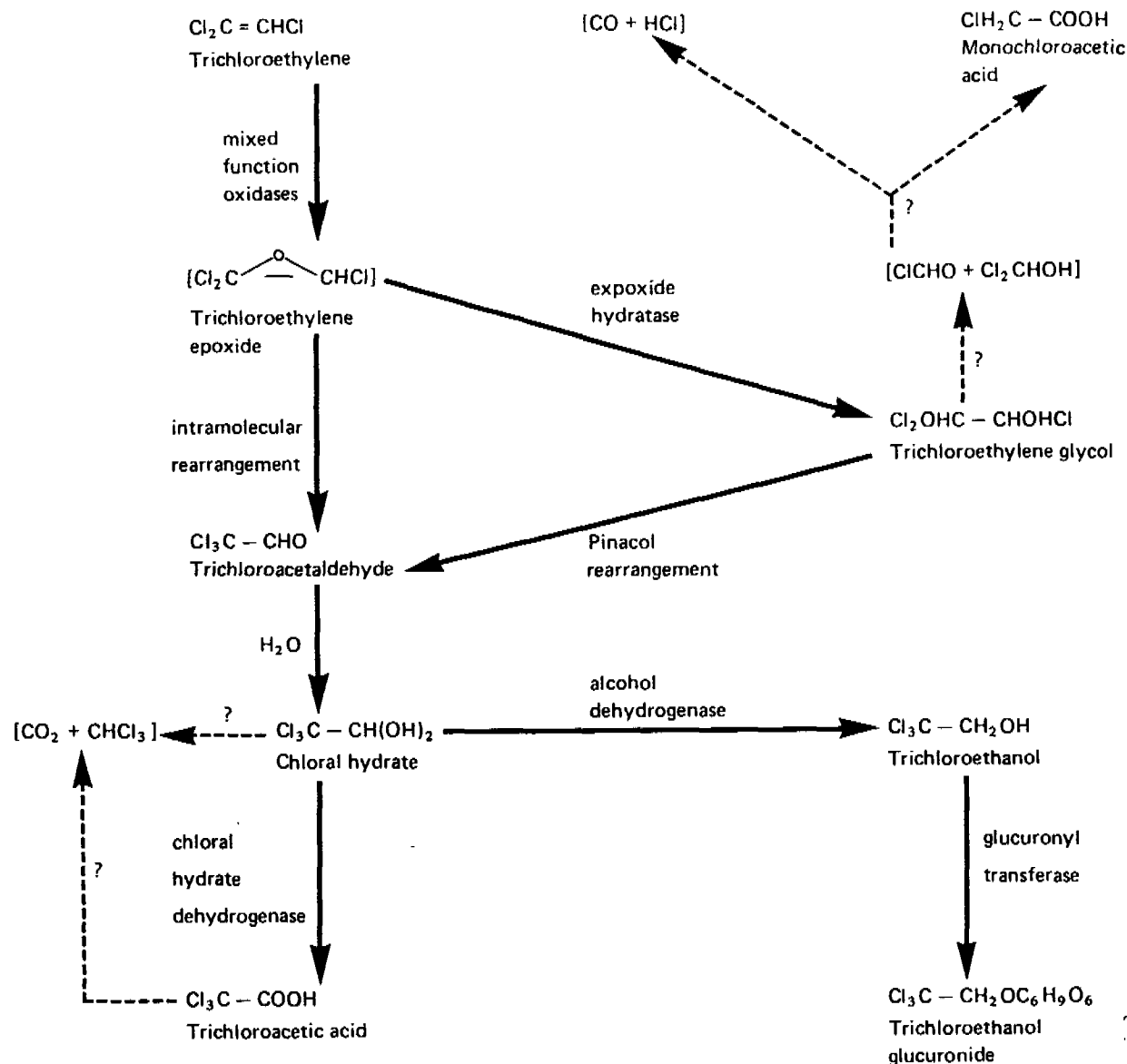


Fig 1 The biotransformation of trichloroethylene

Thus to summarise, the metabolism of trichloroethylene has been studied in a number of animal species. It is well absorbed both orally and through the lungs but less well through the skin. Following absorption, it is rapidly distributed to the tissues, the elimination from the blood being bi- or triphasic, depending upon the degree of exposure. In the rat the $t_{1/2}$ for the rapid phase was 1-4 minutes and for the slowest phase 20-60 minutes. Significant quantities of trichloroethylene are excreted unchanged in the breath, the remainder being metabolised predominantly to trichloroacetic acid and trichloroethanol and excreted in the urine; the latter is excreted mainly as the glucuronide.

Studies in humans

The toxicokinetics of trichloroethylene have been studied following inhalation and percutaneous absorption.

It has been shown that following inhalation 28-70% of the trichloroethylene was absorbed.^{27, 28, 29, 30, 31, 32, 33} The percentage absorbed decreased during exercise but, due to the increased ventilation, the absolute quantity increased.³¹ Continuous exposure to atmospheric trichloroethylene resulted in a steady increase in blood levels, which on some occasions

reached a plateau depending upon the level of exposure.^{34,35,36,37} Trichloroethylene appears to be fairly well absorbed through the skin. In one study blood levels increased to a maximum of 2 mg/l after immersion of a hand in the liquid for 30 minutes.³⁸ In another study immersion of a thumb in neat trichloroethylene resulted in the excretion of trichloroethylene in the breath within ten minutes.³⁹

Following inhalation, elimination of trichloroethylene from the blood conformed to a three-compartment model similar to that observed in animals, with $t_{1/2}$ values of 2.5, 25 and 204 minutes for the first, second and third phases respectively.⁴⁰ A multiphasic elimination of trichloroethylene from blood was also seen following percutaneous absorption, the $t_{1/2}$ for the slowest phase being 228 minutes, comparable to the third phase following inhalation.³⁸

After inhalation, significant quantities of the trichloroethylene absorbed are excreted unchanged in the breath (values of 16–19% being reported in women and 19–28% in men).^{28,30,41,42} The excretion of trichloroethylene in the breath is multiphasic with a rapid initial phase, $t_{1/2}$ in the range 2.5–11 minutes, and the $t_{1/2}$ of the slowest phase being 2.2–8 hours.^{37,38,40,41,43} Few data are available on the percentage of trichloroethylene excreted unchanged through the lungs following percutaneous absorption but it would appear that the $t_{1/2}$ for its rate of elimination by this route is in the range 1–4 hours.^{38,39}

The trichloroethylene not exhaled is metabolised mainly in the liver. The pathways are as established in animals, proceeding through trichloroethylene oxide to

chloral hydrate with the further metabolism of chloral hydrate resulting in the excretion of trichloroethanol (mainly as the glucuronide) and trichloroacetic acid in the urine. The presence of chloral hydrate in the blood has been established following exposure to trichloroethylene.⁴⁴ The excretion of chloroform in the breath and monochloroacetic acid in the urine have also been proposed as minor routes of metabolism.^{43,45} The general scheme of the metabolism of trichloroethylene is shown in Fig 1.

The excretion of trichloroacetic acid and trichloroethanol in the urine have been shown to be biphasic with the trichloroethanol being the more rapidly excreted. The $t_{1/2}$ value for the first phase is in the range 6–43 hours for trichloroethanol and 27–50 hours for trichloroacetic acid.^{27,40,46,47,48,49,50,51} Some sex differences in the rates of excretion of metabolites of trichloroethylene in the urine have been noticed but this has not been confirmed.^{43,49} A list of the amounts of metabolites excreted in the urine and the time of maximum urinary levels are given in Table 1.

Thus to summarise, in man trichloroethylene is absorbed rapidly through the lungs and also fairly readily through the skin. The elimination from the blood conforms to a three-compartment model with $t_{1/2}$ values of 2.5, 25 and 204 minutes for the first, second and third phases respectively. Significant quantities of trichloroethylene are excreted unchanged in the breath, the remainder being metabolised and excreted predominantly in the urine. The major metabolites are trichloroacetic acid and trichloroethanol, the latter being excreted mainly as the glucuronide.

Toxicity to animals

Acute toxicity

The acute toxicity of trichloroethylene has been extensively investigated in animals. It has low toxicity by the oral route and by inhalation. The very low toxicity observed following percutaneous administration may be due to the decreased rate of absorption by this route. A summary of the acute toxicity studies is given in Table 2.

Inhalation

The inhalation LC_{50} value in the rat has been reported to be about 26 000 ppm for a one-hour exposure⁵² and 12 000 ppm for a four-hour exposure,⁵³ the lowest lethal dose was reported as 4800 ppm following a four-hour exposure.⁵⁴ Signs of toxicity noted included stupor, irritation, incoordination, narcosis and respiratory failure.^{54,55,56} Full anaesthesia was noted

at concentrations of about 5000 ppm and above, this occurring within ten minutes at 15 000 ppm. Transient changes in serum enzyme markers of liver dysfunction (e.g. alanine aminotransferase and aspartate aminotransferase) were noted in rats following exposure to about 10 000 ppm for one hour or 100 ppm for six hours.^{54,57,58,59} At autopsy slight effects on the liver were noted, including increased weight, oedema and fatty infiltration, but not in other organs.^{54,57,58} Pre-treatment of the rats with phenobarbitone, or other enzyme inducers, increased the effect of trichloroethylene on the liver.^{57,58,60,61}

Similar acute toxicity was noted in the mouse, the four-hour LC_{50} being reported as 8450 ppm.⁶² Complete anaesthesia was shown after about five minutes exposure to 12 000 ppm and about ten minutes exposure to 7000 ppm of trichloroethylene.⁶² About 50% of the animals were anaesthetised after 46

minutes exposure to 5500 ppm.⁶³ Signs of toxicity were similar to those occurring in the rat.^{63, 64, 65}

Rabbits survived exposure to about 15 000 ppm of trichloroethylene for 40 minutes but some deaths were noted if the duration of the exposure was extended.⁶⁶ Signs of toxicity noted included hyperactivity, dyspnoea and narcosis.⁶⁶ The anaesthetic level was found to be 9250 ppm for one hour.⁶⁷ At autopsy congestion of the liver, lungs, heart, kidney, spleen and brain were noted; other lesions were also observed in the liver, kidney and brain.⁶⁶ In another study marked cerebral lesions were noted in rabbits exposed to about 11 000 ppm for about 50 minutes.⁶⁸

The effect of trichloroethylene on the behavioural activity of rodents has been investigated in a number of studies. Some effect on spontaneous climbing was noted in rats at 200 ppm and above⁶⁹ while decreased swimming time (a test of fatigue), and reduced spontaneous alternation in a maze test was noted after exposure to 800 ppm of trichloroethylene.⁷⁰ Studies in mice showed decreased spontaneous activity at about 700 ppm.⁷²

Trichloroethylene, at high concentrations, has been shown to sensitise the heart to the action of catecholamines. Cardiac arrhythmias were noted in most dogs exposed to 10 000 ppm of trichloroethylene and then given adrenaline (8 µg/hour i.v.); similar effects were noted in 1/12 animals exposed to 5000 ppm, and also in both rabbits and rats pretreated with phenobarbitone.^{73, 74}

Oral

Oral LD₅₀ values have been reported in the range 5.4–7.2 g/kg in rats and about 2.9 g/kg in mice, the compound being given neat, in water or in vegetable oil.^{75, 76, 77, 78, 79} The lowest lethal dose was found to be 5.6 g/kg (in corn oil) in rats and 10 g/kg (in corn oil) in mice.⁸⁰ Narcosis was noted in mice following doses of 0.7 g/kg (in olive oil) and above; liver lesions (fatty infiltration) were noted at autopsy.⁷⁹ Abnormal liver function, as indicated by alterations in serum biochemistry including increased aspartate and alanine aminotransferase activities, was also found in rabbits given 1.7 g/kg.⁸¹ All dogs survived doses of 3–6 g/kg, given as a suspension in acacia mucilage.⁸²

Percutaneous

The LD₅₀ value in rabbits by this route, using an occlusive dressing has been reported as being greater than 29 g/kg.^{75, 76} No deaths were noted in guinea-pigs given 7.8 g/kg, using a similar method: the only sign of toxicity noted was reduced weight gain.⁸³

Intraperitoneal

The intraperitoneal LD₅₀ in the rat has been reported as 2.75 g/kg when given as a solution in peanut oil.⁸⁴ Serum enzyme markers of liver dysfunction were elevated shortly after dosing but no histological evidence of liver damage was noted at autopsy.^{84, 85, 86}

⁸⁷ In another study dosage of 1.5 g/kg and above resulted in increased serum alanine and aspartate aminotransferase and on microscopic examination, glycogen accumulation, mitochondrial swelling and cytoplasmic vacuoles were noted in the liver.⁸⁸ In the mouse, LD₅₀ values in the range 2–3 g/kg have been reported^{56, 89, 90} with increases in the serum enzyme markers of liver dysfunction being noted following doses of 1.5 g/kg and above.^{88, 91} A similar LD₅₀ value was obtained in dogs; some evidence of slight liver damage (neutrophil infiltration of sinusoids and portal areas) and kidney damage (calcification of tubules) was noted at autopsy.⁹¹

Skin and eye irritancy

Skin

Trichloroethylene has been shown to produce severe skin irritation when tested neat on the rabbit skin using a 24-hour occlusive dressing.⁹² In another study marked erythema and oedema were noted but no experimental details were given.⁷⁶

Eye

Application of 0.1 ml trichloroethylene directly to the eye produced a mild-moderate conjunctivitis with some epithelial abrasions being noted on examination with fluorescein. Microscopic examination on day seven revealed epithelial keratosis in the process of healing. The eye had returned to normal within two weeks.⁹² In another study instillation of 0.1 ml trichloroethylene caused necrosis of 80–100% of the cornea.⁷⁶ Insufficient data are available to fully evaluate this study.

Subacute and subchronic toxicity

The toxicity of trichloroethylene following repeated administration has been extensively studied in a number of species by the oral route and following inhalation. A summary of the studies is given in Table 3.

Inhalation

The effect of repeated exposure to trichloroethylene has been studied most extensively in the rat, animals being exposed for periods of up to about eight months.

Wistar rats survived exposure to 3000 ppm of trichloroethylene (7 hours/day, 5 days/week) for about eight months.⁵⁴ The only signs of toxicity noted were decreased weight gain, and some CNS disturbances, particularly during the early exposure period (hyperactivity and disturbances in equilibrium).

Increased liver and kidney weight were noted at autopsy, but there was no evidence of any histological damage. The no effect level in this study was 200 ppm.

In another study, using an unspecified strain of rat, some deaths occurred when animals were exposed to

3000 ppm (6 hours/day, 5 days/week) for six months.⁹³ Signs of slight narcosis were noted at 2000 ppm but all animals survived. No effect was noted on growth rate nor any adverse effect on haematology or clinical chemistry. At autopsy some evidence of congestion of liver and kidneys was noted in animals that died at 3000 ppm. No organ damage was noted at 2000 ppm during gross or microscopic examination. All rats survived exposure up to 5000 ppm of trichloroethylene (6 hours/day, 5 days/week) for a shorter period (8–11 exposures). Deep narcosis was noted at 5000 ppm, and light drowsiness at 2000 ppm.

No signs of toxicity were noted in rats exposed to 1000 ppm of trichloroethylene (18 hours/day) for 90 days,⁹⁴ or 771 ppm (8 hours/day, 5 days/week) for six weeks.⁹⁵ In neither of the studies were any effects noted on haematology, nor were any lesions noted on gross or microscopic examination at autopsy. No signs of toxicity were noted in rats exposed to 35 ppm of trichloroethylene continuously (24 hours/day) for 90 days. Again no adverse haematological effects were noted nor any lesions on gross or microscopic examination at autopsy.⁹⁵

In one study specifically to investigate effects on the liver and kidney, rats were exposed to 372 ppm of trichloroethylene (30 mins/day) for up to 120 days.⁹⁶ Serum enzyme markers for liver dysfunction (amino transferases) were elevated from 40 days. Some histological evidence of liver damage, limited to hyperaemia and oedema, was noted in animals killed at this time. The liver lesions were more marked in animals killed after 120 days when some degenerative changes in the hepatocytes were observed.

An increase in the liver mixed function oxidase enzyme system (cytochrome P-450) has been noted in animals exposed to 50 ppm of trichloroethylene (5 hours/day) for 28 days.⁹⁷

Similar results have been obtained in rabbits. All animals survived exposure to 3000 ppm of trichloroethylene (7 hours/day, 5 days/week) for about eight months.⁵⁴ The only signs of toxicity noted were evidence of CNS disturbance (lack of co-ordination) and an increase in liver and kidney weights at autopsy. Histological examination revealed no evidence of liver or kidney damage. The no effect level in this study was 200 ppm, a similar value to that found in the rat. In a separate study exposure of rabbits to about 2800 ppm of trichloroethylene (4 hours/day, 5 days/week) for up to 50 days resulted in no deaths but extensive liver damage (degenerative changes in hepatocytes including necrosis) was noted at autopsy.⁶⁶ Lesions were also noted in the lung, spleen, brain, and occasionally the kidney. Some haematological changes (reduced red and white cell count) have been noted in rabbits exposed to this concentration of trichloroethylene.⁹⁸

Trichloroethylene has also been shown to have low toxicity in a range of other species. No toxic effects were noted when guinea-pigs, dogs or squirrel monkeys were exposed to about 700 ppm of trichloro-

ethylene (8 hours/day, 5 days/week) for six weeks,⁹⁵ nor when dogs were exposed to 1000 ppm trichloroethylene (18 hours/day, 5 days/week) for 90 days.⁹⁴ Some evidence of liver dysfunction was noted however in another study in dogs, after exposure to 500 ppm for three weeks or more.⁹⁹ The effects were shown to be reversible in animals allowed a recovery period. No toxic effects were noted when guinea-pigs, dogs or squirrel monkeys were exposed continuously (24 hours/day) to 35 ppm of trichloroethylene for 90 days.⁹⁵

Guinea-pigs survived exposure to up to about 7450 ppm of trichloroethylene (30 mins/day) for 10–16 weeks.¹⁰⁰ Deep narcosis was noted within about seven minutes exposure to this concentration. No adverse haematological effects were noted apart from a transient neutrophilia. At autopsy gross inspection showed marked discoloration of the liver and kidneys; histological examination revealed only minor liver lesions, but more extensive kidney damage.

No signs of toxicity were noted when Rhesus monkeys were exposed to 400 ppm of trichloroethylene (7 hours/day, 5 days/week) for about seven months.⁵⁴ No adverse effects were noted on haematology nor on gross or microscopic examination at autopsy.

Only limited data are available on the cat; however from a single study the toxicity of trichloroethylene appears to be of the same order of magnitude as in other species.¹⁰¹ Signs of CNS disturbances (lack of co-ordination, collapse) were reported when the animals were exposed to about 5500 ppm (1–1½ hours/day) for 4–6 months. At autopsy marked lesions were noted in the liver, kidney, spleen and lymphatic system.

In addition to the above studies the effect of repeated exposure of trichloroethylene has been investigated in the rat using a number of behavioural tests. These have shown effects at lower concentrations than in the conventional toxicity studies. Impairment of avoidance response to unpleasant stimuli was noted in rats exposed to 125 ppm of trichloroethylene and above.^{71, 102, 103} Increased activity (ambulation, preening, rearing) was noted during repeated exposure to 200 ppm of trichloroethylene.¹⁰⁴ These results thus suggest that exposure to concentrations of trichloroethylene that produce no overt signs of CNS toxicity, may produce subtle effects on the CNS resulting in adverse effects being noted in certain behavioural tests; these effects being observed at 125–200 ppm and above. The relevance of these results is, however, unknown.

Summary of subacute inhalation toxicity of trichloroethylene

Rats survived exposure to trichloroethylene at up to 2000 ppm (6 hours/day, 5 days/week) for up to six months, the only toxic effect noted being signs of CNS disturbances during exposure. In one study liver damage was however noted at about 370 ppm. Deaths occurred in animals exposed to 3000 ppm using a

similar regime; evidence of liver and kidney damage was noted at autopsy. Rabbits survived exposure to 3000 ppm (7 hours/day, 5 days/week) for about eight months with only increased liver and kidney weight being noted at autopsy. However in a second study 2800 ppm (4 hours/day) for five days produced lesions in liver, lungs, spleen, brain and kidney. Some haematological changes were also noted in this study (reduced red and white cell count). No effects were noted in guinea-pigs or squirrel monkeys exposed to about 700 ppm of trichloroethylene (8 hours/day, 5 days/week) for six weeks, nor when Rhesus monkeys were exposed to 400 ppm (7 hours/day, 5 days/week) for seven months. Liver toxicity was noted in one study in dogs exposed to 500 ppm of trichloroethylene (4-8 hours/day, 5-6 days/week) for three weeks but not at 700-1000 ppm in two separate studies. Some adverse effects in behavioural studies were noted in rats exposed to 125-200 ppm of trichloroethylene but the relevance of these observations is not known.

Thus trichloroethylene has been shown to have low toxicity in a range of species in repeated dose studies of up to eight months duration. Some evidence of liver damage was occasionally noted at 400-500 ppm, and more frequently at near lethal concentrations (around 3000 ppm). There was no evidence of liver damage at lower concentrations in any species.

Oral

Few data are available on the subacute toxicity of trichloroethylene following administration by the oral route.

In one study in rats all animals died following dosing with 5.6 g/kg in corn oil (5 days/week for six weeks).⁸⁰ Signs of toxicity noted at 3 g/kg and above included loss of weight, hunching, alopecia or laboured breathing. No significant adverse effects were noted on gross examination at autopsy but no histopathology was performed. In mice all animals died following administration of 10 g/kg in corn oil (5 days/week for six weeks) and no gross lesions were noted at autopsy. As in the case of the rats no histopathology was performed.

Another study, limited primarily to effects on the liver, revealed no effect on the liver function of rats, as indicated by serum aminotransferase levels, when animals were given 1 g/kg in corn oil daily for up to ten consecutive days.¹⁰⁵ However, increases in the relative liver weight and in the hepatic levels of certain enzymes concerned with the biotransformation of chemicals were seen. Similar effects were observed in mice dosed with 0.5 g/kg (in corn oil) for ten consecutive days, together with a significant increase in liver non-protein sulphhydryl content.¹⁰⁵

Induction of the mixed function oxidase enzymes were also seen in mice dosed with up to 1.6 g/kg trichloroethylene (in corn oil) for six weeks¹⁰⁶ but not in mice treated with 5 mg/kg in the drinking water for up to six months¹⁰⁷ although an increase in liver

weight was noted in the latter study. Few data were given in these papers with which to assess the significance of the results.

A dose-dependent suppression of the humoral and cell-mediated immune response was noted in female mice given up to 2 mg/ml of trichloroethylene in the drinking water for 120 days.¹⁰⁸ No effect was noted in male mice.

Mutagenicity

Tests for point mutations in bacteria

There are several reports of studies to investigate the mutagenicity of trichloroethylene using the Ames-developed strains of *Salmonella typhimurium*; these, however, have been limited to the two strains capable of detecting base pair substitutions, TA 1535 and TA 100. The results of the studies are summarised in Table 4. Negative results were usually obtained, although in two cases the results were equivocal. In one study using *Escherichia coli* a positive result has been quoted.¹⁰⁹ Only one concentration was, however, tested and insufficient data are available for an assessment of the significance of the result.

Tests for point mutations, gene conversion and mitotic recombination in yeast

In vitro

A number of studies have investigated the mutagenicity of trichloroethylene in various strains of *Saccharomyces cerevisiae*.

In one study an increase in point mutations was noted in the strain XV185-14C at loci *lys-1*, *his 1-7* and *hom 3-10* when tested in the presence of a metabolising system (mouse S-9).¹¹⁰ The loci *lys-1* and *his 1-7* are believed to detect base pair mutations whereas *hom 3-10* detects frame shift mutations. An increase in revertants was noted following treatment with 10 and 20 μ l/ml of technical grade trichloroethylene for one or four hours. At these levels the trichloroethylene was extremely toxic (only 0.1% survival). No increase in mutation was noted in cells treated with 0.5 μ l/ml or below where the toxicity was less (65-95% survival). No mutagenic activity was noted at any concentration in the absence of the metabolising system. The increased reversion noted at all loci suggests that trichloroethylene produces both base pair and frame shift mutations in this test system. However, since effects were noted only at concentrations highly toxic to yeasts, the significance is questionable. In addition no information was given regarding the impurities present in the technical grade trichloroethylene.

In another study trichloroethylene (ACS purity) induced both point mutation and gene conversion at the *ilv* and *trp* loci of the D7 strains of *Saccharomyces cerevisiae* respectively.¹¹¹ These effects were observed only in the presence of a metabolising system (mouse

liver 10 000 g supernatant). A dose response was observed in both instances over the range 10–40 mM with the top dose resulting in 50% survival of the cells. This activity was likely to have been due to trichloroethylene itself, rather than any epoxide stabilisers that may have been present, since negative results were obtained in the absence of an enzyme activation system.

The D7 strain of yeast has also been used by other workers to investigate the mutagenic effect of trichloroethylene (purity not given) on mitotic recombination (at the *ade 2* locus) and gene conversion (at the *trp 5* locus and the *ilv* locus).¹¹² Effectively only one concentration of trichloroethylene was used, 15 mM, since the higher concentration 22 mM, was extremely toxic to the cells with only 0.3% surviving. A marked increase in mitotic recombination and gene conversion was noted but only a small increase in reversion at the *ilv* locus (about two-fold after allowing for the 67% cell survival). No mammalian metabolism system was used in the studies but yeast cells when grown in a glucose medium, as in these studies, have been quoted by the authors to contain an adequate cytochrome P-450 mono-oxygenase system.

In vivo — host mediated assay

Trichloroethylene (ACS purity) has produced genetic conversion and point mutation in a host-mediated assay system using strains D4 and D7 of *Saccharomyces cerevisiae*; these acted as marker organisms for gene conversion and point mutation respectively.¹¹¹ The micro-organisms were injected into male CD-1 mice via the retro-orbital sinus and were isolated from liver, kidneys and lungs four hours later. In an acute study 400 mg/kg trichloroethylene (in 0.5 ml corn oil) was administered orally immediately following the injection of the yeast, whilst in a subacute study 150 mg/kg (in 0.5 ml corn oil) was given orally 5 days/week for 22 administrations, followed by a dose of 400 mg/kg orally, immediately following the injection of the yeast, on the day of the assay. An increase in both point mutation and gene conversion of the D4 and D7 strains of yeast was noted in micro-organisms isolated from both liver and kidneys but only slight effects were noted in cells isolated from the lungs. All the effects were more marked following repeated exposure to trichloroethylene.

Thus to summarise, trichloroethylene has been shown to produce point mutations and gene conversions in certain strains of yeast both when tested *in vitro*, and *in vivo* using a host-mediated assay.

Tests for chromosome effects

Micronucleus test

There is one report of an investigation of trichloroethylene in a micronucleus test using mice.¹¹³ Six groups of ten mice were given two doses of analytical grade trichloroethylene (dispersed in gum arabic) orally at concentrations in the range 375–3000 mg/kg, each dose being separated by 24 hours. An untreated

control group and vehicle-treated control group each of 20 mice were also used. The mice of all groups were killed 16 hours post-dose, bone marrow smears of each animal prepared and examined. The number of micronuclei in 1000 polychromatic and also in 1000 normochromic erythrocytes was calculated in each animal. It was found that in mice dosed with trichloroethylene a marked increase in the number of micronuclei was noted in polychromatic cells (about 2–16% of cells being affected with increasing concentration), compared to untreated and vehicle treated controls (0.5% of cells with micronuclei). Some increase in normochromic cells containing micronuclei was seen in treated animals (1–3% with increasing dose) as compared to 0.3% in controls. Thus a positive result was obtained with the micronucleus test; a very marked increase in polychromatic erythrocytes with micronuclei being noted at the highest dose level. The analytical trichloroethylene used in this study did not contain any stabilisers; the effect observed was thus due to trichloroethylene itself.

Sister chromatid exchange

One study has been reported in which the ability of trichloroethylene to induce sister chromatid exchange *in vitro* has been investigated.¹¹⁴ Dividing Chinese hamster ovary cells were exposed to 1700 ppm for one hour in the presence of a metabolising system. One hundred cells were then analysed for the presence of sister chromatid exchanges. No increase in the number of exchanges was found in the trichloroethylene exposed cells, as compared with carbon dioxide-treated controls.

Dominant lethal assay

In one study male mice were exposed to trichloroethylene vapour at concentrations of 50, 200 and 450 ppm for 24 hours, using 50 animals at each dose level.¹¹⁵ Each animal was then mated with one untreated female of the same strain (NMRI) during four consecutive days. The groups of females were changed every fourth day, a total of 12 groups being investigated. The female animals were killed 13 days after removal from the males and the number of implantations and pre- and post-implantation losses calculated. No significant changes in the fertilisation rate, nor in the pre- or post-implantation losses were noted in the animals mated with exposed mice, as compared with controls. There was thus no evidence of any dominant lethal effect in this study.

Mammalian spot test

The mutagenicity of trichloroethylene has been investigated *in vivo* using the mouse spot test.¹¹⁶ Embryos derived from the mating of male T stock mice with female C57BL mice were exposed to trichloroethylene, *in utero*, by treatment of the pregnant dams with 140 or 350 mg/kg by intraperitoneal injection on day 11 of gestation. The number of white spots, produced by a mutation of the wild type allele of the pigment cells, in the offspring

was noted in animals examined between two and five weeks of age. The incidence of coat spots in the offspring from animals treated with 350 mg/kg trichloroethylene was 2/51 (4%) as compared to 2/145 (1.4%) treated with 140 mg/kg and 0/144 in untreated controls. In pooled untreated control animals 6/794 (0.8%) exhibited colour spots. No statistical analysis of these results was performed. The trichloroethylene used in this study was 99.5% pure but no mention of the presence of stabilisers was given. Thus trichloroethylene produced some evidence of a mutagenic effect in this study but the significance of this effect was not known.

Mouse sperm morphology

In one limited study groups of 13-week-old male mice were exposed to trichloroethylene vapour at 200–2000 ppm for four hours on each of five consecutive days.¹¹⁷ Twenty-eight days following the start of exposure the mice were killed, the cauda epididymus removed and sperm morphology examined. A statistically significant ($p < 0.001$) increase in the percentage of abnormal spermatozoa were noted in mice exposed to 2000 ppm (2.58%), as compared with controls (1.42%). No significant increase was seen however in mice exposed to 200 ppm (1.68%). No information was given on the type of abnormality observed and hence the significance of these results is difficult to assess. No figures on the purity of trichloroethylene or on the presence of stabilisers were given.

Mammalian cell transformation

In one study the ability of trichloroethylene to transform rat embryo cells *in vitro*, as measured by growth in semi-solid agar, was investigated.¹¹⁸ Cells of the Fischer rat embryo system (F1706) were grown in culture on agar plates and treated with 1.1 mM and 11 mM trichloroethylene for 48 hours. The cells were examined at each subculture following treatment for the presence of microcolonies and, where present, the numbers of the colonies counted. Transformed foci were first observed in the trichloroethylene treated cells after five subcultures. At that time an average of eight and nine colonies were noted in cultures treated with 1.1 mM and 11 mM respectively, as compared to nil in the control cultures. Injection of 1×10^6 of these transformed cells resulted in fibrosarcoma at the point of subcutaneous inoculation in all 25 animals within 55 days. No microcolony formation was noted in the controls after nine subcultures when the experiment was terminated. Thus in this study, trichloroethylene produced an increase in transformed cells as measured both by ability to grow in semi-solid agar and by the development of tumours in animals following inoculation of these cells. No details were, however, available on the purity of the material used or on the presence of stabilisers. Surprisingly these results were obtained in the absence of any ancillary metabolic activation system. The significance of these results is therefore questionable.

In a brief report a negative result was obtained when unstabilised trichloroethylene was tested for mammalian cell transformation.¹¹⁹ In this study cell transformation was measured by the ability of kidney fibroblast cells from baby Syrian hamster (BHK) to grow in semi-solid agar. No further details were, however, given.

Summary of the mutagenicity of trichloroethylene

Trichloroethylene produced no evidence of any point mutations in bacteria when tested against strains of *Salmonella typhimurium* capable of detecting base pair mutations. The compound has not however been tested against strains capable of detecting frame shift mutations. Both point mutations and gene conversions were however produced in yeasts both *in vitro*, and *in vivo* using the host-mediated assay.

Positive results were also obtained when trichloroethylene was investigated in the micronucleus test in the mouse, suggesting that the compound may produce chromosome abnormalities.

Chronic toxicity/Carcinogenicity

The carcinogenicity of trichloroethylene has been investigated in chronic toxicity studies in animals following administration by inhalation and also by the oral, percutaneous and subcutaneous routes. The results obtained are summarised in Table 5.

Inhalation

In one series of studies the carcinogenicity of trichloroethylene has been investigated by inhalation in the rat, mouse and Syrian hamster.¹²⁰ Two dose levels were investigated, 100 ppm and 500 ppm (6 hours/day, 5 days/week) for 18 months with 30 animals of each sex and species used at each dose level, together with a similarly sized control group.

In the rat study Wistar animals were used and were observed for a total of 36 months. No signs of toxicity were reported, nor was any increase in mortality noted at either dose level. Over 90% of the males and 77% of the females from the high dose group survived 100 weeks or more. No significant increase in tumour incidence was noted at any site at either dose level. No information was given regarding the time of appearance of the tumours, nor were any details of organ weights, gross changes or non-tumorous pathological changes given.

This study thus provided no evidence for any carcinogenic effect in this strain of rat but the investigation was limited by the small number of animals used.

In the mouse study, NMRI strain animals were used and they were observed for a total of 30 months. No signs of toxicity were reported by a statistically significant decrease in survival rate was noted for both test groups, as compared with controls. Only 14 males and

24 females survived to week 80 at the higher dose and 18 male and 18 female at the lower dose, as compared to 25 male and 26 female controls. A significant increase in the incidence of lymphomas was noted in female mice with 18/28 (64%) found at 500 ppm and 17/30 (57%) at 100 ppm, as compared to 9/29 (31%) in controls. These tumours appeared earlier in test animals and the significance increased if age adjustment was performed. No significant increase in lymphomas occurred in the male animals, nor were there any significant increases in tumours at any other site in either sex of mouse. No details of organ weights, gross changes or non-tumorous pathological changes were given.

These results suggest that trichloroethylene produced an increase in the incidence of lymphomas in female mice; however this type of tumour appears to possess a high spontaneous incidence in female mice of this strain. No historical data were available for comparison and the significance of the result is therefore difficult to assess. The value of the study was severely limited by the small numbers of animals surviving 1½ years.

The Syrian hamsters were observed for a total of 30 months. No signs of toxicity were reported, and no significant increase in mortality was noted in any test group, as compared to controls. However, only 60-70% of the males and 20-30% of the females survived 100 weeks; no females survived to the end of the study. No significant increase in the incidence of tumours of any type was noted in any test group.

The value of this study is severely limited by the small group size and the very low two-year survival, especially of the females.

Thus to summarise this series of chronic toxicity studies, no evidence of any carcinogenic effect was obtained when rats or hamsters were exposed to up to 500 ppm of trichloroethylene. However insufficient animals were used and, in addition, poor two-year survival was noted in hamsters, especially in the female animals. No conclusions can therefore be drawn from this work regarding the carcinogenicity of trichloroethylene in rats or hamsters.

A statistically significant increase in the incidence of lymphomas was noted in female mice exposed to both 100 and 500 ppm trichloroethylene. However the incidence of such tumours was about 30% in the control group, making interpretation difficult. No data were given on the spontaneous incidence in historical controls. In addition insufficient animals were used for a proper evaluation of the carcinogenicity of trichloroethylene. No conclusions can therefore be drawn from this work regarding the carcinogenicity of trichloroethylene in mice.

Oral

Trichloroethylene has been investigated in an NCI carcinogenicity bioassay in both the rat and mouse.⁸⁰

Two dose levels (given by gavage in corn oil) were investigated using 50 animals of each sex per group.

The Osborne-Mendel strain of rat was used. The low dose group was dosed five days a week with 650 mg/kg for seven weeks, followed by 750 mg/kg for nine weeks and then by 500 mg/kg in a cycle of four weeks treatment and one week no treatment. The high dose group was given exactly double the dose level of trichloroethylene, using the same dosing regime.

A dose-related decrease in body weight gain was noted in both sexes, and a decrease in survival in the male animals; only 12/50 of the high dose group survived 78 weeks. Less than 50% of female mice in both test groups survived 78 weeks.

No significant increase was noted in the occurrence of tumours at any site in any test group.

The only non-tumorous lesions noted at autopsy that appeared to be compound-related were in the kidneys (nephrosis) and heart (inflammatory changes).

Trichloroethylene does not appear to be carcinogenic to this strain of rat in this study, however the value of this study was severely limited by the small numbers of animals surviving 1½ years. No definite conclusion can, therefore, be drawn regarding the carcinogenicity of trichloroethylene.

Studies in mice used the B6C3F1 strain. The male low dose group were given 1000 mg/kg for 12 weeks followed by 1200 mg/kg for a further 66 weeks. The females were given 700 mg/kg for 12 weeks and then 900 mg/kg for a further 66 weeks; dosing schedules were five days a week in all cases. In the high dose groups, males and females were given double the quantities of trichloroethylene as the respective low dose animals. The experiment was terminated after 90 weeks.

No significant change in body weight gain was noted in any of the treated groups although bloating and abdominal distension was seen, especially in the males, after 50 weeks. Survival was low in all groups with only 2/20 (10%), 9/50 (18%) and 10/50 (20%) of the females in the control, low and high dose groups respectively surviving 1½ years. The corresponding figures for the males were 8/20 (40%), 40/50 (80%) and 24/50 (48%) respectively.

Primary hepatocellular carcinoma were seen in significantly increased numbers in both treated male and female mice. The incidence in the males was 31/48 (64.5%) at the high dose and 26/50 (52%) at the low dose, as compared to 1/20 (5%) of the matched controls and 5/77 (6.5%) of the colony controls. The corresponding figures for the females were 11/47 (23%) at the high dose and 4/50 (8%) at the low dose as compared to 1/80 of the colony controls; none were seen in the matched controls. Metastases of the liver tumours were seen in 7/98 (14%) of the treated males. An increase in the number of primary tumours of the lung was seen in treated animals (predominantly

benign adenoma) though this increase was not statistically significant.

Thus the trichloroethylene utilised in this study produced a marked increase in the incidence of primary hepatocellular tumours in both male and female B6C3F1 mice when given at high dose levels. It should be noted however, that the material tested contained significant quantities of 1, 2 epoxybutane (0.19%) and epichlorohydrin (0.09%) as stabilisers. These materials have been shown to be mutagenic to bacteria.¹²¹

No conclusions can, therefore, be made with regard to the carcinogenicity of pure trichloroethylene from this study.

Skin application

There is one report of a very limited chronic toxicity study in mice using the percutaneous route.¹²² Thirty female non-inbred Ha:ICR mice were treated with 1 mg/animal applied to the shaved dorsal region 3 days/week for 83 weeks. No signs of toxicity were reported during the observation period. No increase in tumour incidence was noted in the limited tissues examined. Insufficient data were given to assess this study. The small numbers of animals and the low dose levels of trichloroethylene used preclude any conclusions being drawn regarding the carcinogenicity of trichloroethylene.

Subcutaneous

There is one report of a very limited study in mice using the subcutaneous route.¹²² Thirty female non-inbred Ha:ICR mice were injected subcutaneously with 0.5 mg/animal weekly for 89 weeks. No data were given on any signs of toxicity noted during the observation period or at autopsy. It was stated that no increase in the incidence of tumours of the liver or at the site of injection occurred. Insufficient data were given to assess this study. The small numbers of animals and tissues examined and the low doses used prevent any conclusions being made regarding the carcinogenicity of trichloroethylene.

Summary

No evidence of any carcinogenicity was obtained in chronic inhalation toxicity studies in the rat and the hamster. However this work was of poor quality, too few animals being used for a proper assessment of the carcinogenicity of the compound. Inconclusive results were obtained in inhalation studies in mice. An apparent increase in the incidence of lymphomas was noted, but in view of the high spontaneous incidence of such tumours in the control group, and other limitations of the study, no conclusions could be drawn.

No evidence of any carcinogenic effect was noted in a chronic oral toxicity study in the rat. However only a small number of animals survived for 18 months and no conclusions could be drawn from this work. A

marked increase in the incidence of hepatocellular tumours was noted in a chronic oral toxicity study in mice. The dose levels used (1 g and 5 g per day) were very large and in addition the technical material used contained epoxide stabiliser (1900 ppm of epoxybutane and 900 ppm of epichlorohydrin). These compounds have both been shown to be mutagenic and they may have influenced the result at the very high dose levels of technical trichloroethylene used. The technical trichloroethylene used in this study was thus carcinogenic to mice at very high dose levels, producing an increased incidence of hepatocellular carcinoma. Further studies are required before the significance of this result can be assessed.

Teratogenicity

The teratogenicity of trichloroethylene has been investigated in the rat and the mouse, exposure being by inhalation.

In one study no evidence of any fetotoxic or teratogenic effects were noted in the rat (Sprague-Dawley) following exposure to trichloroethylene at 300 ppm (7 hours/day) on days 6-15 of gestation.¹²³ Some evidence of slight fetotoxic effects indicative of delayed development (subcutaneous oedema and undescended testes) was noted in mice exposed to trichloroethylene under the same conditions. No evidence of any teratogenic effect was, however, noted.

In another investigation rats (Long-Evans) were exposed to 1800 ppm of trichloroethylene (6 hours/day, 7 days/week) on days 0-20 of gestation.¹²⁴ No teratogenic effects were noted but there was some evidence of delayed development, consisting of an increased incidence of displaced right ovary and incomplete ossification of the sternum. Pre-mating exposure (6 hours/day, 5 days/week) for 2-3 weeks together with exposure throughout gestation resulted in a depression in the growth of offspring of exposed mice but no behavioural abnormalities were noted. No teratogenic effect was noted following this exposure.

In another study rats (Wistar) were exposed to 100 ppm (4 hours/day) on days 6-20 of gestation.¹²⁵ A significant decrease in fetal body weight and an increase in the number of resorption sites was noted. Insufficient data were available to make an assessment of this work.

Trichloroethylene has been shown to produce an increased incidence of malformations when injected into developing hens' eggs.¹²⁶ The concentration used (10 μ l) was toxic, producing some deaths; the significance of the observation and relationship to the teratogenicity in mammals is very doubtful.

Thus in summary, no evidence for any teratogenic effects of trichloroethylene has been seen in inhalation studies in the rat or mouse. Some fetotoxic effects, indicative of delayed development were, however, noted in the rat following exposure to 1800 ppm.

Toxicity to man

Acute toxicity: Inhalation

Trichloroethylene has a depressant action on the central nervous system (CNS), and is a narcotic at high concentrations. Acute toxicity is characterised by CNS symptoms, including lightheadedness, dizziness, mental dullness, fatigue, drowsiness and headache. Nausea and vomiting have also occurred and in severe cases unconsciousness, coma and death. There have been several reports of accidental exposure to high concentrations of trichloroethylene resulting in narcosis and death in some cases. Lung oedema has sometimes been noted at autopsy, but this may have been due to decomposition to phosgene, rather than the trichloroethylene itself. Liver or kidney damage has only rarely been noted.¹²⁷

In cases where recovery from trichloroethylene narcosis has occurred, this has usually been complete, with no serious sequelae, and the material has been used as an anaesthetic.

A clinical study has been carried out on ten men who suffered from acute trichloroethylene intoxication, due to accidental spillage of the material.¹²⁸ Most of the men became unconscious for a short period. Later effects noted included cramps, diarrhoea, headaches, and lower back pain, which persisted for one month or more. Blood tests at intervals over a two-month period following the incident gave no indication of any impaired liver function, using the insensitive cephalin flocculation test. None of the men showed any signs of jaundice. Hypercalcaemia and hyperglobulinaemia were noted in several, and transient haematuria in one subject, one week after exposure. Apart from this instance all urine samples were normal; there was no indication of any nephrotoxicity.

Neurological damage, particularly involving the trigeminal and optic nerve, has occasionally been noted, following accidental exposure to narcotic concentrations of trichloroethylene, especially in earlier reports. There is some evidence to suggest that this was due to decomposition products of trichloroethylene, rather than the compound itself. Trichloroethylene may decompose to form more toxic products such as phosgene and dichloroacetylene, under the influence of heat and light or in contact with strong alkalis. Trichloroethylene usually contains stabilisers to protect against such decomposition. Neurotoxicity has been noted after anaesthetic use of trichloroethylene, but only when closed-circuit systems containing soda-lime were used, when there was the possibility of alkaline decomposition to dichloroacetylene (see section on anaesthetic use). It has been claimed that no cases of trigeminal nerve toxicity have been associated with exposure to purified or stabilised trichloroethylene under conditions where decomposition was unlikely.¹²⁹

Between 1916 and 1927 about ten cases of loss of sensation in areas of trigeminal nerve distribution were

reported following acute exposure to high levels of trichloroethylene.¹²⁹ In some cases oculomotor paralysis and corneal ulceration were also noted. The effect on the trigeminal nerve led to the use of trichloroethylene in the treatment of trigeminal neuralgia or *tic douloureux*. However the results were disappointing, the purified trichloroethylene used producing only general analgesia.

Cranial nerve injuries have more recently been reported in two workers after acute exposure to trichloroethylene, and possibly its decomposition products, whilst cleaning out the inside of tanks containing a deteriorating paint mixture.¹³⁰ Both developed trigeminal paraesthesia, hyperaesthesia, facial palsies with ptosis, and extraocular motor palsies with diplopia. Vision was still abnormal 2½ years after the incident.

Cranial neuropathy was also reported in a young woman accidentally exposed to several thousand ppm of trichloroethylene for an unknown period.¹³¹ The subject was unconscious for two hours. On recovery, complete loss of sensation in the trunk and lower extremities was noted, together with disturbances of vision, indicating an effect on the optic nerve. Nerve conduction velocity studies revealed the absence of peripheral neuritis and it was suggested that these effects were due to lesions in the spinal cord. The sensory loss was persistent, with only a slight recovery being noted over the nine-month observation period. Much milder effects were noted in a second woman who was unconscious for only one hour.

Another case of trigeminal sensory loss has been noted after accidental exposure to high concentrations of trichloroethylene, for a few minutes, whilst investigating a leak in a degreasing machine.¹³² The trichloroethylene levels present were sufficient to produce nausea, vomiting, and giddiness, but not anaesthesia. Extensive sensory loss occurred over the face, with numbness being noted also in the mouth and pharynx. The subject also experienced blurred vision, suggesting involvement of the optic nerve. Complete numbness over a large area of the face was maintained for about three months, with areas of hyperanalgesia for over a year. A slow improvement in function of the facial nerve was noted over this period, with recovery being essentially complete after 80 weeks.

Purified trichloroethylene has been fairly widely used as an anaesthetic; experience obtained in its use in this area is summarised below.

Experience from anaesthetic use

The use of trichloroethylene as an anaesthetic has been mainly limited to short procedures requiring light anaesthesia but good analgesia. Inhalation of concentrations in the range 5000–20 000 ppm (0.5–2.0%) have been used to produce light anaesthesia.¹³³ Blood levels required to produce anaesthesia have been stated to be

of the order of 10 mg/100 ml; these would result from sustained inhalation of air containing 7000 ppm (0.7%) of trichloroethylene.¹³⁴

Trichloroethylene has been regarded as a relatively safe anaesthetic. In general, no untoward effects occur after recovery from unconsciousness, provided that the gas is not used in a closed-circuit system, where the soda-lime used to eliminate carbon dioxide, may result in decomposition of the trichloroethylene to toxic products, including phosgene, dichloroacetylene and carbon monoxide. This restriction has limited the use of the material as an anaesthetic.

Hepatotoxicity has not been a problem, cases of serious effects on liver function being very rare following trichloroethylene anaesthesia.¹³⁵ In one study to investigate the effect of trichloroethylene on liver function (using a flocculation test), some evidence of impairment was noted in most of the patients (34/35) 24 hours after the operation. This was however transient, and all patients were normal after two weeks.¹³⁶ There is a case report of severe liver necrosis following the prolonged (4½-hour) use of trichloroethylene as an anaesthetic.¹³⁷

Cardiac arrhythmias have been reported in subjects undergoing trichloroethylene anaesthesia. In one study the electrocardiogram (ECG) was recorded throughout the period of anaesthesia (30–90 minutes). Relatively minor arrhythmias (principally sinus bradycardia and auriculoventricular nodal rhythm) were noted in the earlier stages of anaesthesia.¹³⁸ Similar effects have been noted with other anaesthetics, and it was suggested that they reflect increased vagal tone. Of greater significance was the development of multifocal ventricular tachycardia in about 10% of patients during the later, deeper stages of anaesthesia. Other studies have reported ventricular tachycardia, with multiple extrasystoles, in a significant proportion of patients both with and without pre-existing myocardial degeneration, whilst undergoing trichloroethylene anaesthesia.¹³⁹ However although cases of cardiac arrhythmia have been reported during trichloroethylene anaesthesia and fatalities have occurred, possibly following serious ventricular arrhythmias, such events are rare. A review of the literature in 1957, about 16 years after the widespread introduction of the compound as an anaesthetic, identified only 34 cases of cardiac arrest under trichloroethylene anaesthesia.¹⁴⁰ Furthermore, it has been suggested that 11 of these were due to causes other than the trichloroethylene.¹⁴¹ A review of the reports of about 70 000 cases of trichloroethylene anaesthesia, in 1960, revealed only two deaths that were likely to have been caused by the anaesthetic.¹⁴¹ No cases of liver damage were noted.

There are a few reports of other serious side effects following trichloroethylene anaesthesia.^{142, 143, 144, 145} In the past there were several reports of cranial neuropathies, principally affecting the trigeminal nerve, but these occurred when the gas was used in a closed-

circuit system with soda-lime to absorb carbon dioxide. These trigeminal palsies were believed to be due to formation of trichloroethylene decomposition products, particularly dichloroacetylene, after reaction with the alkaline soda-lime. Such neuropathies have not been reported in situations where soda-lime was not used.^{143, 144, 145}

Studies in volunteers under controlled conditions

Studies to investigate performance on behavioural tests

There are several reports of investigations of the acute effects of trichloroethylene in volunteers, under controlled conditions. It is known that trichloroethylene has CNS effects and these studies have, in the main, concentrated on the effect of exposure to relatively low levels of trichloroethylene on the performance of certain psychological or psychomotor tests. Anaesthetic grade trichloroethylene was usually used in these studies, which are summarised below.

In one study eight male volunteers were subjected to a range of psychomotor tests whilst exposed to 0, 100, 300 and 1000 ppm of trichloroethylene, using a breathing tube, for two hours.¹⁴⁶ Each individual performed six different tests to measure visual-motor function. These were the Krasno-Ivy flicker photometer test (dependent on complex visual/CNS processes), the Howard Dolman depth perception test (visual motor performance), the Muller-Lyer two-dimensional illusion test (perception), a groove-type steadiness test (eye-hand co-ordination), the Purdue pegboard test (manual dexterity) and a written code substitution test. Each subject performed all the tests three times during each two-hour session, with the exception of the pegboard test, which was performed only immediately prior to and immediately after exposure to 0 and 1000 ppm of trichloroethylene.

Symptoms of CNS toxicity (lightheadedness, dizziness and lethargy) were noted in some of the subjects when exposed to 1000 ppm, and in one individual at 300 ppm. No symptoms were noted by any of the volunteers when exposed to 100 ppm of trichloroethylene.

Significant impairment in performance was noted in both the Howard Dolman perception test and the steadiness test at 1000 ppm. Five subjects also showed impairment in performance of the pegboard test at this concentration, but the other three subjects showed some improvement in performance. No effects were noted in performance of any of the tests at 300 ppm.

Thus in this study some symptoms of CNS toxicity, together with impaired performance in certain visual-motor tests occurred in subjects exposed to 1000 ppm of trichloroethylene, but not at 300 ppm or below.

In a later study by the same investigators exposure of volunteers to 1000 ppm of trichloroethylene was again shown to produce significant impairment in these two visual-motor tests.¹⁴⁷ Slight effects were also noted at 300 ppm but these were not statistically significant.

Alcohol (0.5 ml/kg) was shown to potentiate the effects of exposure to 1000 ppm of trichloroethylene; marked subjective symptoms were noted (dizziness, inability to concentrate, floating sensation) together with a greater impairment in the performance of the visual-motor tests. Alcohol alone, at the dose given, had no significant effect.

Similar impairment in psychomotor performance had been noted previously in very limited studies, involving only one subject.¹⁴⁸ He performed a range of tests to measure psychomotor performance whilst exposed to 100, 200, 300 or 500 ppm of trichloroethylene for about 2¾ hours. The tests were designed to measure manual dexterity, card sorting and response to a dial display. Two experiments were carried out at each level, the trichloroethylene exposure being in ascending and then descending concentrations. Control exposures were alternated between each trichloroethylene exposure. In all cases lavender oil, in the form of a perfume atomiser, was used to mask the smell of the trichloroethylene.

Symptoms of toxicity noted at 500 ppm included mild irritation to the upper respiratory tract, a dull and woolly-headed feeling and somnolence. The effects were reversed within 15 minutes of leaving the exposure chamber. The only symptom noted at lower concentrations was a slight tendency to somnolence.

No effects were noted on performance in any of the behavioural tests at 100 ppm, but a progressive impairment was noted at 300 ppm and above. However, since only one subject was used, no conclusions can be drawn from this very limited study.

In a larger study 15 men were subjected to a range of tests to measure psychological function whilst being exposed to 540 mg/m³ (100 ppm) and 1080 mg/m³ (200 ppm) of trichloroethylene for 70 minutes, the gas being supplied through a breathing tube.¹⁴⁹ An attempt was made to disguise the taste and smell of the vapour by the incorporation of a canister of menthol crystals in the tube to the mouthpiece valve. However, in spite of this about one half of the volunteers could distinguish between exposure to air and trichloroethylene.

Each man performed four separate tests designed to measure numerical ability, reaction time (simple and complex choice) and short-term memory. Each test was repeated twice at each concentration of trichloroethylene.

No effects were noted on the short-term memory or the reaction time tests. A significant difference ($p < 0.05$) was reported in performance of the numerical ability tests using different exposure regimes; increasing impairment was noted with increasing concentrations of trichloroethylene. However, full details of the results were not given, and interpretation was apparently complicated by the pronounced learning effect noted in this test, and also the greater individual variability, as compared with the other tests.

It is not therefore possible to assess the significance of this result. Since no effect was noted on the two psychomotor tests (reaction time) and the one cognitive test (short-term memory) at either concentration, it is unlikely that the results obtained in the numerical ability tests represented a significant impairment in the psychological function of the men exposed to trichloroethylene.

In another study six young male volunteers (aged between 20 and 22 years) were subjected to a range of behavioural tests whilst exposed to about 110 ppm of trichloroethylene for two four-hour periods, separated by a lunch break of 1½ hours.¹⁵⁰ The trichloroethylene atmosphere in the exposure chamber was generated by intermittent use of an atomiser. The atmospheric levels were measured periodically; values in the range 90–130 ppm were noted. Each subject was tested on two separate days, once whilst exposed to trichloroethylene, and once under control conditions (air only). The tests performed comprised a test for perception (1/20th second exposure with tachistoscopic presentation), memory (immediate memory test using Wechsler scale), complex reaction time and manual dexterity.

No toxic symptoms were noted during the exposure period apart from a slight sense of dizziness and transient eye irritation. However all subjects complained about the odour of trichloroethylene, and hence realised when they were being exposed to the vapour rather than to air.

A statistically significant decrease in performance was reported in all the tests, the effect being greater in the more complex tests. However only a statistical analysis of the results was given, not the actual data, and the magnitude of the effect was not given. In addition the results may have been influenced by the subjective complaints about the smell of the trichloroethylene, and the fact that the men knew when they were being exposed to the vapour rather than the air.

The experiment was repeated with another six workers who, unlike the earlier volunteers, had previously been occupationally exposed to trichloroethylene and were thus more used to its smell. Similar results were apparently obtained, but no further details were given, and it is not possible to assess the significance of this work.

Thus the results suggest that some impairment of performance in these psychomotor tests occurred in persons exposed to trichloroethylene levels of only slightly above 100 ppm (up to 130 ppm). However, insufficient details were given to allow a full assessment of this work.

Other investigators have subjected volunteers to similar behavioural tests and obtained no significant impairment at 100 ppm. In one study nine subjects were used, and the effects of two concentrations investigated (50 and 110 ppm), exposures being for 24-hour periods separated by a 1½-hour lunch break (supervised to ensure no alcohol consumption).¹⁵¹

Each individual was given a comprehensive medical examination both prior to the first exposure, and after the last exposure. Electroencephalograph tracings were recorded by telemetry throughout the exposure period.

A range of six tests were investigated. These comprised a complex reaction time test, a tachistoscopic perception test (ability to reproduce the pattern of images seen on a screen), a digit span test (ability to repeat a list of numbers given orally in the correct or reverse order), a finger dexterity test (placing pins in holes), the Flannigan co-ordination test (ability to do pencil tracings) and a digit inspection test (speed taken to delete a given number from a list of random numbers). In addition an assessment of any symptoms noted was made. Each individual performed these tests soon after entering the exposure chamber in the morning, and 1½ hours prior to termination of exposure in the afternoon.

No significant abnormalities were noted in any subject during the medical examination, prior to or after the test, nor were any abnormalities detected in the electroencephalograph tracing during the exposure period. No significant impairment was noted in any of the tests during the trichloroethylene exposure at either concentration. A slight impairment was noted in the performance of the Flannigan co-ordination test in two individuals at 110 ppm, but only in the mornings. In view of the lack of effects in the afternoon, and in performance of the other tests, this was not believed to be significant. However there was fairly high individual variability in most of the tests and it was felt that a larger group size should have been used.

Thus in this study no significant reduction in performance was noted in a range of behavioural tests when healthy volunteers were exposed to 50 or 110 ppm of trichloroethylene for eight hours.

In another experiment 12 volunteers were subjected to a range of behavioural tests whilst exposed to 50 ppm of trichloroethylene.¹⁵² No details of the exposure chamber used, nor of the method of generating the trichloroethylene atmosphere were given. The investigations included reaction time test, tapping test (measurement of hand/arm speed) and the pursuit rotor test (precision of pursuit tracking by measuring time on target). Control values were obtained for each individual under the same conditions, but in the absence of trichloroethylene.

No significant difference was noted in the performance of any of these tests when the subjects were exposed to 50 ppm of trichloroethylene, as compared to the results obtained under control conditions.

The effect of exposure to both 50 ppm of trichloroethylene and alcohol was investigated in a second series of studies. The volunteers were given ethanol (600 mg/kg) in orange juice one hour after exposure started. They were then exposed to trichloroethylene for a further two hours, and then performed the same series of behavioural tests as previously. Blood alcohol levels at that time were of

the order of 0.30% (30 mg/100 ml). Significant ($p < 0.05$) impairment in performance was noted in both the pursuit rotor test and the tapping test (reduced maximum 'tapping time') under these conditions. However the alcohol alone produced a similar effect on the pursuit rotor test, but not on the tapping test.

Thus in this series of studies exposure to 50 ppm of trichloroethylene produced no effect on performance of a range of behavioural tests. Exposure to small amounts of alcohol, to produce blood levels of about 0.3%, resulted in a significant impairment in performance of the pursuit rotor test but not in the other tests. This was not potentiated by simultaneous exposure to 50 ppm of trichloroethylene. Exposure to both trichloroethylene and alcohol produced some impairment in the maximum 'tapping time'. However in view of the lack of any potentiation in any of the other measurements, the significance of this observation is doubtful.

The effect of an exposure to 150 and 300 ppm of trichloroethylene on performance of a range of behavioural tests has been investigated in healthy volunteers, and the results compared with the results of small amounts of alcohol.^{153, 154} In this study a total of 47 young adult males (aged between 19 and 27 years) were randomly divided into three groups of 15 or 16 individuals. They were exposed to 0, 150 or 300 ppm of trichloroethylene during which time they were subjected to a range of behavioural tests. These consisted of binary choice tasks (separate tests using auditory and visual signals), the Bourdon-Wiersma test (identifying those groups of dots on paper that contain four or five dots), identification test (detecting small differences in columns of similar figures or words) and a memory test (repeating lists of common words). Any symptoms noted during the exposure period were recorded, and heart rate was monitored continuously using a cardiometer. An estimate of sinus arrhythmia, based on the number of times the heart rate varied from the mean value was also made. This figure was used as an index of mental load since increased mental load was believed to induce suppression of sinus arrhythmia.

No significant differences were noted in performance of these tests in any group, nor were any differences noted in symptoms or heart rate. A slight, but not statistically significant, impairment in performance of the Bourdon-Wiersma test was noted in subjects exposed to 300 ppm of trichloroethylene. A slight effect was also noted on sinus arrhythmia when performing the binary choice tasks, but the effect was not statistically significant, nor dose-related.

Thus in this study exposure to up to 300 ppm of trichloroethylene had no significant effect on performance of a range of behavioural tests. In contrast in separate experiments oral doses of alcohol (20 g giving blood levels of the order of 45 mg/100 ml) resulted in definite impairment of performance in both the binary choice tests and the Bourdon-Wiersma test.

Further work has been carried out by this group of investigators to study the combined effects of trichloroethylene and alcohol.¹⁵⁵ In this instance the behavioural tests were limited to a binary choice test using visual stimuli and the pursuit rotor test (following the movement of an illuminated point). These tests were performed in a separate room immediately after exposure ceased, rather than during exposure, as in the previous studies.

In one experiment a group of 24 male students (age 19–26 years) was subdivided into four groups of equal size. One served as a control group, and the others were exposed separately to alcohol alone, 200 ppm of trichloroethylene, or 200 ppm of trichloroethylene plus alcohol; each group spent 2½ hours in the exposure chamber. The alcohol was given as a 35% solution in orange juice, at a dose level of 350 mg/kg, 50 minutes prior to the end of the exposure. Physiological parameters monitored during the exposure included heart rate and sinus arrhythmia (as previously) and also breathing rate using a nasal thermistor.

Blood alcohol levels (measured 30 minutes after leaving the exposure chamber) in those exposed to trichloroethylene were similar to those given alcohol alone (270 ± 70 mg/litre as compared to 270 ± 40 mg/litre). Blood trichloroethylene levels were however considerably higher in those exposed to alcohol than those only exposed to trichloroethylene (63 ± 12 µg/litre as compared to 29 ± 3 µg/litre) indicating that trichloroethylene metabolism had been markedly inhibited by simultaneous exposure to alcohol.

No significant impairment was noted in the performance of either test in any of the exposed groups as compared to the controls. The only effect noted was a decrease in sinus arrhythmia amongst all the exposed groups whilst performing the binary choice test, as compared to the controls, possibly suggested increased mental load. This decrease was more marked in those exposed to both ethanol and trichloroethylene. However it was stated that somewhat similar differences, but of smaller magnitude, were also noted in the various groups in practice tests carried out prior to exposure. Hence the effects may not have been related to the exposure conditions.

In a second experiment 15 volunteers were used, each serving as his own control. Each was subjected, in random order, to similar exposure conditions as previously, a two-week break being observed between exposures. In this study the alcohol was given ten minutes prior to the end of the 2½-hour period in the exposure chamber. Blood alcohol levels were measured ten and 20 minutes after leaving the exposure chamber. These were 480 ± 90 mg/litre and 410 ± 60 mg/litre at ten and 20 minutes respectively in those not exposed to trichloroethylene. The levels were not significantly different in those also exposed to trichloroethylene.

No impairment was noted in performance of the binary choice test under any of the exposure

conditions. Some impairment was however noted in those exposed to alcohol in the pursuit rotor test; time on target decreased especially in those exposed to alcohol and trichloroethylene, mean values being 104.9 ± 41.2 seconds and 93.4 ± 37.2 seconds respectively as compared to 110.6 ± 20.4 seconds in the controls. No reduction was noted in those exposed to trichloroethylene alone (116.8 ± 49 seconds). However there was much individual variability in the results obtained, and the decrease in those exposed to alcohol was not statistically significant.

No significant difference was noted in heart or breathing rate in any of the exposure conditions, but sinus arrhythmia was significantly lower ($p < 0.05$) in those exposed to both trichloroethylene and alcohol whilst performing both tests, suggesting increased mental load.

Thus in this study a slight decrease was noted in performance of the pursuit rotor test in subjects with blood alcohol levels of about 45 mg/100 ml. This impairment was more marked in those simultaneously exposed to 200 ppm of trichloroethylene. However there was much individual variability and the decrease was not statistically significant. Administration of the alcohol was shown to markedly inhibit the metabolism of trichloroethylene. No impairment in performance was noted in subjects exposed to 200 ppm of trichloroethylene alone.

Summary of effects of trichloroethylene on performance of behavioural tests

Significant impairment in performance was noted in a range of behavioural tests to measure visual motor effects, when volunteers were exposed to 1000 ppm of trichloroethylene. Symptoms of CNS toxicity (dizziness, lightheadedness, lethargy) were also noted at this concentration. No significant impairment was noted at 300 ppm or below, except in one study, where this occurred in subjects exposed to 90–130 ppm of trichloroethylene. However insufficient details were given for a full assessment of this work. In addition several other studies failed to reveal any significant adverse effects on performance of a range of tests when volunteers were exposed to 100–300 ppm of trichloroethylene.

The combined effect of trichloroethylene and alcohol has been investigated by several workers. Exposure to alcohol alone, sufficient to give blood levels of 30–45 mg/100 ml produced clear adverse effects in the performance of certain behavioural tests. Simultaneous exposure to trichloroethylene, at 200 ppm and above, increased this impairment. The metabolism of trichloroethylene was markedly inhibited by simultaneous exposure to such alcohol levels.

Studies in volunteers other than those involving behavioural studies

The effect of trichloroethylene on optokinetic nystagmus has been investigated in 12 volunteers.¹⁵⁶

Slight changes were observed after two hours exposure to the single concentration used (1000 ppm) indicating some effects on the CNS. No other effects were noted. More marked changes in optokinetic nystagmus were observed with alcohol.

Another study concentrated on the effect of trichloroethylene on serum marker enzymes for liver dysfunction and on leucocyte levels of acid phosphatase and naphthol-AS-D esterase.¹⁵⁷ Twenty healthy volunteers were exposed to 95 ppm of trichloroethylene for four hours and the enzyme levels measured immediately prior to exposure, and at 0, 4 and 20 hours post-exposure. No effect on the serum enzyme levels was noted, suggesting that no liver damage had occurred during the short time period of the experiment. The leucocyte enzyme levels increased after four hours, and remained elevated at 20 hours post-exposure; the significance of this observation is not known.

Symptoms of CNS depression were noted when groups of 5-6 volunteers were exposed to 50 and 100 ppm of trichloroethylene for six hours.¹⁵⁸ These consisted of fatigue and decreased ability to concentrate, and were experienced by all subjects at both concentrations. However this study was aimed primarily at investigating the metabolism of trichloroethylene, and no attempt was made to qualify these observations. No controls were used, and the symptoms may have been due to the enforced sedentary period throughout the exposure. Headache was noted in one subject at each concentration. In view of the limited nature of this study, no conclusions can be drawn as to whether the symptoms were related to trichloroethylene exposure or other factors.

Summary of acute inhalation toxicity of trichloroethylene

The main signs of toxicity associated with acute exposure to trichloroethylene are those of CNS depression, exposure to high concentrations resulting in narcosis, which may be fatal in extreme cases. Liver or kidney damage has only rarely been noted at autopsy. When recovery from narcosis occurred, this was usually complete with no serious sequelae, and the material has been widely used as an anaesthetic for operations of short duration; concentrations of about 5000-10 000 ppm (0.5-1%) of trichloroethylene are usually employed. Effects on cardiac rhythm, including potentially serious multiple ventricular ectopics, have been recorded during trichloroethylene anaesthesia, but cases of cardiac arrest are very rare. Cranial neuropathies have occurred in the past when closed-circuit anaesthetic systems were used; these were due to decomposition products of the trichloroethylene by the action of alkaline soda-lime used to absorb carbon dioxide. The anaesthetic should not therefore be used in such systems. Trichloroethylene is known to decompose, under the influence of heat and light, or strong alkalis to more toxic

products (dichloroacetylene, phosgene, carbon monoxide) and it usually contains stabilisers to prevent this breakdown. The dichloroacetylene is believed to be responsible for the cranial neuropathies, principally affecting the trigeminal nerve, which have in the past been noted both in anaesthetic use, and in cases of accidental exposure to narcotic levels of trichloroethylene.

Studies in volunteers have concentrated on investigating the effect of exposure to relatively low levels of trichloroethylene on performance of certain behavioural tests. A significant impairment in performance of a range of visual-motor tests was noted at 1000 ppm. No significant effects have been noted in this or other studies at 300 ppm or below apart from in one case where some impairment was noted in subjects exposed to 90-130 ppm of trichloroethylene. Insufficient details were given of this work to enable a full assessment to be made. Several other investigations using a similar range of behavioural tests failed to show any adverse effects on performance at 100-300 ppm. In none of these studies were significant symptoms of CNS toxicity noted at 300 ppm or below. Some effects (dizziness, light-headedness, lethargy) were noted at 1000 ppm.

Oral toxicity

There are a few reports of acute poisoning following oral ingestion of trichloroethylene.

Death occurred in a young man 6-7 hours after ingestion of 200-300 ml trichloroethylene. At autopsy only minor changes were noted in the liver (fatty infiltration, with fat droplets in the Kupffer cells and congestion of the Glisson capsule), in addition fat droplets in the brain cells were noted.¹⁵⁹ Similar effects were also noted in the liver and brain, together with lesions in the lung and intestines, in four deaths due to accidental ingestion of unknown quantities of trichloroethylene in Germany.¹⁶⁰

Hepatorenal failure was the cause of death in a man who accidentally drank some trichloroethylene. He developed jaundice and oliguria and died in acute renal failure. Autopsy findings indicated tubular necrosis without glomerular damage and severe centrilobular necrosis of the liver.¹⁶¹

Severe hepatotoxicity has also been reported in three out of seven cases of poisoning due to accidental ingestion of unspecified quantities of trichloroethylene in Italy.¹⁶² Two cases were fatal, with death being due to liver failure. Analysis of the samples of trichloroethylene involved showed that in all the cases where hepatotoxicity was evident the material contained appreciable quantities of 1, 2-dichloroethane and 1, 2-dichloropropane. No evidence of liver damage was noted in cases of ingestion of purer samples of trichloroethylene, and it was believed that the liver toxicity was due to these impurities rather than the trichloroethylene.

No serious sequelae were noted in several individuals who accidentally ingested about 0.5 oz (about 14 ml) of trichloroethylene. Signs and symptoms of toxicity included prolonged inebriation, vomiting, dizziness, deafness, amnesia and numbness in the limbs. Complete recovery occurred in 5–10 days.^{163, 164} In another case a man went into a deep coma for 36 hours after the accidental ingestion of what was described as a 'good swig' of trichloroethylene.¹⁶⁵ This was followed by a period of paranoid psychosis with hallucinations for a few days. The patient returned to normal within 15 days when he was discharged from hospital. At no time was there any indication of hepatorenal damage.

A suicide attempt has been reported, by ingestion of a 'glassful' of 25% aqueous suspension of trichloroethylene.¹⁶⁶ The subject was found in a coma and recovered in hospital. Signs of kidney damage (albuminuria with many epithelial cells, granular cylinders, leucocytes and red blood cells) were noted initially but these were transient, and no urine abnormalities were noted after eight days. No signs of toxicity were present after two months; there was no evidence of any hepatotoxicity at any stage.

No evidence of any adverse effects on the liver or kidney were noted in seven cases of acute poisoning (five accidental ingestions, two deliberate) with trichloroethylene.¹⁶⁷ The actual amounts consumed were not known but they were sufficient to produce coma in most cases; in one instance this lasted for five days. Other signs of toxicity noted included burns on the skin and gastric mucosa.

There is another report of survival following prolonged coma (five days) produced by the deliberate ingestion of 150 ml of trichloroethylene.¹⁶⁸ The only effect noted on recovery was a transient paraesthesia. No effects on liver or kidney function were noted.

Stupor and abnormal ECG findings, suggestive of an ischaemic lesion, were noted in one patient after the ingestion of about 20 ml of trichloroethylene.¹⁶⁹ Functional tests carried out periodically for up to six months post-exposure revealed no significant adverse effects on the liver or kidney at any time.

Skin and eye irritancy

Skin irritancy

Trichloroethylene is mildly irritating to the skin. Repeated contact may, as with other solvents which produce defatting, lead to roughening, chapping, erythema and possibly secondary infection.¹⁷⁰ Eczematous lesions, and also cases of generalised exfoliative dermatitis have been reported in workers exposed to trichloroethylene.^{171, 172, 173}

Eye irritancy

Direct eye contact with trichloroethylene produced smarting and injury to the corneal epithelium, due to

its defatting action. Complete recovery usually occurred within a few days, even in cases of extensive contact.¹²⁹

Exposure of unconscious subjects to high concentrations of trichloroethylene vapour, with the eyelids open, has been reported to produce temporary clouding of the cornea as well as loss of epithelium. Recovery occurred with little or no permanent damage.¹⁷⁴

Effects of repeated exposure

Studies in volunteers

The effect of repeated exposure to trichloroethylene over a four-week period has been investigated in a small number of healthy male volunteers (age range 19–46 years).⁴³ They were exposed to 20 ppm of trichloroethylene for the first week, 100 ppm for the second and third weeks (fluctuating between 50 and 200 ppm in the third week) and 200 ppm for the fourth week, all exposures being for five days a week. The men were divided into three groups of 3–4 men, who were exposed for different time periods each day (1, 3 or 7½ hours). Each subject was given a full medical examination prior to the start of the study, and was subjected to close medical surveillance throughout the exposure period. Pulmonary function tests were carried out prior to and at the end of the exposure period. Blood was taken for haematology and clinical chemistry three times each week. Electroencephalograph tracings were recorded at approximately hourly intervals (pre- and post-exercise) during each exposure period. In addition each subject performed a number of behavioural tests twice weekly during the exposure period and electroencephalograph recordings were carried out in the subgroup exposed for 7½ hours a day.

No symptoms of toxicity were noted which could be related to trichloroethylene exposure. No effects were reported on the pulmonary function tests (mean mid-maximal flow rates, mean forced vital capacity, and mean peak flow rates), the results obtained at the end of the exposure period being comparable to the pre-exposure values. However the actual results obtained were not given. Electroencephalograph recordings apparently showed no abnormalities at any time interval.

No impairment was noted in performance of a range of behavioural tests to measure cognitive function (arith-metical test, 90-minute alertness test, response to light and sound stimuli, the Flannagan co-ordination test, a number of choice inspection tests, and a time estimation test). Again the actual results obtained were not given, and an assessment of the significance of this study is not possible. The only changes noted in the electroencephalograph were at 200 ppm; these were described as 'minimal' and of no serious consequence.

As part of this study, the effect of administration of alcohol was investigated during the latter part of the experiment, when the subjects were exposed to 200 ppm of trichloroethylene.^{43, 175} Administration of relatively small amounts of alcohol (below 0.5 ml/kg either as beer or brandy) was shown to produce a marked but transient vasodilation of the superficial skin vessels ('degreasers' flush'). The onset was detected about 20 minutes after drinking the alcohol, the maximum response being obtained about 30 minutes later, and the reaction fading completely after a further 60 minutes. The vasodilation was localised to the superficial vessels in the skin of the face, shoulders and trunk and was not accompanied by any other observable physiological response. The reaction could be demonstrated 72 hours after exposure to the trichloroethylene ceased. In addition it was known to have occurred in one individual after consuming alcohol six weeks after the last exposure to trichloroethylene.

Repeated exposure to trichloroethylene was believed necessary before the alcohol-induced vasodilation could occur. It was known that, contrary to instructions, several of the volunteers consumed alcohol in the evenings; the characteristic 'flush' was only noted in some of these during the third week of exposure. No cases occurred earlier.

Experience in use: general health survey of workers exposed to trichloroethylene

Symptoms of CNS disturbances (principally fatigue, headaches, dizziness, memory loss, and inability to concentrate) have frequently been reported in health surveys of workers exposed to trichloroethylene. Only very little information was available on the atmospheric trichloroethylene levels present and in addition no control groups were, in general, used; it is therefore difficult to assess the extent to which these symptoms were related to exposure to trichloroethylene. A summary of the studies to investigate the general signs and symptoms of toxicity in workers exposed to trichloroethylene is given below.

The results of a health survey of 50 workers, from 24 different workshops using trichloroethylene degreasing tanks in Switzerland were reported in 1955.¹⁷⁶ Analysis of the atmospheric trichloroethylene levels at the time of the study revealed that in most cases the concentration near the degreasing bath was in the range 20-40 ppm. However the values obtained showed great variation between sites, and also at different times of the day at the same site; the range recorded was 1-335 ppm.

The average age of the workers was 43 years and the mean length of employment was 3¼ years (range 1 month-15 years). Each was subjected to an extensive medical examination including physical examination, neurological examination of papillary reflexes, cutaneous and deep sensitivity, cutaneous and proprioceptive reflexes and also hearing and sight. In addition note was taken of any symptoms experienced

during work. The individuals were also subjected to a clinical psychiatric examination.

No significant abnormalities were noted in haematology or in blood biochemistry of any of the workers; there was no indication, from serum protein, bilirubin or alkaline phosphatase levels of any marked hepatotoxicity, although serum alkaline phosphatase levels were slightly elevated in four subjects.

Symptoms of CNS disturbances were reported in most of the workers. These included vertigo (50%), fatigue (44%), intolerance to alcohol (36%), headaches (32%), paraesthesia (20%), emotional lability (20%) and memory loss (15%). Neurological examination revealed that some evidence of adverse effects had occurred in 28% of the workers. These included tremors, ataxia, visual disturbances, nystagmus and reduction in cutaneous sensitivity. Disorders suggesting effects on the autonomic nervous system were noted in 36%; these included excessive perspiration, disorders of the circulation and heart rhythm and of the gastrointestinal tract. Examination of the mental state of the subjects indicated some slowing of the mental processes in 40%, reduction in memory in 38% and emotional instability in 26%.

No further details of these toxic effects were given, apart from the statement that they occurred with higher frequency in those exposed to above 40 ppm of trichloroethylene (mean level 85 ppm). The workers were from a relatively low socio-economic class, and the results were not compared with those from a comparable population not exposed to trichloroethylene.

Thus in this study a relatively high incidence of neurological symptoms (affecting both the CNS and peripheral nervous system) together with psychological disturbances were noted in the trichloroethylene-exposed workers. However no control group was used and the significance of the finding is difficult to assess. Clinical examination revealed no evidence of any significant hepatotoxicity.

A high incidence of symptoms of CNS disturbances together with signs of irritant effects on the mucous membranes was noted in an investigation of 75 persons occupationally exposed to trichloroethylene, either at dry cleaning establishments (12 subjects) or through the use of trichloroethylene in industry as a degreasing agent (55 subjects).¹⁷⁷ Atmospheric trichloroethylene levels in the dry cleaning establishment were estimated to be in the range 0.16-3.4 mg/l (30-632 ppm) and those in the degreasing workshops 0.028-0.83 mg/l (5-154 ppm). Symptoms of CNS disturbance were widespread in both groups; the most common effects were headache, sleepiness, feelings of inebriation, nausea and tinnitus. Signs of local irritation to the eyes (lachrymation), skin (reddening) and respiratory tract were also common in both groups. When the workers were subdivided into four groups, based on their duration of exposure (below 1 year, 1-2 years, 2-9 years and over 10 years) the following effects were shown to be

related to length of exposure: irritancy to skin and eyes, sleep disturbances, giddiness, tremors, intolerance to alcohol, 'severe neuraesthesia syndrome with anxiety state' and bradycardia. No abnormalities were noted in clinical tests for liver and kidney function (thymol turbidity test and Weltmann test).

Symptoms of CNS disturbances were commonly reported in a detailed study of 104 workers (87 men, 17 women) exposed to trichloroethylene in Sweden.¹⁷⁸ The subjects worked mainly in factories using trichloroethylene for degreasing purposes, but some were from dry cleaning establishments and the rubber industry. At the start of the study about half these individuals had been occupationally exposed to trichloroethylene for two years or more. Few data were available on the atmospheric levels of trichloroethylene to which the workers were exposed, but urinary trichloroacetic acid levels were measured in most cases.

Symptoms of CNS effects were noted in about two-thirds of the subjects. These included headache, dizziness, vertigo, fatigue, nausea, vomiting, tremors, sleepiness and feelings of inebriation. The incidence showed some correlation with increasing urinary trichloroacetic acid levels, with most of the individuals having urinary levels of above 75 mg/l showing some symptoms. Mild symptoms were however also noted in the group with the lowest urinary trichloroacetic acid levels. The relevance of these results to exposure to trichloroethylene is not clear, as it was stated that 35 of the workers had personal social problems which probably affected these findings.

There was only very little evidence of any effect on the cranial or peripheral nervous system of these workers. This consisted of an isolated case of transient numbness in the area covered by the fifth cranial nerve, and paraesthesia and tremors of the fingers in a few instances. No abnormalities were noted in haematology or clinical chemistry, and liver function tests performed on a few individuals indicated no adverse effects.

In a follow-up study on a number of workers, it was shown that all symptoms disappeared within 4-5 months of exposure to trichloroethylene ceasing.

Clinical findings have been reported in a small group (8) of Japanese workers following an outbreak of symptoms of narcosis and general malaise, shortly after the start of the use of trichloroethylene as a solvent for degreasing purposes.¹⁷⁹ An open tank heated to 50 °C was used, with no ventilation. Trichloroethylene levels of 230-380 ppm were detected in the breathing zone of workers using the tank; a single measurement in the centre of the room gave a value of 115 ppm.

The health survey was carried out 13 days after the start of trichloroethylene usage. During the first week most of the men missed one or more days work due to severe fatigue; other effects also noted included muscular pains, nausea and vomiting. Blood tests

showed no significant haematological effects, but an increase in plasma gamma-globulin and a decrease in albumin was noted. Abnormal values in the cephalin cholesterol flocculation test were noted in most (75%) of the workers. An increase in urinary albumin and urobilinogen, but not urobilin was noted. These tests were repeated ten days later, during which time the workers had not been exposed to trichloroethylene. No abnormalities were detected at that time.

These results suggest that workers exposed to levels of trichloroethylene, sufficient to produce marked symptoms of toxicity, showed some evidence of liver damage. The effects were however rapidly reversible when exposure to trichloroethylene ceased.

Results of a health survey at another Japanese machine plant have been reported.¹⁸⁰ All 50 employees working in the degreasing area, and the adjacent room were included. Most had been employed for 2½ years at the time of the initial survey at the plant. Atmospheric trichloroethylene levels at that time in the degreasing room were in the range 100-600 ppm, the highest concentrations being obtained in air samples taken from near the floor. The concentrations in the adjacent room were usually between 50 and 100 ppm.

Most of the workers had symptoms of CNS toxicity (vertigo, fatigue, headaches, sleeplessness). Many had slight to moderate visual disturbances, and 15% had experienced diplopia. No significant haematological abnormalities were noted, but blood biochemistry revealed an increase in serum gamma-globulin and a decrease in serum albumin levels. Urine analysis showed the presence of albumin and urobilinogen in 30% and 36% of the workers respectively.

A second survey was carried out at the same factory ten months later. The men were divided into three groups, on the basis of their exposure to trichloroethylene. These consisted of eight workers from the degreasing room, where average trichloroethylene concentrations were in the range 150-250 ppm, 14 workers from that part of the assembly room adjacent to the degreasing area, where average concentrations were 50-100 ppm, and 16 workers from the other end of the assembly room, where levels were below 50 ppm. The average urinary trichloroacetic acid levels at the end of the work week were 311 ± 119 mg/l, 141 ± 53 mg/l and 50 ± 24 mg/l in the three groups respectively.

The following symptoms were noted by more than 50% of the workers from the high exposure group: headache, dizziness, giddiness, feelings of drunkenness, flushing in the face, burning in the throat, skin effects and fatigue. Fewer symptoms were noted by 50% of the group exposed to intermediate trichloroethylene levels: these consisted of headache, burning sensation in the eyes, flushing of the face and fatigue. In no case were any symptoms reported by 50% of the workers exposed to below 50 ppm of trichloroethylene.

No effect on haematology was noted in any group, but a marked decrease in serum albumin, and an increase in serum gamma-globulin levels were noted in the group exposed to the highest trichloroethylene concentrations. Slight effects were noted in the intermediate group, but none in those exposed to the lowest trichloroethylene levels.

Thus in this study extensive symptoms of CNS toxicity, together with alterations in blood albumin and gamma-globulin levels, were noted in workers exposed to average trichloroethylene levels in the range 150–250 ppm. Similar but less marked effects were noted in the workers exposed to 50–100 ppm of trichloroethylene, with possible excursions to higher levels. These effects were not however observed in the group exposed to below 50 ppm of trichloroethylene.

Results of a health survey on a group of 70 young workers at a Rumanian semi-conductor plant have been reported.¹⁸¹ These were mainly women (about 75%), mostly below 30 years of age. They had usually been employed at the plant for less than two years, the maximum duration being six years. Only very limited data were available on the environmental trichloroethylene concentrations. These were stated to have exceeded the 'MAC' value of 50 mg/m³ (9 ppm) on 40% of determinations and were above 200 mg/m³ (37 ppm) on 12% of the determinations. No further details were given.

Pre-narcotic type symptoms were noted by most of the workers during the work-shift. These occurred nearly every day in about one-third of the individuals. Symptoms included, in decreasing order of incidence: dizziness (88%), headache (74%), nausea (43%), euphoria (31%), sleepiness at end of shift (29%), palpitations (29%) and visual disturbances (21%). In nine cases the workers had marked episodes of inebriation, and had to go outdoors. In one case loss of consciousness occurred for a short time. Other symptoms, stated to appear insidiously after exposures for between several months and two years, included irritability (56%), loss of appetite (50%), excessive sweating (39%) and alcohol intolerance (21%).

Physical examination of the workers revealed few significant abnormalities, apart from some neurological disturbances: tremor was present in 31%, hyperactive tendon reflexes in 34%, and nystagmus in 7%. No other effects were noted.

Thus in this study, a high incidence of CNS disturbances, together with some effects on the peripheral nerves (reduced tendon reflexes) were noted in workers exposed to trichloroethylene levels claimed only to exceed 37 ppm occasionally. However many workers experienced periods of inebriation whilst at work, and one became unconscious. The atmospheric trichloroethylene levels were therefore likely to have been much higher on occasions than that reported.

Widespread occurrence of similar signs and symptoms were reported in a survey of about 130 workers from several factories in the UK using trichloroethylene.¹⁸²

These included, in decreasing order of incidence, fatigue (75%), dizziness (56%), gastrointestinal disturbances (25%), headache (18%) and effects on the autonomic nervous system (8%). No information was given on the environmental levels at the factory, but an increased incidence of symptoms was shown with increasing urinary trichloroacetic acid levels. It was stated that about 61% of the workers had urinary levels below 20 mg/l, 21% had levels of 20–60 mg/l and the remaining 18% had levels above 60 mg/l. The average number of symptoms recorded in individuals from each group was 1.3, 1.8 and 2.7 respectively.

Involvement of both the CNS and peripheral nervous system was noted during medical examination of 50 Polish workers (28 male and 22 female) who complained of symptoms of trichloroethylene toxicity.¹⁸³ The individuals were from various small factories and dry cleaning establishments. The age range of the subjects was 21–55 years, and they had been occupationally exposed for 1–23 years. No data were available on the exposure levels.

The most frequent symptoms were somnolence (50%), loss of appetite and nausea (20%), intolerance to alcohol (20% incidence manifest by reddening of cheeks and skin — trichloroethylene 'flush') and headaches (18%). Neurological examination revealed a number of adverse effects on cranial and peripheral nerves. Impairment of sensation in the face was noted in six (12%), and weakness of the optical reflex in four (8%). Paraesthesia was noted in seven (14%) and sensory disorders, in the wrists and forearm, in nine individuals (18%).

Thus in the study a high incidence of symptoms of CNS depression and inhibition of sensory nerves was noted in workers exposed to trichloroethylene. However no information was available on the atmospheric levels present.

The health status of 140 women workers at three Polish workshops using trichloroethylene has been reported.¹⁸⁴ The average age of the women was 37 years, and the average length of exposure 9.2 years. The results were compared with those obtained in a control group of 44 women stated to be of comparable ages and training, but who were not exposed to trichloroethylene; no further details of this group were however given. The mean atmospheric trichloroethylene levels in the three workshops was stated to be 200 mg/m³ (37 ppm) but no information was given on the concentration range or the variability between sites. No details of the analytical methods used nor the frequency of monitoring were given.

A much higher incidence of the following symptoms was noted in the women exposed to trichloroethylene: drowsiness, general malaise, intolerance to alcohol, reduced appetite and muscle pains. Slight differences were also noted in the haematology findings between the groups (reduced haemoglobin levels, red blood cell and lymphocyte count, and increased monocyte count in the exposed workers). Insufficient data were given for a full assessment of these results, but they

appear to be of doubtful significance. No significant difference was noted in serum proteins (including electrophoretic pattern) or bilirubin levels between the exposed and control groups. Sickness records increased number of accidents at work in the workers which the authors suggested may have been due to an increased number of accidents at work in the workers exposed to trichloroethylene.

These results thus show a high incidence of symptoms of CNS depression in women workers exposed to trichloroethylene. There was no significant effect noted on haematology, nor any indication of liver damage from blood biochemistry. It was claimed that the mean atmospheric trichloroethylene levels were 200 mg/m³ (37 ppm) but no information was given as to the range, or the variability at the three different sites, nor on the method or frequency of monitoring.

Results of a clinical examination of 30 male workers from an Egyptian printing factory indicated a widespread incidence of CNS disturbances and irritant effects.¹⁸⁵ Trichloroethylene was used at the factory for cleaning the plates used in rotogravure printing. Mean atmospheric trichloroethylene levels were 41–163 ppm at different parts of the plant. Most of the workers had been employed for more than three years, and all but two were below 50 years of age. The results obtained were compared to those found in a group of 30 workers, of comparable age and social class; 20 of these had no occupational exposure to chemical substances whilst ten were workers from the printing industry but with no occupational exposure to trichloroethylene.

Signs and symptoms noted in the trichloroethylene-exposed workers included, in decreasing order of incidence, headache (87%), dizziness (67%), sleepiness (53%) nausea and vomiting (47%) lachrymation (40%), reduced libido (33%), skin manifestations (30%) and fatigue (30%). In the control group the only symptoms with an incidence of 10% or more were headaches (30%) and diminished libido (10%).

Thus in this study a high incidence of symptoms of CNS disturbances was noted, together with signs of irritancy to the skin and eyes, in workers exposed to mean trichloroethylene levels of up to about 160 ppm. Clinical examination showed no evidence of any adverse effects on the liver.

Similar symptoms were noted in a health survey of a small group of workers at a tannery where trichloroethylene was used for degreasing purposes.¹⁸⁶ Twenty-four out of a total workforce of 30 men were examined. The average age of the men was 40.5 years, and the mean length of exposure to trichloroethylene was only 16.5 months. No information was given on the trichloroethylene levels at the plant, but ventilation was known to be inadequate. Urinary trichloroacetic acid levels 24 hours post-shift were stated to be mainly in the range 50–100 mg/l.

A high incidence of symptoms, mainly relating to CNS disturbances or to irritancy, was noted in the

trichloroethylene workers. These included, in decreasing order, vertigo (79%), irritability (75%) drowsiness (67%), asthenia (67%), dyspeptic disorders (62%), cephalalgia (54%), eye irritation (46%), pruritis (37%), smarting in the throat (37%), hyperhidrosis (29%) and alcohol intolerance (21%).

Clinical examination indicated hepatomegaly in five workers (21%) and hyperbilirubinuria was noted in nine (29%), suggesting some hepatotoxicity in the exposed workers. However no effects were noted on serum aminotransferase levels, nor on total serum protein or cholesterol levels. No effect on renal function was noted in any of the workers, nor was there any evidence of peripheral neurotoxicity.

The value of this study is severely limited by the lack of any details regarding atmospheric trichloroethylene levels, and the failure to compare the results obtained with a matched control group. The results suggest that some mild hepatotoxicity may have occurred in the workers exposed to trichloroethylene levels sufficient to produce marked disturbances in the CNS. However insufficient data are given to draw a definite relationship between the liver toxicity and exposure to trichloroethylene. There was no evidence for any renal effects, nor any peripheral neuropathy.

Another group of investigators has reported increased serum beta- and gamma-globulins and some abnormalities in the cephalin flocculation test in workers regularly exposed to trichloroethylene.¹⁸⁷ No details were given on environmental trichloroethylene levels, nor whether any symptoms were noted in these workers.

Some evidence of liver damage was also noted in a group of 12 women workers from an Italian factory where trichloroethylene was used.¹⁸⁸ All the women examined had experienced symptoms of CNS disturbances and had been employed at the factory for 2–3 years. The trichloroethylene was used as an adhesive to join rubber strips; it was spread over one side of the strip, and allowed to evaporate partially, before joining the strips. No information was given regarding the atmospheric trichloroethylene levels, but these were probably high.

Symptoms noted in all the workers included headaches, dizziness, and feeling of elation; some had dyspepsia. Physical examination revealed slight enlargement of the liver in six of the subjects, the liver being painful on palpation. Serum gamma-globulin levels were raised in these six individuals, and increased serum bilirubin levels were noted in two. No effects were however observed on serum total protein, albumin, cholesterol (total and esterified) and alkaline phosphatase.

The value of this study is limited by the very small numbers involved, the lack of information regarding the atmospheric trichloroethylene levels, and the failure to use a control group. However as in the previous investigation the results suggest that some

liver damage occurred in women exposed to trichloroethylene levels sufficient to produce marked CNS disturbances.

Abnormalities in liver function were also reported in an investigation of 22 workers (15 male, seven female) exposed to trichloroethylene at a dry-cleaning establishment.¹⁸⁹ Two tests were carried out, bromosulphophthalein clearance and colloid stability. Abnormal results were obtained in eight individuals in one test only, and in three subjects in both tests. However it appeared that these effects could be related to excessive alcohol consumption rather than exposure to trichloroethylene, and it was felt that any potential hepatotoxicity of the compound was low.

Brief details only have been reported of a later study by the same group involved in measuring serum aminotransferase levels in persons chronically exposed to trichloroethylene.¹⁹⁰ Of the 31 workers examined, values in the pathological range were noted in only three subjects. Ingestion of alcohol (40 ml as brandy) was shown to result in a marked increase in serum aspartate aminotransferase levels in those workers exposed to trichloroethylene; this dose had no effect in individuals not exposed to trichloroethylene. Insufficient details were given for any assessment of the significance of these results.

There is another report of evidence of liver damage being noted in 14 workers exposed to trichloroethylene.¹⁹¹ In no case were the results complicated by alcohol or drug abuse, nor malnutrition or any disorders of metabolism such as diabetes. Only brief details were however given regarding exposure conditions. It was stated that in ten of the cases environmental levels of trichloroethylene at work had exceeded the East German MAC value ($50 \text{ mg/m}^3 - 9 \text{ ppm}$), but no further details were available. It was known that the patients had experienced symptoms of trichloroethylene toxicity (vertigo, headaches, tiredness, nausea, vomiting and loss of appetite).

Physical examination revealed three cases of enlarged liver. Raised serum enzyme markers for liver damage (aspartate and alanine aminotransferase and aldolase) were noted in nine individuals, and raised serum gamma-globulin levels in five. Some impairment in a liver function test (bromosulphophthalein clearance) was noted in five of the men. Liver biopsies were carried out in 13 of the 14 subjects. Fatty deposits were noted in 11, with distinct fatty liver being diagnosed in seven of these cases. Considerable iron deposits were noted in eight, and lipofuchsin deposits in two of the samples.

These results suggest that repeated exposure to trichloroethylene levels sufficient to produce marked signs of CNS toxicity and gastric disturbances may produce liver damage (fatty liver) with some impairment of function.

Some evidence of slight impairment of liver function was noted in 70 workers (including 43 women)

occupationally exposed to trichloroethylene in Yugoslavia.¹⁹² The subjects worked either in factories using trichloroethylene for degreasing purposes, or for cleaning textiles. Limited data on environmental trichloroethylene levels in the factories using degreasing tanks indicated that these were very variable depending on the sampling position; values in the range $500-4000 \text{ mg/m}^3$ (93-743 ppm) were obtained. The corresponding values where trichloroethylene was used for cleaning textiles were $1500-5800 \text{ mg/m}^3$ (279-1078 ppm). Each individual was subjected to medical and clinical examination, aimed primarily at investigating for hepatotoxicity. The following methods of assessing liver function were carried out: thymol turbidity test, flocculation test and cephalin-cholesterol test.

Physical examination revealed slight liver enlargement in 14 individuals (20%), and some abnormalities in the liver function tests were noted in 23 persons (33%). These appeared to be related to length of exposure, being noted in 2/19 subjects (11%) with under one year's exposure, as compared to 9/19 (47%) in those with over ten years' exposure. Most changes were in the thymol turbidity test, but the effects were regarded as mild. Serum bilirubin levels and total serum protein levels were all within the normal limits. However electrophoretic examination of serum proteins showed some decrease in serum albumin levels in 28 (40%) of the workers. This again appeared to be dependent on duration of exposure.

These results suggest that prolonged exposure to levels of trichloroethylene of the order of several hundred ppm produces some slight liver impairment. However no control group was used, and the mild hepatotoxic effects noted may have been due to factors other than exposure to trichloroethylene.

Hepatomegaly has also been noted in a health survey of 118 male workers at a Brazilian motor factory.¹⁹³ Most were painters and no details were given of the atmospheric trichloroethylene levels. Signs and symptoms of toxicity noted included asthenia (10%), abdominal pain (7%), flatulence (3%) and weight loss (3%). No symptoms of CNS disturbances were noted. Hepatomegaly was noted in 16%. However alcoholism was common amongst the men with an overall incidence of 33%, and alcohol consumption was probably responsible for the increase in liver size.

It is unlikely that any of the toxic effects noted in this study were due to exposure to trichloroethylene. No symptoms of CNS disturbances were noted, and there was no evidence of alcohol intolerance (the incidence of alcoholism increasing with duration of exposure). Although the study was aimed at investigating the potential hepatotoxicity of trichloroethylene, the relevance of any of the effects to trichloroethylene exposure is doubtful.

No evidence of any liver damage was however noted in an investigation of a small group (12) of workers involved in degreasing operations at a factory in

Paris.¹⁹⁴ All the individuals had complained repeatedly of symptoms of CNS disturbances, and atmospheric trichloroethylene levels were believed to be in the range 900–3000 mg/m³ (167–558 ppm). Tests for liver damage were limited to a flocculation test, measurement of the electrophoretic pattern of serum proteins and measurement of prothrombin levels. No abnormalities were noted in any individual. In addition physical examination revealed no signs of liver damage.

Thus in this limited study there was no evidence for any hepatotoxicity in a small group of men with symptoms of trichloroethylene toxicity.

Summary of results of general health surveys of workers exposed to trichloroethylene

Although there are numerous reports of health surveys being carried out on workers occupationally exposed to trichloroethylene, their value was usually severely limited by the lack of any detailed information on the environmental trichloroethylene levels. Furthermore in most cases no control group was incorporated, and it is therefore difficult to assess the significance of many of the symptoms observed.

A high incidence of symptoms of CNS disturbances has been noted in workers exposed to mean trichloroethylene levels of about 100 ppm and above. These included fatigue, vertigo, dizziness, headaches, memory loss and impaired ability to concentrate. There are reports of visual disturbances (including diplopia) when the concentration was sufficient to produce 'pre-narcotic symptoms' (including feelings of drunkenness); mean trichloroethylene levels were probably around 200–300 ppm or more in these instances. Other effects noted at about 100 ppm and above have included inhibition of sensory nerves (paraesthesia), muscular pains and gastrointestinal disturbances. Intolerance to alcohol, presenting as a transient redness affecting mainly the face and neck (trichloroethylene 'flush') has also been frequently observed. In one study in Japanese workers symptoms of CNS disturbances have been reported in at least half the workers when exposed to mean trichloroethylene levels in the range 50–100 ppm, but not when the concentration was maintained below 50 ppm.

No significant hematological abnormalities were noted in any of these studies but some evidence to suggest liver damage was obtained from blood biochemistry measurements when the mean trichloroethylene concentration was around 250 ppm or more. In one case liver biopsy samples taken from a small group of workers with evidence of liver damage, not associated with alcohol or drug abuse, revealed signs of fatty liver in the majority of cases. No information was available on the environmental trichloroethylene levels to which these workers were exposed. No effect on serum enzyme markers for liver toxicity was noted in workers exposed to mean trichloroethylene levels of up to 160 ppm.

Neurotoxicity of trichloroethylene

Electroencephalograph (EEG) recordings have been made on workers whilst operating a trichloroethylene degreasing tank.¹⁹⁵ A total of six workers were investigated at two separate factories.

Trichloroethylene levels were monitored by sampling near the breathing zone during the shift. These were usually below 100 ppm, with an average exposure of about 50 ppm, except in one case where the average was near 100 ppm, with a maximum of about 115 ppm. The EEG was recorded using a telemetric procedure, with readings being taken every hour during the shift, when the subject stood or sat for a few minutes with his eyes closed. The results obtained were compared with those found in three of the individuals when subjected to work of similar physical activity, but not involving exposure to trichloroethylene.

In four of the six workers exposed to trichloroethylene, an increased appearance of alpha waves was noted. This alpha phase activity was usually of about 1–2 seconds duration, the amplitude increasing during exposure, but the frequency remaining unchanged. In no case was any theta or delta activity noted. Alpha activity was weaker or absent during exposures under control conditions.

These results in a very small group of workers, suggest that very minor changes in the EEG pattern occur in workers exposed to about 100 ppm of trichloroethylene. The significance of the slight effect observed is not known.

To investigate this further EEG recordings were made in volunteers exposed, under controlled conditions, to 95 ppm of trichloroethylene.¹⁹⁶ A total of 20 healthy male subjects, average age 27 years, was used. Subjects, in groups of four, spent the mornings in the exposure chamber. The EEG was recorded for one minute every hour whilst the subject had his eyes closed, and all external stimuli were excluded. The first readings were taken under control conditions; the second readings were exactly one week later, during which time the individual was exposed to mean levels of trichloroethylene of 95.3 ± 8.2 ppm (monitored continuously). All EEG tracings were recorded manually, with emphasis on alpha wave activity; the duration, amplitude and frequency were noted.

The EEG pattern found in the volunteers under control conditions revealed no marked abnormalities. No significant changes were noted when the same individuals were exposed to trichloroethylene. A slight increase in the duration of alpha activity was noted during the first two hours of exposure only: no effects were noted on the amplitude or frequency of these alpha waves and the changes were minor and felt to be of no biological relevance.

Thus in this study no significant EEG changes were noted in volunteers exposed to about 95 ppm of trichloroethylene.

Thus to summarise, the limited evidence available suggests that no significant abnormalities occur in the EEG tracings of workers exposed to about 100 ppm of trichloroethylene.

Investigations of motor nerve conduction velocity

Symptoms of peripheral neurotoxicity (paraesthesia) have been noted in health surveys of workers exposed to trichloroethylene. Two studies have been reported in which this aspect has been investigated in greater depth, by measuring motor nerve conduction velocity.

One investigation involved a very small group of workers (two women, five men) in a printing works.¹⁹⁷ Their age range was 19–32 years and their duration of exposure varied between six months and nine years. The average environmental trichloroethylene levels to which the men were exposed at the time of the study was 20–40 ppm. The results obtained were compared with those found in a small control group (four women, nine men) stated to be of comparable age to the exposed workers. No further details were given.

Clinical examination and enquiry revealed no signs of neurological illness in any of the workers. The maximum and the minimum motor nerve conduction velocity was measured, using both the ulnar and the radial nerves, in each worker. The values found in the exposed workers for the maximum nerve conduction velocity in the ulnar were in the range 52.8–63.9 m/s and those for the minimum conduction velocity were 38.5–57.9 m/s. These were not significantly different from the values found in the control group, nor from normal values found by other workers. Similarly no difference was noted between the exposed and the control group in either maximum or minimum conduction velocity measurements in the radial nerve.

Thus in this study, using very small numbers of workers exposed to mean trichloroethylene levels of up to 40 ppm, nerve conduction velocity measurements gave no evidence of any peripheral neurotoxicity.

In a second study the maximum nerve conduction velocity was investigated in the ulnar nerve, in a small group (17) of workers who had developed symptoms of trichloroethylene toxicity whilst working at various different factories in Poland.¹⁹⁸ The subjects were mainly women (14 out of the 17), and they had been occupationally exposed to trichloroethylene for between two and 20 years. The principal symptoms noted were dizziness, headaches, fatigue, irritability, sleep disturbances, and reduced appetite. Paraesthesia in the extremities was noted in three of these workers and facial sensory loss in one.

Values obtained for the motor nerve conduction velocity in the exposed workers were in the range 55–62 m/s. These values were stated to be in the normal range expected, but no control group was used for comparison purposes. Electromyographic measurements were obtained from a small sub-group (five); there was no evidence of any abnormal response.

This study in only a small number of workers provided no evidence of any impairment of nerve conduction velocity in subjects with symptoms of trichloroethylene toxicity.

Thus the effects of occupational exposure to trichloroethylene on motor nerve conduction velocity have not been extensively investigated. The very limited evidence available suggests that there is no impairment of nerve conduction velocity in workers showing symptoms of trichloroethylene toxicity. These studies provide no evidence for any peripheral neurotoxicity in persons occupationally exposed to trichloroethylene.

Studies using behavioural tests

The effect of repeated exposure to trichloroethylene on performance of a range of behavioural tests has been investigated both in volunteers, under controlled conditions, and in workers occupationally exposed to trichloroethylene.

Studies in volunteers

The effect of exposure to trichloroethylene at 100 ppm on performance of a range of tests designed to measure a number of psychological/psychomotor parameters has been investigated.¹⁹⁹ Only a very small number of subjects (four) was used in this study. Exposures to 100 ppm of trichloroethylene were for six hours a day (with a one-hour break after the first three hours) on four successive days. Each subject performed a range of tests during every morning and afternoon period. These included simple reaction time test, hand steadiness test, time estimation test and critical flicker fusion test. Control values were obtained when the same individuals were subjected to identical conditions, over a separate four-day period, but with no exposure to trichloroethylene.

Exposure to 100 ppm of trichloroethylene for five days produced no significant impairment in performance in any of the tests.

A similar trichloroethylene concentration has been used in another study, again using very small numbers of volunteers.²⁰⁰ The exposed group consisted of three male and four female students aged 19–28 years. They were exposed to 100 ppm of trichloroethylene for six hours a day (8am–2pm) on five successive days. During each exposure period a range of behavioural tests were performed. The results obtained were compared to those found in a similar control group exposed to a 'placebo' atmosphere produced by a mixture of hair lotion and disinfectant.

The following tests, designed to measure a wide range of psychomotor/psychological functions, were performed twice during each exposure period (once near the beginning and once near the end). These tests included the d-2 test designed to measure attention concentration and perseverance, and the 'short syndrome' series of tests comprising a set of nine tests to demonstrate perceptive and cognitive function. Full

details of the actual tests were not given. In addition an assessment of mood/anxiety state was made.

No significant difference was reported in the performance of any of the behavioural tests between the exposed and the control groups. However only brief details of the overall results obtained in each series of tests were given; the results of individual tests were not available. A full assessment of this work is thus not possible.

The only significant difference noted between the exposed and control workers was in anxiety state. Anxiety levels fell to a greater extent in the control group during the course of the investigation. However the two groups were not strictly comparable in this aspect, since the individuals in the group exposed to trichloroethylene knew each other prior to the start of the study, whereas those in the control group did not. Thus social factors may have accounted for this difference.

Thus in this study in a small group of volunteers, no impairment in performance of a range of behavioural tests was noted in subjects exposed to 100 ppm of trichloroethylene for six hours a day for five days. Insufficient details were however given for a full assessment of the work.

Studies in persons occupationally exposed to trichloroethylene

A small group (eight) of workers exposed to trichloroethylene at a screen-offset printing works, were subjected to a range of tests, designed to measure psychological/psychomotor performance, after work.²⁰¹ The mean atmospheric levels of trichloroethylene in the room air at various locations were about 50 ppm. The exposed group consisted of seven men and one woman, their age range being 23-38 years. Each individual was subjected to a range of behavioural tests shortly after the end of the work-shift on Friday afternoon, and prior to work on the following Monday. The tests were repeated six weeks later immediately prior to, and after a 15-day vacation period. The tests included the d-2 test (to measure attention and perseverance), the MWT-A test (a short intelligence test) and short-tests to measure motor performance, recognition and memory. Mean urinary trichloroacetic acid levels at the time of the first batch of tests (end of Friday workshift) were 140 µg/mg of creatinine; values the following Monday morning were 88 µg/mg of creatinine. The values obtained in the second series of tests were 153 µg/mg of creatinine and 25 µg/mg of creatinine before and after vacation respectively.

No significant difference was noted in the performance of any of these tests, at any time. The results obtained in the d-2 tests were somewhat complicated by a slight improvement being noted during the series of tests, due presumably to a training effect; the results obtained were believed to be comparable to those expected in a normal population, but no control group was included for comparative purposes.

No significant effects on performance of a range of behavioural tests were noted in this study in workers occupationally exposed to mean atmospheric levels of trichloroethylene of about 50 ppm. However the value of this study was very limited by the small number of subjects used.

The reaction times of a small group of women workers involved in the operation of trichloroethylene degreasing baths, at two separate Australian factories, have been investigated.²⁰² Again only very small numbers were involved, with four workers at each site. Mean breathing zone concentrations of trichloroethylene near the degreasing tanks were about 245 ppm (range 148-418 ppm) at one factory and 27 ppm (range 3-87 ppm) at the second factory. The study was apparently prompted by complaints of symptoms of drunkenness in some women operating the degreasing bath; it is not clear whether these complaints were solely from the first factory, or whether they had occurred in workers from both sites.

Each worker performed a complex reaction time (eight-choice) test during four separate sessions. These were prior to and at the end of the morning shift (four hours), and at the beginning and end of the afternoon shift. The results obtained were compared to those obtained in control groups, consisting of four women workers from other areas of each factory, where trichloroethylene was not used. No further details of the comparability of the exposed and control groups were given.

The initial mean reaction times were comparable in the exposed and control groups, being 102-103 x 10⁻² seconds at the first factory and 95-97 x 10⁻² seconds at the second factory. Reaction time decreased somewhat during the day in both the control groups, showing some improvement in performance due presumably to a training effect. However a marked increase in reaction time was noted during the day in the exposed workers at the first factory, where the environmental trichloroethylene levels were highest. In these workers mean reaction times at the end of the day were 124 x 10⁻² seconds as compared to 96 x 10⁻² seconds in the control group at the comparable time. No increase was noted during the day in the workers at the second factory and only a small difference was noted between the exposed and control groups at the end of the day (98 x 10⁻² seconds as compared to 89 x 10⁻² seconds respectively).

These results suggest that exposure to mean trichloroethylene levels of about 250 ppm resulted in some impairment of performance in reaction time tests. Symptoms of marked CNS disturbances (drunkenness) had been noted in these workers. No marked impairment was noted in workers exposed to up to about 90 ppm trichloroethylene. However no details were given as to the comparability of the control and exposed groups regarding age, physical activity during the work shift, or any other factors. The significance of the results obtained cannot therefore be fully assessed.

Thus summarising the effects of trichloroethylene on performance in behavioural tests, studies in volunteers provided no evidence to suggest that repeated exposure to 100 ppm of vapour over a five-day period resulted in any impairment of performance. Studies in workers exposed to mean levels of trichloroethylene of about 250 ppm showed that this resulted in a marked impairment of performance in reaction time tests. Symptoms of CNS disturbances had been noted in these workers during the workshift. No effects were observed in the performance of a range of psychological/psychomotor tests by workers exposed to mean trichloroethylene levels of about 50 ppm. The value of all these results was however limited by the small numbers of individuals studied.

Cardiovascular effects

Experience of the use of trichloroethylene as an anaesthetic has shown that acute exposure to anaesthetic concentrations may result in cardiac arrhythmias, including potentially serious multifocal ventricular ectopics during the deeper phase of anaesthesia. Cardiac arrest has however occurred only very rarely during trichloroethylene anaesthesia.

Sudden death has also been reported in four men occupationally exposed to trichloroethylene during the operation of a degreasing tank.¹⁶¹ Trichloroethylene levels were known to have been sufficiently high to produce symptoms of CNS disturbances, and all the men had continued work despite repeated complaints of drowsiness, dizziness and vomiting. All died within several hours of leaving work, and no significant autopsy findings were recorded. It was suggested that death was produced by ventricular fibrillation, due to the sensitising effect of trichloroethylene on the action of endogenous catecholamines on the myocardium. There are a few other reports of isolated cases of sudden death from cardiac arrest following exposure to high concentrations of trichloroethylene, either occupationally²⁰³ or following repeated deliberate exposure (trichloroethylene sniffing).²⁰⁴

The effect of occupational exposure to trichloroethylene on the cardiovascular system, and particularly on heart rhythm, has been investigated in a number of studies. These are summarised below.

Electrocardiographic examination was included as part of a health survey of a small group of workers (30) at an Egyptian printing factory; most were below 40 years of age and had been employed for more than three years.¹⁸⁵ Mean trichloroethylene levels were in the range 41–163 ppm at different parts of the plant at the time of the study. A high incidence of symptoms of CNS disturbances was noted in these workers. No abnormalities in the ECG recording were noted.

Electrocardiograms have also been recorded from 77 workers occupationally exposed to trichloroethylene in various industries in Sweden.¹⁷⁸ Symptoms of marked CNS disturbances were noted in many of these workers. Pathological ECG tracings were noted in approximately one-third of those studied; these were

mostly indicative of disturbances in cardiac autonomic mechanism. It was suggested that abnormalities such as ectopic auricular rhythm, shifting pacemaker and perisinus rhythm were sequelae of exposure to trichloroethylene, whilst the disturbances in the conduction system were not related to exposure. However insufficient information is available to determine whether any of the effects were related to exposure to trichloroethylene.

Haemodynamic measurements, and electrocardiograms, were recorded during examination of 44 workers (mainly women below 30 years of age) exposed to trichloroethylene at a Rumanian factory.¹⁸¹ Although it was reported that routine atmospheric monitoring only occasionally gave readings above 200 mg/m³ (37 ppm), pre-narcotic symptoms had commonly been experienced by the workers. These included marked episodes of inebriation, making it necessary to go out into the fresh air; in addition there was one instance of loss of consciousness for a short period. Atmospheric levels of trichloroethylene were thus likely to have been very considerably higher at times than 200 mg/m³ (37 ppm).

Electrocardiography revealed a few abnormalities but these were believed to be related to pre-existing heart conditions rather than exposure to toxic chemicals. Comparison of the systemic haemodynamic measurements (Broemser Ranke physical method) obtained in the exposed workers with the results obtained using a small control group of ten subjects revealed a number of differences. The control group was stated to be of comparable age and sex to the exposed workers but no further details were given. A significant increase ($p \leq 0.02$) was noted in stroke volume, cardiac output, cardiac index and heart work in the exposed workers. The values obtained were 84.4 ± 18.9 ml, 6615 ± 1640 ml/l, 4036 ± 1100 ml/l/m² and $10.86 \pm 2.84 \times 10^8$ ergs respectively in the exposed workers, as compared to 68.4 ± 5.4 ml, 4830 ± 710 ml/l, 3077 ± 479 ml/l/m² and $7.84 \pm 0.91 \times 10^8$ ergs in the controls. These increases were considered to reflect an adrenaline-type increased sympathetic tone, which, it was suggested, could play a part in the possible sensitising effect of trichloroethylene on the action of endogenous catecholamines on the myocardium. However in view of the very limited details given of the control group no conclusions can be drawn from this investigation.

Effects on the cardiovascular system have been specifically investigated in a small group (20) of women workers at a factory in Sofia.²⁰⁵ The age range of the subjects was 34–47 years and they had been employed for between seven months and four years. The results were compared with those obtained in a control group of 58 healthy individuals of approximately the same age and stated to have 'similar work histories but without exposure to toxic chemicals'. No further details were given regarding the comparability of individuals in the control group to the exposed workers. No information was given regarding the

atmospheric trichloroethylene levels at the factory, apart from the statement that these were above the MAC value. Mean urinary trichloroacetic acid levels at the time of the study were 40.71 ± 6.61 mg/l in the exposed group and 1.58 ± 0.68 mg/l in the controls, but no details were given as to the time post-shift that these samples were taken. Urinary trichloroethylene levels were also determined in 11 of the exposed workers. The mean value obtained was 45.70 mg/l. However appreciable amounts were also present in the control workers, a mean value of 28.45 mg/l being obtained in this group. It is thus likely that the control workers had been exposed to significant amounts of trichloroethylene.

Cardiac effects measured in each subject included the simultaneous recording of ECG, carotid sphygmogram and phonocardiogram. In addition phase analysis of the left ventricular systole was carried out using a polycardiographic method. Significant differences were noted between the exposed and the control group in a number of polycardiographic indices. The cardiac cycle was shortened, the isometric period and the tension phase was prolonged, and the intrasystolic index was decreased. These results suggest some impairment of cardiac function, due to a prolongation of the ineffective phase of systole, in the trichloroethylene worker. However in view of the lack of details regarding the comparability of the exposed and control groups, and the possibility that the controls were also exposed to trichloroethylene, the significance of the cardiac changes noted cannot be assessed.

Results have been reported of a cross sectional study to investigate cardiac effects in 75 workers involved in degreasing operations using trichloroethylene at a West German factory.²⁰⁶ All the workers were subjected to medical examination, during which an ECG recording was made. The average age of the workers was 43 years (range 20-64), and the duration of employment was from two months to 20 years. Limited data available on atmospheric trichloroethylene levels suggested that these were about 100 ppm in the vicinity of the degreasing tank. Electrocardiographic recordings were made in a number of the workers at yearly intervals after the initial reading.

Abnormal ECGs were noted in three of the workers. In one case (right-heart block) the history suggested that this had existed for some years prior to working at the factory, and could not therefore be associated with exposure to trichloroethylene. In another case ventricular extra-systoles were noted in one healthy young worker (aged 29) who had been employed for six months. He was then transferred to another area and further ECGs were not recorded. The third case was a 50-year-old man who had been employed for 20 years. His ECG was normal during the first examination, but two years later signs of first degree AV heart block were present. Clinical and radiological examination revealed no abnormalities in this individual.

Thus of the three cases of abnormal ECGs noted in

the exposed workers, one was known to be unrelated to occupational exposure to trichloroethylene. It is not possible, in view of the very limited nature of the study, to assess the significance of exposure to trichloroethylene in the other two instances.

In a second study by the same investigators, ECG recordings of six workers using a degreasing tank were continually monitored, by telemetry, during one workshift.²⁰⁶ Average trichloroethylene levels at the time were 87 ppm. The results obtained were compared to those obtained in the same individuals during the workshift the next day when they were involved in jobs not entailing exposure to trichloroethylene. Ventricular extra-systoles were repeatedly noted in an apparently healthy 34-year-old man during and after the workshift involving exposure to trichloroethylene. No abnormalities were however noted during or after the second work-shift, which did not entail exposure to trichloroethylene. Examination (consisting of medical history plus clinical and radiological examinations) revealed no evidence of any ill-health in this individual.

A further group of six workers was monitored in a similar fashion over a 40-week period whilst exposed to trichloroethylene using the degreasing bath. In no case were any ECG abnormalities noted.

To investigate the effects on cardiac rhythm further studies were then carried out on a small group (20) of healthy male volunteers, under controlled conditions.²⁰⁶ The average age of the men was 27. Each subject was exposed to 95 ppm of trichloroethylene for four hours in an exposure chamber, during which time the ECG was monitored continuously; each subject remained seated throughout the exposure period. Abnormalities during the exposure period were noted in one individual. These again consisted of regular ventricular extra-systoles, which appeared after about 15 minutes exposure, and continued for about one hour. The ECG then returned to normal. No changes were noted in any subject during comparable conditions but in the absence of trichloroethylene.

Thus in this second series of studies, involving a total of 32 individuals exposed to 90-100 ppm of trichloroethylene either under occupational or controlled conditions, disturbances in cardiac rhythm were noted in two individuals. In both cases these consisted of ventricular extra-systoles, and in neither instance were any effects noted in the absence of trichloroethylene. The results suggest that such ventricular arrhythmias may occur in a small proportion of workers exposed to around 100 ppm of trichloroethylene. However in view of the small number involved, further work is required in this area before any definite conclusions can be drawn.

Thus to summarise, a number of studies have been carried out to investigate the effect of occupational exposure to trichloroethylene on the cardiovascular system, particularly cardiac rhythm. The value of these

has however usually been severely limited both by the lack of data on environmental levels present, and the failure to use an adequately matched control group. Some evidence is available to suggest that exposure to about 100 ppm of trichloroethylene may produce ventricular arrhythmias in a small proportion of the persons exposed. However the numbers involved were very low, and further work is needed to investigate this aspect before any definite conclusions can be drawn.

Effects on hearing and the vestibular system

There are a few reports of detailed studies being carried out for ototoxicity and effects on the vestibular system during health surveys of workers exposed to trichloroethylene.

Twenty-two workers from a tannery with a total workforce of 30 men, were investigated for auditory and vestibular defects.¹⁸⁶ No data were available on the environmental trichloroethylene levels to which these workers were exposed, but there was a high incidence of symptoms of CNS disturbances and also signs of irritant effects on the mucous membranes in the workforce.

Some impairment in auditory function (hypacusis at 4000 Hertz) was noted in six of the workers, but this was likely to have been due to noise; all worked in the drum department which was described as 'very noisy'. Vestibular examination revealed abnormalities, described as symmetrical bilateral vestibular hyperreflexia, in 11 individuals (50%). These were apparently markedly reduced in a few instances where the men were re-examined two months after exposure ceased.

In a separate survey, the results of studies to investigate effects on hearing (audiometric test) and balance (rotary and calorific tests) were reported in 40 workers exposed to trichloroethylene at various factories in Poland.^{183, 207} The age range of these men was 19-50 years and all had experienced symptoms of trichloroethylene toxicity.

Audiometric tests revealed hearing defects in 26 of these men (65%); these consisted of perceptive impairment at high frequency (2000-3000 Hertz). The frequency of this impairment appeared to be related to the length of exposure, with 13/22 cases (59%) in those employed for 4-10 years and 10/11 cases (91%) in those employed for more than ten years. This may however have been complicated by the increasing age of the men with longest employment. Disorders of balance (revealed as diminished excitability of the vestibular organ) were noted in 19 subjects (48%). Hearing disorders were present in all of these individuals, and most had been employed for over 14 years.

Thus to summarise, these studies provide some limited evidence to suggest that prolonged occupational exposure to trichloroethylene, in concentrations sufficient to produce marked symptoms of toxicity, may result in hearing defects, consisting of perceptive

impairment at high frequency. Abnormalities in the vestibular system have also been noted in these workers.

Carcinogenicity

Mortality studies

A mortality study has been reported on a small group of workers exposed to trichloroethylene at various work places in Sweden.²⁰⁸ The main supplier of trichloroethylene in that country has provided a biological monitoring service, based on urinary trichloroacetic acid measurements, to users since the early 1950s. The subjects for this investigation were determined from the records of that laboratory. A total of 518 male workers were identified as having been monitored prior to 1970; this number was relatively small compared with the total number potentially available, as many of the records prior to 1967 were destroyed, in an apparently random manner. The mortality in the cohort of 518 workers over the period 1955-75 was investigated, and the cause and age at death identified. The results obtained were compared to those expected from the cause- and age-specific mortality data from national statistics for the appropriate calendar year. No data were available on the atmospheric levels to which men had been exposed, but the results from urinary monitoring of trichloroacetic acid suggested that these were low (trichloroacetic acid concentration usually below 100 mg/litre).

A total of 49 deaths occurred in the exposed cohort during the period, as opposed to 62.0 expected from national statistics. Eleven of the deaths in the trichloroethylene workers were due to malignant tumours as opposed to 14.5 expected. No particular tumour type was significantly over-represented, although two stomach tumours and two leukaemias were noted; one of the leukaemia deaths occurred less than four years after initial exposure (as judged by monitoring data). The results were also available on a subgroup of workers where ten years or more had elapsed since the initial monitoring for exposure to trichloroethylene. Again no increase in observed deaths was noted, with 37 identified as compared with 39.8 expected, nor in deaths due to malignancies, with nine as compared with 9.5 expected.

Thus this study provides no evidence of any increased incidence of death due to malignant tumours or due to any other cause in workers exposed to trichloroethylene. No data were directly available on the atmospheric levels of the material, but these were probably low. The numbers involved in this study were too small, and the latent period since initial exposure - too short, to allow any conclusions to be drawn regarding the carcinogenicity of trichloroethylene.

A similar mortality study, but based on a slightly larger group of individuals, has been carried out in Finland.²⁰⁹ A total of 2205 persons were identified

from the records of the main laboratory in that country responsible for urinary analysis of trichloroacetic acid for diagnostic or monitoring purposes, as having been exposed at some time between 1963 and 1976. The laboratory concerned was known to carry out over 90% of analyses for such purposes in Finland. Most of these individuals (2084, 91%) were traced. These, together with an additional 33 workers known to have been exposed to trichloroethylene during the period, formed the exposed cohort of 2117 subjects (1148 men, 969 women). The urinary trichloroacetic acid levels found in the subjects were usually low, being below 100 mg/l in about 91% of the readings, suggesting that exposure to trichloroethylene was low.

The vital status, or cause of death of members of the cohort was ascertained, as of November 1976, from the Population Data Registry of the Central Statistics Office in Finland. Additional information was obtained on cancer deaths from the Finnish Cancer Registry. The age-, sex- and cause-specific mortality rates were compared to the expected rates, calculated on the basis of national statistics, for the year 1971, both for the total cohort and a subcohort consisting of those exposed before 1970.

The total number of deaths in the exposed cohort during the period under investigation was 58, as compared with 84.3 expected (SMR 69). This decreased mortality, as compared with the expected value, has frequently been shown in studies on workers, and may be explained by the 'healthy worker effect'. No statistical difference was noted in the age or sex specific overall mortality pattern, nor in cancer deaths, either in the total cohort, or in the sub-group exposed before 1970. There were 11 cancer deaths in the total group, as compared with 14.3 expected. These consisted of four cases of lung cancer (three men, one woman), three cases of cancer of the uterus, and single cases of other types of malignancies. A total of nine deaths due to malignancies were noted in those exposed prior to 1970, as opposed to 12.3 expected in this group.

Thus this study provided no indication of any increased risk of death from cancer or any other causes in the exposed group. However the work has a number of serious limitations regarding the detection of carcinogenic effects. The time interval between initial exposure and the study was too short, in view of the known latency of the disease. Even in the sub-group exposed before 1971, the range was only 6-13 years. The age of the cohort was relatively young, with 60% of the men and 40% of the females being below 40 at the end of the study period. These limitations were recognised, and it is planned to follow-up the cohort at five-year intervals to obtain more meaningful data. Other limitations include the fact that no direct data were available on exposure levels. The urinary trichloroacetic acid values suggest that these were low, but in a number of cases the laboratory analysis may have been requested in error (for example the person may have been exposed to tetrachloroethylene rather

than trichloroethylene). Inclusion of workers not exposed to trichloroethylene would result in a marked dilution effect, reducing the sensitivity of the method. In view of these limitations, no conclusions can be drawn from this study regarding the carcinogenicity of trichloroethylene.

The cause of death in a small group of laundry and dry cleaning workers has been investigated in the Kansas and St Louis area.²¹⁰ A total of 330 deaths were identified in members of the two local branches of the Laundry, Dry Cleaning, and Dye-houseworkers' Union between 1957 and 1977. It was accepted that this figure did not give complete coverage of all deaths amongst the branch union members over that period, and obviously did not include non-union workers in the industry. Most of the individuals (279; 85%) had worked solely in dry cleaning establishments. The workers' exposure to trichloroethylene was likely to have been low since tetrachloroethylene was known to have been the predominant cleaning fluid used since the early 1950s. There may have been some exposure to trichloroethylene, particularly prior to 1950; at this time some exposure to carbon tetrachloride may have occurred. The sex, race, age at death and cause of death was obtained from the death certificate of each of the workers. The values obtained were compared with those expected from national statistics for the years 1957-70.

An increased incidence of death due to malignancies was noted in the deaths amongst the laundry and dry cleaning workers, with 87 observed as compared with 67.9 expected (PMR 128). This was due primarily to an excess of lung cancer (17 as compared with ten expected. PMR 170) and cervical cancer (ten as compared with 4.8 expected. PMR 208). An increase was also noted in the incidence of leukaemia (five compared with 2.2 expected. PMR 227) and cancer of the liver and bile duct (four as compared with 1.7 expected. PMR 235, but only one case of primary liver cancer was identified). However it was recognised that the group of exposed workers was low paid, and these results may reflect socioeconomic factors. No attempt was made to compare the results with a more appropriate control group. In addition the value of the study is severely limited by the small numbers involved, the possibility of some bias in the selection of subjects, and the exposure to mixed solvents (mainly tetrachloroethylene rather than trichloroethylene).

In view of the limitations listed above, no conclusions can be drawn from this study regarding the carcinogenicity of trichloroethylene.

A similar, but slightly larger investigation of mortality amongst workers in the metal polishing and plating industry has been reported²¹¹ some exposure to trichloroethylene may have occurred during degreasing operations. The deaths of 1292 white male workers were identified from the obituary columns of the national union journal (the *Journal of Metal Polishers, Buffers, Platers and Allied Workers*) over the period 1951-69. The cause of death was established from the

death certificates, and the results compared with the number expected from similar aged groups of white males using national statistics.

The total number of deaths due to malignancies was only slightly greater than expected (244 compared with 223.7). The only specific types of tumour showing an increased incidence were cancer of the oesophagus (ten as compared with 5.4 expected, PMR 185) and primary liver cancer (five as compared with 1.8 expected, PMR 278). The increase was apparently confined to that group where metal polishing or plating was mentioned specifically as occupation on the death certificate (about 66% of the cohort). No increase in the two types of cancers were noted when other occupations were given; presumably this covers metal degreasers using trichloroethylene.

It is difficult to assess the significance of these results. The numbers were small, and the method of selection may not have been representative of a cross-section of the workers in the metal industry. Interpretation is further complicated by the mixed exposure particularly to metals (chromium, nickel, copper, iron, lead, zinc) as well as corrosive acids and alkalis, and solvents, including tetrachloroethylene. The slight increase noted in cancer of the oesophagus and liver appears to involve workers concerned solely with metal plating or polishing, rather than those exposed to solvent during degreasing operations.

No information can be obtained from this study regarding the effects of exposure to trichloroethylene.

A mortality study has been carried out on workers from dry cleaning establishments in Prague, Czechoslovakia.²¹² Again only very small numbers were involved. A total of 65 workers were identified as having been exposed to trichloroethylene for at least one year between 1950 and 1975. It was not stated how these individuals were identified, nor was any indication given of the extent of coverage of dry cleaning workers in that area. Only 57 (86%) of these workers could be traced, and their vital status determined. The age of the men at the time of the study (or death) ranged from 25–85 years, with most (80%) being over 45, and their duration of employment at the dry cleaning establishment was 1–35 years (being over five years in 60% of the cases). The time period from initial exposure to the time of the study was greater than 20 years in nearly 50% of the cases (range 5–50 years). No details were available on the atmospheric trichloroethylene levels to which the men were exposed, but the results of urinary trichloroacetic acid measurements indicated that considerable exposure had occurred, with urinary concentrations being above 100 mg/l in 60% of the cases, and maximum values being about 1000 mg/l.

The presence of tumours was established in six of the 57 workers, (three lung, two rectal, one bladder [occurring in a person who also had cancer of the rectum] and one tongue), but apart from the latter these all occurred in subjects aged 58 or over (range

58–75). Comparison with national statistics indicated that this distribution was roughly similar to that expected in a population of the age range concerned. No cases of liver cancer were identified.

These results suggest that no increase in cancer incidence occurred in a very small group of workers exposed to trichloroethylene. However the numbers involved were far too small to draw any definite conclusions from this study.

An alternative approach has been used to investigate any association between exposure to trichloroethylene and liver cancer.²¹³ The work history of all patients with liver tumours treated at hospitals in Prague during the years 1972 and 1974 were investigated, in an attempt to establish whether there was any over-representation of workers exposed to trichloroethylene. It was estimated that there were about 550 persons occupationally exposed to trichloroethylene, either at dry cleaning establishments or using degreasing baths in the metal industry, in the Prague area. A total of 63 cases of primary liver tumours, confirmed histologically, were treated during the two years of the study. Some limited occupational data were available, from the records of the Old Age Pensions Office, but this was available on only 56 of the patients. These consisted of 39 men (average age 69) and 17 women (average age 56). The last recorded occupation was most frequently labouring, followed by office working and driving. In no case was there any record of any individual having worked in a job categorised as Hazard Category II (this includes exposure to trichloroethylene, and has required legal notification for the 15 years preceding the study).

No association was shown in this study between patients with liver cancer and occupational exposure to trichloroethylene. However the numbers involved were too small, and the data on occupational exposure too limited, to draw any conclusions from this study regarding the carcinogenicity of trichloroethylene.

Summary of mortality studies

Although a number of mortality studies have been reported on workers potentially exposed to trichloroethylene, these all have serious limitations. There is at present no evidence to suggest that exposure to trichloroethylene is associated with an increased incidence of cancer to man.

Cytogenetic studies

A cytogenetic study has been reported on a small group (28) of men involved in metal degreasing operations using trichloroethylene at various plants in West Germany.²¹⁴ The average age of the men was 42.5 years, but the age range was wide (23–67 years). The duration of exposure was between 1–21 years. The results were compared with those obtained in a small group (ten) of men of somewhat younger age (mean 28.3 years, range 15–45 years). No further details were given regarding the comparability of the two groups.

Metaphase analysis was performed on phytohaemagglutinin-stimulated subcultures of peripheral lymphocytes from the workers. In the exposed workers 100 mitoses were analysed in 16 individuals but a smaller number (23-86) in the remainder. In the controls 71-100 mitoses were analysed. In both cases these included hypodiploid cells, containing less than the full complement of chromosomes.

A slightly increased incidence of breaks was noted in the exposed workers (3% of cells as compared with 0.6% in the controls), but in view of the uncertainties in the comparability of the exposed and control groups this was unlikely to be significant. No other chromosome aberrations were noted in the exposed workers, apart from a small marker chromosome in one individual. A somewhat higher incidence of hypodiploid cells was noted in the exposed workers, with an incidence of over 12.8% being noted in 9/28 (32%) of the exposed workers as compared with 1/10 (10%) of the controls. However in view of the lack of any significant chromosomal aberrations in the exposed workers, this is likely to represent an artifact produced during the preparation of the cells, and to have no biological significance.

Thus no evidence of any significant chromosomal abnormalities was noted in this study on a very small group of workers exposed to trichloroethylene. No data were available on the atmospheric levels to which these men were exposed.

Effects on the reproductive system

Evidence of teratogenicity

An attempt was made to obtain information on the incidence of congenital malformations in the offspring of women workers exposed to trichloroethylene, during a retrospective mortality study in Finland.²⁰⁹ The subjects were identified on the basis of records from the main laboratory in that country responsible for determining urinary trichloroacetic acid levels for diagnostic or monitoring purposes. From their records over the period 1963-76 a total of 969 women were identified as having been possibly exposed to trichloroethylene. No data were available on the actual exposure levels, but these were probably low, as over 90% of the urinary trichloroacetic acid determinations were below 100 mg/l. The number of offspring with congenital malformations born to these women during the period of the study was determined by reference to the Register of Congenital Malformations kept by the Finnish Medical Board since 1963 (registration is compulsory and 100% coverage of all severe malformations is believed to occur, with about 60-70% coverage of the minor types of malformation).

No malformed offspring were recorded as having been born to any of the exposed women. Although the actual number of pregnancies occurring among the women during the study period was not known, a

rough estimate was made on the basis of national age-specific fertility rates. From these figures it was calculated, using national figures for the incidence of congenital malformations, that about three malformed offspring would have been expected in this population.

These results thus suggest that no increased incidence of malformations occurred in women workers exposed to trichloroethylene. However the numbers involved were very small, and furthermore no direct data were available on exposure levels. Urinary trichloroacetic acid levels suggested that exposure was usually low, and may have been negligible in some cases (if, for example, the laboratory analysis had been requested in error in a person exposed to tetrachloroethylene rather than trichloroethylene). In view of the limitations no conclusion can be drawn from this study regarding the teratogenicity of trichloroethylene.

Effect on the female reproductive cycle

An increased incidence of menstrual disorders has been reported in a health survey of women workers at three Polish workshops.¹⁶⁴ The average age of the women was 37 years, and their average length of exposure 9.2 years. A control group of 44 women of similar age and 'training' but not exposed to trichloroethylene was used; no further details were given.

The mean atmospheric trichloroethylene levels at the three workshops was stated to be 200 mg/m³ (37 ppm) but no information was given on the concentration range, variability between sites, or methods used. A high incidence of symptoms of CNS disturbances was noted in the women, suggesting that exposure levels were frequently above 200 mg/m³.

A higher incidence of amenorrhoea was reported in the women exposed to trichloroethylene (18%), as compared with the control group (2%). However absenteeism due to 'female disorders' was stated to be lower in the exposed workers than the control group. Results suggest that exposure to levels of trichloroethylene sufficient to produce marked CNS disturbances may result in menstrual disorders in women workers. However, insufficient details were given regarding the control group, and as to how adequately this was matched to the exposed workers, to come to any definite conclusion.

A high incidence of menstrual disorders has also been reported amongst women workers from various Czechoslovakian metal factories and dry cleaning establishments.¹⁷⁷ A high incidence of CNS disturbances was noted amongst these women, suggesting that trichloroethylene levels were relatively high. No further details were given, and the significance of the report cannot be assessed.

Effects on the male reproductive system, and urinary excretion of adrenocorticosteroids

Reduced libido has been reported in male workers exposed to trichloroethylene levels sufficient to

produce marked CNS disturbances.^{177, 185} In one study at factories where complaints of decreased potency were described as 'very common' among the male workers, no significant effects were noted on the urinary excretion of 17-ketosteroids.¹⁷⁷ However no details were given of the results obtained, or of the controls used and it is not possible to assess the significance of this observation.

The effect of occupational exposure to trichloroethylene on the urinary excretion of adrenocorticosteroids, has also been investigated in a small group of workers (14) exposed to trichloroethylene at a factory in the Netherlands.²¹⁵ Urinary levels of both 17-oxogenic steroid (derived from the adrenal gland) and 17-ketosteroid (derived from both the adrenals and the testes) were measured. The average age of the exposed men was 42 years, and their length of exposure varied from a few months to many years. No data were available on the atmospheric levels at the factory, but all subjects were stated to excrete trichloroacetic acid in their urine. The results obtained were compared with those found in a similarly sized group of male workers, matched for age, work-load, working and social environment, and

activity pattern. No trichloroacetic acid was detected in the urine of any of the control group.

No significant difference was noted between the exposed and the control groups as regards the urinary excretion of either steroid. The value of this study is however severely limited by both the small number of subjects investigated, and the absence of any data on exposure levels.

Summary of effects on the reproductive system

There is no evidence of any increased incidence of adverse effects on the offspring of women workers exposed to trichloroethylene. This aspect has not however been studied in any detail. There are reports of an increased incidence of menstrual disorders in women workers, and of decreased libido in male workers, exposed to levels of trichloroethylene sufficient to produce marked disturbances in the CNS. The effect in male workers did not appear to be related to any significant decrease in urinary excretion of adrenocorticosteroids. However these results were only briefly reported, no details of any control group being given in either the studies on the male or female workers, and it is not possible to assess the significance of results.

Tables

Table 1 The excretion of urine metabolites in humans following exposure to trichloroethylene

Exposure conditions	Trichloroacetic acid				Trichloroethanol				Total trichloro compounds				Ref
	% eliminated	Time of max excretion	Correlation coefficient	100 ppm /8 hr equivalent	% eliminated	Time of max excretion	Correlation coefficient	100 ppm /8 hr equivalent	% eliminated	Time of max excretion	Correlation coefficient	100 ppm /8 hr equivalent	
93-160 ppm/5 hrs	19	24-48hrs			50	2 hrs							27
370 ppm/10 mins	6-16	20-50hrs											29
100-200 ppm/30 mins		9-13hrs							16-18 in 22h	5-9hrs			32
70 ppm/4hrs on 5 days	24				43								33
Anaesthetic levels		2-4 days											34
40 ppm/4 hrs						4 hrs							47
27-200 ppm/1-4 hrs		5-8 hrs then steady for 5 days				1-4 hrs				1 hr			48
250-380 ppm/160 mins	32.6 in males 43.9 in females	24-48 hrs			48.6 in males 42.7 in females	immediately post-exposure							49
180 ppm/5 hours	32	48-72hrs			46								51
170 ppm/3-7 hours	18-29	42-67 hrs	0.94	321 mg/l s.g. 1.024	44-53	1-3 hr	0.89	531 mg/l s.g. 1.024	60-75		0.93	852 mg/l s.g. 1.024	50
Field studies													
10-30 ppm TWA/8 hr			< 0.3 at end of shift < 0.06 next morning				0.9 at end of shift 0.5-0.8 next morning				0.5-0.75 at end of shift 0.5-0.8 next morning		216
30-80 ppm TWA/8 hr							0.6 in 24 hr sample	216 mg/g creat					217
0-175 ppm TWA/8 hr				281 mg/l				560 mg/l				730 mg/l	218
0-100 ppm			0.89 next morning	192 mg/g creat.			0.95	519 mg/g creat.					219
			next morning samples				next morning samples						

Table 2 Acute toxicity of trichloroethylene in animals

Species	Concentration/dose and duration	Observations
INHALATION		
Rat ⁵² Sprague-Dawley male	26 000 ppm for 1 hr	LC ₅₀ value. 95% confidence limits, 23 700–29 200 ppm
female	25 700 ppm for 1 hr	LC ₅₀ value. 95% confidence limits, 22 300–29 500 ppm
Rat ⁵³ NMRI: 0 (SD) strain Sprague-Dawley derived	12 500 ppm for 4 hrs	LC ₅₀ value
Rat ^{75, 76} Sherman	8000 ppm for 4 hrs	4/6 animals died within 14 days.
Rat ⁵⁴ Wistar-derived	3000–20 000 ppm for up to 14 hrs	LD _{LO} values were: 3000 ppm for 14 hrs 4800 ppm for 4 hrs 6400 ppm for 2 hrs 9600 ppm for 1 hr 12 000 ppm for 1 hr 20 000 ppm for 0.4 hr. All 20 animals died during, or within mins of the end of, a 5-hr exposure to 20 000 ppm. Signs of intoxication included 'drunkenness', stupor, narcosis and respiratory failure. Full anaesthesia was apparent at 4800 ppm and above. 10 000–20 000 ppm for 0.3–7 hrs The animals were killed 16–24 hrs post-exposure. The only biochemical or haematological change noted was an increase in liver lipid levels. At autopsy, the only effects noted were an increase in liver weight and cloudy swelling of the liver on histological examination.
Rat ⁵⁷ male	6900–16 000 ppm for 2 hrs	1/4 and 3/5 animals died during exposure to 12 000 and 16 000 ppm, respectively. The survivors were killed 22 hrs post-exposure. There were significant increases in the serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) following exposure to 10 400 ppm ($p < 0.05$). Histological changes in the liver comprised oedema, some ballooning of cells in the central and mid-zonal areas and a few small areas of necrosis. Pre-treatment with phenobarbitone, 3-methylcholanthrene, but also corn oil alone, enhanced the toxicity of trichloroethylene (TCE).
Rat ⁵⁸ Sprague-Dawley male	100–10 000 ppm for 1.5–8 hrs	3/6 animals died from exposure to 10 000 ppm for 1.5 hrs. The survivors were killed 24 or 48 hrs post-exposure. Investigation of liver function revealed statistically increased serum AST levels after exposure to 10 000 ppm for 1.5 hrs ($p < 0.001$). The serum ALT levels were doubled after exposure to 2000 ppm for 4 hrs. No marked increases were noted in serum isocitrate dehydrogenase (ICD) levels. Pathological observations were reported for animals exposed to 5000 ppm. The only change noted was fatty infiltration of the liver. Pre-treatment with alcohol significantly increased the effect of TCE on serum enzyme levels at 5000 ppm: AST ($p < 0.05$), ALT and ICD ($p < 0.01$). Again, pathological observations were limited to animals exposed to 5000 ppm. The livers showed early centrilobular necrosis and slight acute inflammation. No effects on other tissues were observed.
Rat ⁵⁵ Wistar-Munich male	9000–16 000 ppm for 5–75 mins	Exposure to 9000 ppm for up to 15 mins caused only a slight difficulty in locomotion. At higher concentrations, there was a dose-dependent loss of righting reflex.

Table 2 Continued

Species	Concentration/dose and duration	Observations
		The time to recover from narcosis was found to increase with greater times of exposure.
		Signs of intoxication at 16 000 ppm included irritation of the eyes and respiratory tract, hyperpnoea, and progressive ataxia leading to the loss of the righting reflex.
		Blood and tissue specimens were taken 24 hrs post-exposure.
		No effects on serum ALT or AST levels were noted.
		No histological evidence of injury to liver or kidneys was observed.
Rat ⁵⁶ female	15 000 ppm for 100-400 secs	Study limited to investigating the anaesthetic effects.
		Within 255 secs, all the animals showed abnormal breathing and some showed one or more of the following: flight response, salivation, closing of the eyes, spasms and convulsions.
		The average time to complete anaesthesia was 547 secs, the average recovery time was 158 secs.
Mouse ²²⁰	c. 100 g/m ³ (18 600 ppm) for 40 mins	LC ₅₀ value.
		A 50% drop in rate of response to auditory and visual stimuli was noted following exposure to approximately 3720 ppm for 10 mins.
Mouse ⁶²	8450 ppm for 4 hrs	LC ₅₀ value.
		Animals were completely anaesthetised after about 5-6 mins exposure to 12 000 ppm or after 10-11 mins exposure to 6800 ppm.
Mouse ²²¹ female	5857 ppm for 6 hrs	LC ₅₀ value.
		Limits, 5489-6250 ppm.
Mouse ⁷⁴ Swiss-Webster male	0.220 g/l (40 920 ppm) for 20 mins	LC ₅₀ value calculated 24 hrs post-exposure. 95% confidence limits, 0.211-0.229 g/l (39 250-42 590 ppm).
		Effects on ECG were measured. No significant changes ($p < 0.01$) in heart rate, PR interval, QRS duration or QRS potential were noted.
Mouse ⁶³ Swiss-Webster female	5500 ppm for up to 1000 mins	Experiments to determine the time to kill (LT ₅₀), anaesthetise or elevate the serum ALT levels (ET ₅₀ s) of 50% of the mice.
		LT ₅₀ = 585 mins. 95% confidence limits, 548-626 mins.
		ET ₅₀ for anaesthesia = 46.0 mins. 95% confidence limits, 40.9-51.8 mins.
		ET ₅₀ for raised serum ALT activity = 400 mins. 95% confidence limits, 336-475 mins.
Mouse ²²²	800-6400 ppm for 4 hrs	2/10 animals died at 6400 ppm.
		The survivors were killed on the third day.
		No changes in serum ornithine carbamyl transferase (OCT) activity or in the amount of extractable fat were noted.
		On histological examination of the liver, no fatty infiltration was noted.
Rabbit ⁶⁶	14 880 ppm for 30-40 mins	No deaths occurred during exposures lasting up to 40 mins (some deaths noted if duration of exposure increased).
		Signs of toxicity noted included hyperactivity, dyspnoea and narcosis.
		Animals were killed by decapitation (time of autopsy not given). The gross changes noted were congestion of the lungs, kidneys, spleen and brain, together with oedema and haemorrhage of the lungs and oedema of the brain. Turgidity of the spleen and moderate swelling of the gall bladder were also noted.
		No gross changes were noted in the heart, liver and adrenals.

Table 2 Continued

Species	Concentration/dose and duration	Observations
		On histological examination, oedema and congestion of the liver, lungs, heart, kidneys, spleen and brain were noted.
		In the liver, slight degeneration and hypertrophy of the hepatocytes were also seen.
		Glomerular enlargement and leucocyte infiltration, together with degenerative changes (turbid swelling) and constriction of the tubules, were noted in the kidneys.
		The alveolar cavities of the lungs were dilated and the septa distended.
		In the brain, submeningeal haemorrhages along with perivascular cellular infiltration were noted.
		Signs of cellular degeneration were also seen.
		No histological changes were noted in the adrenal glands.
Rabbit ⁶⁷	16 850 ppm for 1 hr	LD ₅₀ calculated 2 hrs post-exposure.
		The anaesthetic level was 9250 ppm.
Rabbit ⁶⁸	c. 11 000 ppm for about 50 mins	Study limited to effects on eyes and brain.
		5/5 animals died.
		After a short period of motor agitation the animals exhibited anterior and posterior spastic paralysis.
		Ophthalmoscopic observations made throughout the exposure period yielded no changes in the fundus.
		On gross examination at autopsy the brain appeared oedematous and, together with the meninges, congested. When sectioned, no specific changes in the cerebral mass were noted.
		Microscopically, vascular lesions and massive hyperaemia were observed, particularly in the cerebral and cerebellar cortex. The lesions consisted mainly of dilation of the perivascular spaces, tortuosity of the capillaries and, at some point, circumscribed ectasia. There were no signs of nerve cell regression or changes in the neuroglia.
Dog ⁷¹ (anaesthetised animals)	500–50 000 ppm for 10 mins, via tracheal cannulas	Study limited to respiratory, bronchopulmonary and cardiovascular effects.
		500 ppm: produced a depression in myocardial contractility.
		1000 ppm: a reduction in pulmonary blood flow.
		2500–10 000 ppm: tachycardia and systemic hypotension, resulting in a decreased cardiac output.
		50 000 ppm: severe depression of myocardial contractility and hypotension.
		No significant effects on pulmonary mechanics were recorded.
Dog ²²³	30 000 ppm for about 20 mins	Animals usually died within 20 mins.
		0–5 mins: dogs began to salivate and showed difficulty in controlling limbs.
		5–10 mins: eyes became glazed, forelimbs were extended and then the animals became semi-comatose.
		10–20 mins: animals became unconscious; this was often accompanied by convulsive movements of the extremities. Death usually occurred within 20 mins.
		Autopsies were limited to the nervous system. No microscopic changes were observed.
<i>Studies to investigate effects on the liver</i>		
Rat ⁶¹ Sprague-Dawley male	10 000 ppm for 2 hrs	Animals were killed 24 hrs post-exposure.
		No effects on serum AST activity nor on liver Na, K, Mg, Ca, Zn or Fe levels were noted.

Table 2 Continued

Species	Concentration/dose and duration	Observations
		The liver appeared normal histologically.
		Pre-treatment with certain metabolic inducers resulted in hepatotoxicity. Morphological injury was most severe in phenobarbitone and Aroclor 1254 pre-treated animals, and was accompanied by marked perturbation of liver electrolyte levels and more than 20-fold increases in serum AST activity.
Rat ²²⁴	10 000 ppm for up to 2 hrs. Animals fasted and pre-treated with phenobarbitone	Animals were killed during the exposure period and up to 6 hrs afterwards. Hepatic levels of calcium and reduced glutathione decreased during the exposure period and then recovered. Hepatocellular ultrastructural changes noted immediately post-exposure included increased cytoplasmic disorder with random dispersion of organelles, encircling of the nucleus by rough endoplasmic reticulum (ER) and segregation of nucleolar components. At 2 hrs post-exposure, coalescence of smooth ER and vacuolation of rough ER was seen, showing evidence of collapse of smooth ER at 6 hrs post-exposure.
Rat ⁴⁰ Sprague-Dawley male	10 000 ppm for 2 hrs	Animals were killed during the exposure period and up to 6 hrs afterwards. A significant decrease in liver NADPH cytochrome c reductase activity was noted 6 hrs post-exposure ($p < 0.001$). Hepatic glutathione levels remained unchanged during exposure but then rose 6 hrs post-exposure. No histological effects were noted. Pre-treatment with phenobarbitone resulted in significant decreases in liver cytochrome P-450 ($p < 0.001$) and cytochrome b ₅ ($p < 0.05$) during and 6 hrs post-exposure. A decrease in liver glutathione levels during exposure ($p < 0.05$) changed to an increase 6 hrs post-exposure ($p < 0.05$). Pre-treatment also resulted in marked centrilobular necrosis.
Rat ⁵⁹ Wistar male	10-1000 ppm for 6 hrs	Serum ALT and AST activities were measured 24, 48 and 72 hrs post-exposure. Increased serum AST levels were noted following exposure to 10 and 100 ppm at 24 hrs post-exposure. Increases 48 hrs post-exposure were also noted. No changes were seen 72 hrs post-exposure. No changes in serum ALT levels were seen.
Mouse ⁶⁴	18 000 ppm for 1 hr	Decreases in the levels of liver glycogen, glucose, fructose diphosphate, dihydroxy-acetone phosphate, lactate, creatine phosphate, ADP and AMP, and increases in blood sugar and liver ATP levels were noted. No significant changes of glucose-6-phosphate, pyruvic acid or lipid levels were noted.
Mouse ²²⁵ female	400-3200 ppm for 4 hrs	Animals were killed 1 or 3 days post-exposure. No significant effect on the amount of histologically detectable or extractable liver lipid, or on serum OCT activity, was noted.
Mouse ⁶⁵ Cb strain female	800 ppm for 3 hrs	Animals were killed 0-20 hrs post-exposure. Transient decreases in ATP levels and increases in total lipid and triglyceride levels in the liver were noted.
<i>Studies to investigate behavioural effects</i>		
Rat ⁷⁰ male	400-1600 ppm for 5 hrs	Study limited to effects on motor activity and fatigue. During TCE exposure, a dose-related decrease in motor activity was noted ($p < 0.01$ at 1600 ppm). Activity 20-80 mins after exposure to 1600 ppm was 58% of the control value.
	400 and 800 ppm for 6 hrs	Fatigue (as measured by swimming times immediately post-exposure) was significantly increased at 800 ppm: unloaded ($p < 0.01$), loaded ($p < 0.001$). No significant effect was noted 1 hr post-exposure.

Table 2 Continued

Species	Concentration/dose and duration	Observations
Rat ⁶⁹ male	200 and 800 ppm for 3 hrs	Study limited to the effect on the food-motivated climbing reaction, which was measured immediately post-exposure. No effects on the conditioned response or on the response time were noted. A significant increase in spontaneous climbing was observed at 200 and 800 ppm ($p < 0.001$ and $p < 0.01$, respectively).
Mouse ⁷² AB strain	600-1400 ppm for 2 hrs	Study limited to the effect on spontaneous activity. There was a statistically significant decrease in activity at all concentrations (at 1010 ppm, $p < 0.001$). Exposure to 950 ppm was calculated to reduce activity by 50%.
Mouse ICR strain male	120-1108 ppm for 2 hrs	Spontaneous activity was reduced significantly at 692 and 1108 ppm ($p < 0.01$ and $p < 0.001$, respectively). Exposure to 1020 ppm was calculated to reduce activity by 50%.
Rat ⁷¹	200-1600 ppm for 1-8 hrs	Study limited to the effect on behaviour in a T-maze. The frequency of spontaneous alternation was significantly reduced after 1 hr exposure to 800 ppm and 8 hrs exposure to 400-800 ppm ($p < 0.05$). The speed of travel through the maze was significantly reduced after 4 hrs exposure to 200 ppm and 8 hrs exposure to 1600 ppm ($p < 0.001$), but was significantly increased after 8 hrs exposure to 400 and 600 ppm ($p < 0.05$).

Studies to investigate sensitising effects on catecholamine-induced cardiac arrhythmias

Rat ⁷⁴ Sprague-Dawley male	25 000 ppm for 1 hr to lightly anaesthetised animals previously induced with Aroclor 1254 or phenobarbitone, or pre-treated with SKF 525A or Lilly 18947. Adrenalin (up to 4 μ g/kg) was given i.v. at various times during TCE exposure	No arrhythmias were noted following adrenalin challenge in SKF 525A pre-treated animals. Cardiac arrhythmias were noted in animals exposed to trichloroethylene. These showed an exposure-time-related increase in cardiac sensitivity to adrenalin, with ventricular tachycardia noted on challenge with 0.5 μ g/kg adrenalin after 40 mins TCE exposure.
Rabbit New Zealand male	3000 ppm for 1 hr to restrained animals induced or pre-treated as above. Adrenalin (up to 4 μ g/kg) was given i.v. at various times during and after TCE exposure	Adrenalin produced arrhythmias in all groups exposed to TCE. Pre-treatment with SKF 525A or Lilly 18947, however, resulted in spontaneous arrhythmia and a more marked response to adrenalin, which could still be observed 30 mins post-TCE exposure.
Dog ⁷³ Beagle male	5000 or 10 000 ppm for 10 mins. Adrenalin, 8 μ g/kg, was given i.v. 5 mins before and 5 mins into TCE exposure	1 dog died at 10 000 ppm from ventricular fibrillation. Arrhythmias were recorded in 1/12 exposures to 5000 ppm and in 7/12 exposures to 10 000 ppm. At autopsy, the dog that died showed no macro- or microscopic abnormalities.
Rabbit ²²⁶ New Zealand male	2000 to 8000 ppm for 1 hr to restrained animals. Adrenalin (up to 3 μ g/kg) was given i.v. at various times during and after TCE exposure	Arrhythmias (premature ventricular contraction) noted at 4000 ppm and above. Exposure to increasing concentrations of trichloroethylene resulted in an increased incidence of arrhythmias after shorter exposure times and following stimulation with lower levels of adrenalin. Exposure to 8000 ppm resulted in all animals exhibiting arrhythmias within 15 mins exposure following 3 μ g/kg adrenalin. Following 60 minutes exposure arrhythmias were induced by 0.5 μ g/kg adrenalin.
Rabbit ²²⁷ New Zealand male	6000 ppm for 1 hr to restrained animals pre-treated with ethanol (1 g/kg) 30 mins prior to TCE exposure. Adrenalin (up to 3 μ g/kg) was given i.v. at various times during and after TCE exposure	Animals treated with ethanol developed adrenalin-induced arrhythmias sooner and at lower doses of adrenalin than did control animals.

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Table 2 Continued

Species	Concentration/dose and duration	Observations
ORAL		
Rat ^{75, 76} Carworth-Wistar male	4.92 ml/kg (7.2 g/kg) by gavage	LD ₅₀ value. 95% confidence limits, 3.75–6.46 ml/kg (5.5–9.5 g/kg).
Rat ⁷⁷ Wistar female	4.7 ml/kg (6.9 g/kg)	LD ₅₀ value. Confidence limits, 4.2–5.2 ml/kg (6.2–7.6 g/kg).
	3.7 ml/kg (5.4 g/kg) in water	LD ₅₀ value. Confidence limits, 3.1–4.2 ml/kg (4.5–6.2 g/kg).
Rat ⁸⁰ Osborne-Mendel male	5.62 g/kg in corn oil by gavage	LD _{1.0} value.
Mouse B6C3F1 female	10.0 g/kg in corn oil by gavage	LD _{1.0} value.
Rat ²²⁸ female	15.2 mmol/kg (2.0 g/kg) by gavage	No effect on the hepatic level of reduced glutathione was noted 2 hrs post-dose.
Mouse ⁷⁸ Swiss-Webster male	2.85 g/kg	LD ₅₀ value calculated 24 hrs post-dose. 95% confidence limits, 2.35–3.4 g/kg.
Mouse ⁷⁹ Swiss	2.92 g/kg in olive oil by gavage	LD ₅₀ value.
	0.72 g/kg in olive oil by gavage	ED ₅₀ value for producing narcosis or liver damage. The survivors were killed 72 hrs post-dose and their livers examined histologically. The following pathological changes were noted: mid-zonal fatty infiltration at 0.72 g/kg, progressing to centrilobular infiltration at 0.9 g/kg and massive infiltration at 1.46 g/kg. No necrosis was observed.
Rabbit ⁸¹ male	13 mmol/kg (1.7 g/kg)	Study limited to investigating hepatotoxicity by measuring a number of blood serum parameters at 1, 2, 3, 14 and 28 days post-dose. The level of serum alkaline phosphatase was significantly reduced at 24 and 48 hrs post-dose ($p < 0.05$ and $p < 0.01$, respectively). The level of serum AST had doubled at 24 hrs, but returned to normal by 72 hrs. Serum ALT had doubled at 24 hrs, but was significantly lower than the control values at 3 and 14 days post-dose ($p < 0.05$ and $p < 0.01$, respectively). Levels of serum triglyceride and lipoprotein were raised at 2 and 3 days post-dose, the increase in serum triglyceride being significant at 3 days ($p < 0.05$).
Dog ⁸²	3.0–6.0 g/kg in mucilage of acacia by gavage	No animals died within 7 days.
PERCUTANEOUS		
Guinea-pig ⁸³	2.0 ml (7.8 g/kg) to an area of 3.1 cm ² . Occlusive dressing used.	The animals were observed for 35 days post-dose. No animals died. Body weights were significantly lower than controls after 1 ($p < 0.001$), 2 and 3 ($p < 0.01$) and 4 ($p < 0.05$) wks.
Rabbit ^{75, 76} New Zealand male	>20 ml/kg (>29.3 g/kg) under an occlusive dressing	LD ₅₀ value.
INTRAPERITONEAL		
Rat ⁸⁴ Wistar male	2.73 g/kg in peanut oil	LD ₅₀ value.
	2.25 g/kg in peanut oil	The survivors were killed 24–48 hrs post-dose and examined for liver toxicity. Increases in liver lipid levels were noted at all times, as were significant increases in serum AST activity ($p < 10^{-3}$). Significant increases in serum ALT and OCT levels were noted at 30 hrs ($p < 10^{-4}$ and $p < 10^{-3}$, respectively). No histopathological changes were observed in the liver.

Table 2 Continued

Species	Concentration/dose and duration	Observations
Rat ⁴⁵ Sprague-Dawley male	0.25-2 ml/kg (0.4-2.9 g/kg) in liquid paraffin	Study limited to the assessment of liver damage 3-24 hrs post-dose. 2.9 g/kg produced a 3-fold increase in serum ALT activity 24 hrs post-dose and an initial decrease in hepatic glutathione levels which progressed to increased levels at 16 hrs. No hepatic lesions were detected histologically 24 hrs after dosing with 1.5 g/kg. No other organs, or animals exposed to other dose levels, were examined histologically. Pre-treatment with phenobarbitone increased the effect of TCE on serum ALT activity. Induction of hepatic cytochrome P-450 by phenobarbitone appeared to be prevented by exposure to TCE. Pre-treatment with phenobarbitone also resulted in centrilobular necrosis, and clarification and ballooning of hepatocytes in animals dosed with 1.5 g/kg TCE.
Rat ²²⁹ Sprague-Dawley male	1 ml/kg (1.5 g/kg) in liquid paraffin	Study limited to effects on hepatic metabolising enzymes. At 1 hr post-dose, the metabolism of hexobarbitone was inhibited but no effects were noted on the liver/body weight ratio, the liver levels of microsomal proteins or cytochrome P-450, or on the activity of NADPH-cytochrome c reductase, aniline hydroxylase, p-nitrophenol glucuronyl transferase, ethylmorphine demethylase or hexobarbitone hydroxylase in the liver. At 8 hrs post-dose, no effects on the liver levels of cytochrome b₅, cytochrome P-450 or total protohaeme were noted. In animals pre-treated with phenobarbitone the levels of cytochrome P-450 and total protohaeme were significantly reduced at 8 hrs post-dose ($p < 0.001$).
Rat ⁴⁶ Sprague-Dawley male	0.3-2.0 ml/kg (0.4-2.9 g/kg) in peanut oil	Study limited to the measurement of serum AST activity. A dose-related increase in AST activity was noted, with a 16-fold increase at 2.9 g/kg. Pre-treatment with phenobarbitone had no potentiating effect.
Rat ⁴⁷	0.5-2.0 ml/kg (0.7-2.9 g/kg) in corn oil	Study limited to the measurement of serum AST levels 24 hrs post-dose. 2.9 g/kg produced an 18-fold increase in serum AST levels. Pre-treatment with phenobarbitone or ethanol produced no change in the toxicity of TCE.
Rat ²³⁰ Sprague-Dawley male	1 mmol/kg (131 mg/kg) in methanol	Study limited to investigating the effects on the liver 24 hrs post-dose. No change in the level of serum ALT was noted, as compared to controls. Microscopically no signs of liver necrosis were observed. The concentration of hepatic cytochrome P-450 was unchanged 24 hrs post-dose as was the level of hepatic glutathione at 4 and 24 hrs post-dose.
Rat ⁴⁸ Alderley Park	0.35-2.9 g/kg	Study limited to investigating effects on the liver. At 1.5 g/kg and above, elevated serum ALT and AST levels were noted. On microscopic examination of the liver, 24 hrs after dosing with 1.5 g/kg and above, glycogen accumulation, mitochondrial swelling and cytoplasmic vacuoles were noted. Doses of below 1.5 g/kg had no effect on hepatic non-protein sulphhydryl content (NPSC).
Mouse Alderley Park	0.3-2.9 g/kg	At 1.5 g/kg and above, elevated serum ALT and AST levels were noted.

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Table 2 Continued

Species	Concentration/dose and duration	Observations
		On microscopic examination of the liver, 6 hrs after dosing with 1.5 g/kg, slight dilation of rough and smooth endoplasmic reticulum was seen.
		A dose-dependent increase in liver NPSC was noted 2 hrs after dosing with up to 1.5 g/kg. The level returned to control values at 12 hrs. Higher doses elicited no increase in NPSC.
Rat ⁷² Wistar female	0.25-1.0 ml/kg (0.37-1.47 g/kg)	Study limited to the effect on avoidance behaviour.
		All dose levels blocked the learning of avoidance behaviour 1 day post-dose, but no dose response was observed.
Mouse ⁸⁹ female	3.0 g/kg in olive oil	LD ₅₀ value. 95% confidence limits, 2.9-3.1 g/kg.
Mouse ⁹⁶	1.31 ml/kg (1.9 g/kg)	LD ₅₀ value. 95% confidence limits, 1.17-1.46 ml/kg (1.7-2.1 g/kg).
Mouse ⁷⁸ Swiss-Webster male	1.20 g/kg	LD ₅₀ value calculated 24 hrs post-dose. 95% confidence limits, 0.89-1.51 g/kg.
Mouse ²³¹ ICR-JCL male	0.075 g/kg	LD ₅₀ value at 22 °C (calculated by the up-and-down method of Brownlee <i>et al.</i> ²³²).
		Experiments conducted at 8 °C and 38 °C gave lower LD ₅₀ values.
Mouse ⁹⁰ Swiss-Webster male	3.2 g/kg in corn oil	LD ₅₀ value. 95% confidence limits, 2.5-4.4 g/kg. Calculated 24 hrs post-dose although animals died up to 10 days post-dose.
	2.3 g/kg in corn oil	Blood and tissue samples were taken 24 hrs post-dose. ED ₅₀ value for increased ALT levels in serum.
	2.9 g/kg in corn oil	ED ₅₀ value for increased bromosulphophthalein (BSP) retention. No changes in kidney function were noted.
		Histopathology of the liver revealed hepatocyte enlargement with cellular infiltration and vacuolation at sublethal doses, and slight necrosis at 3.2 g/kg. Little or no changes were noted in the kidney at these levels.
		Ethanol pre-treatment had no effect on TCE toxicity.
Mouse ^{233, 234} ICR male	2.0 ml/kg (2.9 g/kg) in corn oil	Lethal to all mice.
	0.5-1.0 ml/kg (0.7-1.9 g/kg) in corn oil	Study limited to effects on liver and kidneys 24 hrs post-dose.
		No effect on organ weights, serum AST activity or on serum urea nitrogen levels was noted.
		A significant decrease in p-aminohippuric acid accumulation in renal cortical slices was noted ($p < 0.05$).
		Pre-treatment with polychlorinated or polybrominated biphenyls increased the renal toxicity of TCE.
Mouse ²³⁵ Swiss-Webster male	1.0 and 1.5 ml/kg (1.5 and 2.5 g/kg) in corn oil	Study limited to the effects of pre-treatment on the serum ALT activity of TCE-dosed animals.
		ALT activity was measured 24 hrs post-TCE dose.
		Pre-treatment with acetone resulted in a significant increase in serum ALT activity following 2.2 g/kg TCE as compared to non pre-treated animals ($p < 0.05$).
		Pre-treatment with isopropyl alcohol resulted in a significant increase in serum ALT activity following 1.5 and 2.2 g/kg TCE as compared to non-pre-treated animals ($p < 0.05$).

Table 2 Continued

Species	Concentration/dose and duration	Observations
Mouse ²³⁶ Swiss male	0.6 and 2.5 ml/kg (0.9 and 3.7 g/kg) in corn oil	Study limited to the effects on the kidneys. 8/10 animals died within 24 hrs of a dose of 3.7 g/kg. No significant effects on the urinary protein or glucose levels, or on the phenol-sulphophthalein (PSP) clearance of survivors were noted 24 hrs post-dose. No abnormality of the kidneys was noted on histopathological examination.
Mouse ⁷² AB strain	0.125–1.0 ml/kg (0.18–1.47 g/kg)	Study limited to behavioural effects. The ability of male and female mice to walk along a rotating rod decreased by 85% and 67%, respectively, when measured 30 mins after dosing with 1.4 g/kg. A dose-dependent decrease in spontaneous activity was noted 30 mins post-dose, with a dose of 0.18 g/kg calculated to reduce activity by 50%.
Guinea-pig ⁴³	2 ml (7.9 g/kg)	9/10 animals died within 6 hrs, the remaining animal surviving 72 hrs (end of observation period).
Dog ⁹¹	1.9 ml/kg (2.8 g/kg) in corn oil	LD ₅₀ value calculated after 24 hrs (by the up-and-down method of Brownlee <i>et al.</i> ⁹⁰). No effect on kidney function, as measured by PSP clearance, was noted at doses near the LD ₅₀ concentration 24 hrs post-dose. At concentrations near the LD ₅₀ value, moderate neutrophil infiltration of the sinusoids and portal areas of the liver and slight calcification of the kidney tubules was noted.
	0.57 ml/kg (0.8 g/kg) in corn oil	ED ₅₀ value for an increase of +2 standard deviations in serum ALT activity 24 hrs post-dose (calculated by method of Brownlee). These increases in ALT activity were reversible. At concentrations near the ED ₅₀ value, histological changes in the kidneys and liver included mild dilation of the renal collecting ducts (24 hrs post-dose) and vacuolation of the centrilobular hepatocytes (48 hrs post-dose). Pre-treatment with ethanol resulted in a significant elevation in serum ALT activity 48 hrs post-dose ($p < 0.05$).
INTRAVENOUS		
Dog ⁴² (anaesthetised animals)	0.15 g/kg in olive oil	LD ₅₀ value calculated 30 mins post-dose.
SUBCUTANEOUS		
Rat ²³⁷ Long-Evans	0.004 mol/kg (0.5 g/kg)	Study limited to the effects on the liver. Transient increases in serum AST levels of up 5-fold were noted 12–16 hrs post-dose. Histologically, slight degeneration of the liver parenchyma was noted 12–16 hrs post-dose, which had returned to normal at 24 hrs. No lipid accumulation was noted.
Mouse ²³⁸ Princeton male	120 mmol/kg (15.8 g/kg) in peanut oil	LD ₅₀ value calculated 10 days post-dose. Range was 67–200 mmol/kg (8.8–26.3 g/kg). ED ₅₀ value for significant increase in pentobarbitone-induced sleeping time 24 hrs post-dose. Range was 8.9–13 mmol/kg (1.2–1.7 g/kg). At 1.8 g/kg, 5/10 animals showed a significant increase in BSP retention 24 hrs post-dose ($p < 0.05$). Microscopic examination of the livers of most animals at the higher dose levels revealed centrilobular necrosis. At the lower dose levels, cytoplasmic vacuolation was observed. No evidence of kidney damage was reported.
Rabbit ⁴²	1.5–2.0 g/kg in olive oil	2/4 animals died within 7 and 20 hrs.

Table 3 Subacute toxicity of trichloroethylene in animals

<i>Species</i>	<i>Concentration/dose and duration</i>	<i>Observations</i>
INHALATION		
Rat ⁴⁴ Wistar	200-3000 ppm for 7 hrs/day. 27-173 exposures over 36-243 days.	No effects on mortality were noted at any concentration. At 3000 ppm, the animals showed mild disturbance of their equilibrium and co-ordination during the first week, progressing to extreme salivation, marked restlessness, hyperexcitability and marked scratch reflexes. The animals recovered quickly at the end of the experiment. Decreased weight gain was noted for males at this concentration and also at 400 ppm. No other signs of toxicity were noted at the latter concentration. No effects on blood non-protein nitrogen, urea nitrogen or serum phosphatase levels, nor on blood coagulation times were noted. At autopsy, the only effects noted were significant increases in liver and kidney weights at 400 and 3000 ppm. No lesions were noted on microscopic examination of these or any other organs. No effects were noted on liver lipid levels The no-effect level in this study was 200 ppm.
Rabbit	200-3000 ppm for 7 hrs/day. 27-168 exposures over 36-248 days.	The only signs of toxicity noted were minor disturbances of equilibrium and co-ordination at 3000 ppm. No effects on blood non-protein nitrogen, urea nitrogen or phosphatase levels, nor on blood coagulation times were noted. At autopsy, the only effects noted were increases in liver and kidney weights at 3000 ppm and a slight increase in liver weight at 400 ppm. No lesions were noted on microscopic examination of these or any other organs. The no-effect level in this study was 200 ppm.
Guinea-pig	100-400 ppm 7 hrs/day. 132-167 exposures over 185-235 days	The only sign of toxicity noted was a significant decrease in final body weight at 200 and 400 ppm. No effects on blood non-protein nitrogen, urea nitrogen or phosphatase levels, nor on blood coagulation times were noted. At autopsy, the only effect noted was a significant increase in liver weight at 400 ppm. No effects were noted on microscopic examination of this or any other tissue at any concentration. No effects were noted on liver lipid levels at any concentration. The no-effect level in this study was 100 ppm.
Rhesus monkey	200 and 400 ppm for 7 hrs/day. 148-161 exposures over 212-225 days.	No signs of toxicity were noted at either concentration. No effects on blood non-protein nitrogen, urea nitrogen or phosphatase levels, nor on blood coagulation times or other haematological parameters, were noted at either concentration. No adverse effects were noted on gross or microscopic examination at autopsy at either concentration. No effects were noted on liver lipid levels at either concentration.
Rat ⁴⁷ Wistar II SPF male	55 ppm for 8 hrs/day, 5 days/wk for 14 wks	No signs of toxicity were noted during the exposure period. No adverse effects were noted on blood glucose levels, liver and kidney function tests, nor on haematology, at the end of the exposure period. Autopsies were limited to gross inspections. No effects were noted apart from increased liver weight ($p < 0.01$).
Rat ⁹³	0.05-0.3% (500-3000 ppm) 6 hrs/day, 5 days/wk for 6 months	3/6 animals exposed to 3000 ppm died within 33 exposures.

Table 3 Continued

Species	Concentration/dose and duration	Observations
		Exposure to 2000 and 3000 ppm resulted in slight narcosis, with ataxia at 3000 ppm.
		No effects on growth rates nor on blood parameters were noted.
		At autopsy, gross examination of the animals that died revealed congestion of the liver and kidneys. No abnormal features were noted in animals killed at the end of the experiment.
		Histological examination of liver, kidneys, heart, lungs, spleen, brain, and femurs revealed no specific substance-related changes apart from a slightly increased tendency to alveolar collapse.
	0.2-0.5% (2000-5000 ppm) 6 hrs/day, 5 days/wk for 8-11 exposures	No compound-related deaths occurred, but 5000 ppm produced deep narcosis after 30 mins exposure. Light drowsiness was noted during exposure to 2000 ppm. All the animals were in good condition at the end of the experiment.
		No degeneration was noted on gross or microscopic examination at autopsy.
Rat ²³⁹ JCL-SD female	40-400 ppm for 1 mth (no more details given on lengths of exposure)	Study aimed at showing the effect of TCE on animals of various ages, i.e. 1, 3, and 12 mths. All animals were killed about 24 hrs post-exposure.
		3/5 animals of 12 mths of age died during exposure to 400 ppm.
		Decreased weight gains were observed in 1 and 12-mth-old animals, with about a 30% decrease at 400 ppm.
		Serum creatine phosphokinase showed a dose-related increase in 1-mth-old rats, with a maximum of about 2.5-fold of control levels at 400 ppm. No changes were seen at the other ages or concentrations.
		No changes were noted in serum AST or ALT activity. Increases in serum alkaline phosphatase and inorganic phosphate and decreases in serum cholinesterase and lipid levels were noted at various ages though no values were given and so significance could not be assessed.
		At autopsy, the liver/body weight ratio for all ages was found to be markedly increased (no gross or microscopic observations were reported).
		5-hydroxytryptamine content of brain cortex and hippocampus was significantly reduced in 12-mth-old rats exposed to 400 ppm as compared to controls ($p < 0.05$). No significant changes in levels of dopamine in the striatum, or noradrenaline in the hypothalamus or other areas of the brain, were noted.
Rat ⁹⁵	189 mg/m ³ (35 ppm) continuously for 90 days	No rats died and no signs of toxicity were noted.
		No changes in haematological parameters were seen.
		At autopsy, no effects on the histopathology of the heart, liver, lungs, spleen or kidneys were noted.
Rabbit New Zealand	As above	No animals died. A decreased weight gain (4%), as compared to controls (33%), was noted.
		No changes in haematological parameters were seen.
		At autopsy, no effects on the pathology of the heart, liver, lungs, spleen or kidneys were noted.
Guinea-pig Hartley	As above	No animals died and no signs of toxicity were noted.
		No changes in haematological parameters were seen.
		At autopsy, no pathological changes to the list organs were seen.
Dog Beagle	As above	No adverse effects were noted during exposure or at autopsy.
Squirrel monkey	As above	No adverse effects were noted during exposure or at autopsy. Haematological parameters were not investigated in this species.
Rat	3825 mg/m ³ (711 ppm) 8 hrs/day, 5 days/wk for 6 wks	No animals died and no compound-related signs of toxicity were noted.
		No adverse effects on haematological parameters were noted.

Table 3 Continued

Species	Concentration/dose and duration	Observations
		At autopsy, no specific compound-related histopathological effects were noted in the liver, lungs, heart, spleen or kidneys. Histochemical examination revealed no changes in the levels of certain enzymes in the liver.
Rabbit New Zealand	As above	No adverse effects were noted during exposure or at autopsy.
Guinea-pig Hartley	As above	No adverse effects were noted during exposure or at autopsy.
Dog Beagle	As above	No animals died, but a loss in body weight was noted.
		No adverse effects were noted on haematological parameters or at autopsy.
Squirrel monkey	As above	No adverse effects were noted during exposure or at autopsy. Haematological parameters were not investigated in this species.
Rat ²⁴	500-1000 ppm, 18 hrs/day for 90 days	No signs of toxicity were noted during the exposure period. No effects on liver function tests, kidney function tests or haematology were seen. At autopsy, no gross or microscopic lesions were noted.
Rabbit	As above	No signs of toxicity were noted during the exposure period. No effects on liver or kidney function tests nor on haematological parameters were seen.
		At autopsy, no gross or microscopic lesions were noted.
Dog	As above	No signs of toxicity were noted during the exposure period. No effects on liver function tests, kidney function tests or haematology were noted.
		At autopsy, no gross or microscopic lesions were noted.
Rat ²⁴⁰ Albino	0.5, 1 and 4 mg/m ³ (0.1, 0.2 and 0.7 ppm) continuously for 98 days	Only brief details of this study were given. During the exposure period animals were examined for weight gain, blood pressure, subordinated chronaxy, sulphhydryl groups in the serum, whole blood cholinesterase and leucocyte count. Exposure to 0.7 ppm resulted in hypotension, disturbed chronaxy of certain muscles and a transient, but statistically significant, decrease in cholinesterase activity. In this study the no-effect level was 0.2 ppm. No further details were given and it is impossible to assess the significance of the observations.
Rat Albino newborn	0.5, 1 and 4 mg/m ³ (0.1, 0.2 and 0.7 ppm) continuously for 98 days from birth	Decreased weight gain was noted in the test animals in all groups on day 5 of the experiment, as compared to controls. The decreased weight gain persisted in animals exposed to 0.2 and 0.7 ppm. At 0.2 ppm and above a statistically significant decrease in body length was noted in test animals as compared with controls ($p < 0.001$). Delayed coat development was also noted in these test animals. At 6 wks hypotension was noted in animals exposed to 0.2 and 0.7 ppm as was inversion of the chronaxial ratio. A change in whole blood cholinesterase activity was observed in animals exposed to 0.2 and 0.7 ppm during the latter stages of the study. No change in the leucocyte count nor in the SH groups in the serum was noted. All abnormalities returned to normal following a recovery period. No quantitative details were given regarding any of the observations and it is impossible to assess their significance.
Mouse ²⁴¹	10 000-15 000 ppm 1 hr/day, 6 days/wk for 2 wks	All animals died after 8 exposures to 15 000 ppm. 6/10 animals died at 10 000 ppm, but in some cases exposures were curtailed to prevent imminent respiratory arrest. Signs of toxicity noted were cyanosis, tachypnoea, gasping respiration and convulsions. At autopsy no substance-related gross changes were seen. No substance-related histological changes in the liver or kidney were noted.

Table 3 Continued

Species	Concentration/dose and duration	Observations
Rabbit ²⁴² female	2, 10 and 100 mg/m ³ (0.4, 2, and 20 ppm) 4hrs/day for 9 mths	No signs of toxicity were noted during the exposure period. Haematology revealed a leucocytosis at 100 mg/m³ ($p < 0.05$), but no data were given. 2 ppm resulted in a dysproteinaemia ($p < 0.05$) and a hyperurobilinuria ($p < 0.05$). At 20 ppm an increase in serum butyrylcholinesterase activity ($p < 0.05$) and a decrease in the albumin/globulin ratio ($p < 0.05$), due to decreased albumin levels, were noted. In glucose tolerance tests a delayed peak and a slower fall was also seen at 20 ppm ($p < 0.05$). No effect on adrenal function or on serum acetylcholinesterase levels was noted. A decrease in the phagocytic activity of the neutrophils was noted at 20 ppm ($p < 0.05$), whereas a decreased ability to produce and maintain an antibody titre was noted at 20 ppm ($p < 0.01$). At autopsy microscopic examination (limited to lungs, liver, heart, kidneys and spleen) revealed congestion of the liver and spleen, but no concentration was given. Insufficient data were given to assess the significance of this study.
Rabbit ⁶⁶	2790 ppm 4 hrs/day, 5 days/wk for 30 or 50 days	No deaths were reported and no signs of toxicity were noted during the exposure period. At autopsy gross and microscopic examination of the lungs, liver, kidneys, spleen, heart, adrenals, brain and spinal cord were performed. Gross changes noted included congestion of the lungs, liver and spleen. On microscopic examination congestion was noted in the liver, spleen, brain and occasionally in the kidneys. In the lungs parenchymal hyperaemia, thickened interalveolar septa, areas of leucocyte infiltration and signs of emphysema were noted. Extensive hepatocyte degeneration, hypertrophy, stroma degeneration, hepatocyte necrosis and evidence of Kupffer cell activation was noted in the liver. In the kidneys thickening of the Bowman's capsule and a tendency to sclerosis of the glomerulus were noted, whilst in the convoluted tubules, degeneration (turbid swelling), distortion and occasionally ectasis were recorded. Increased macrophage activity and signs of haemosiderosis were seen in the spleen, together with stasis of the veins and hyperplasia of the red pulp. Slight cellular degeneration was noted in the brain and spinal cord.
Rabbit ¹⁷⁸	12-190 ml/l (2200-35 400 ppm) 5 mins-5hrs daily for up to 12 mths	The study was limited to investigating narcotic, hepatic, cardiac and pulmonary effects. No anaesthesia was noted during any exposure to 2200 ppm. At higher concentrations the frequency, speed of induction of narcosis and time for recovery increased with the concentration and the number of exposures. Tonic spasms and clonic twitching of the extremities were noted in most animals during deep anaesthesia. At concentrations of greater than 2000 ppm signs of irritation of the upper respiratory tract and conjunctivae were noted. A transient increase in thymol turbidity was the only abnormality noted in liver function. Electrocardiographic changes noted were reversible increases in PI and PII and in RI and RII together with a decreased heart rate during exposure. Radiography of the chest in animals exhibiting signs of irritation during months 6-7 revealed no abnormality. In animals which had died during exposure, autopsy revealed signs of stasis in parenchymatous organs, emphysema of the lungs with oedema and haemorrhages. No pathological changes of the heart were observed. No signs of liver injury were noted in survivors.
Rabbit ⁹⁸	15 mg/l (2800 ppm) 4 hrs/day, 6 days/wk for 45 days	The study was limited to effects on the haematological system 15, 30 and 45 days after the onset of exposure. A progressive decrease in red cells, total white cells, platelets and haemoglobin value was noted in blood samples taken throughout the study. Examination of blood films revealed a decrease in the number of neutrophils and a normochromic anaemia. Bone marrow samples collected at the end of the exposure period

Table 3 Continued

Species	Concentration/dose and duration	Observations
Guinea-pig ¹⁰⁰	10-40 mg/l (1860-7440 ppm) for 30-75 mins/day for 10 or 16 wks	revealed minor changes to the granuloblastic parenchyma, evidence hypoplasia in the erythroblastic parenchyma with a decrease in the numbers of all cells of the erythropoietic series. No effect on weight gain was noted. Transitory intoxication was noted during exposure to the lower levels with deep narcosis evident within 7 mins at 7440 ppm. The animals recovered quickly at the end of each exposure. No increase in the number of red cells, total white cells or reticulocytes were observed in blood samples taken periodically throughout the study. A transient neutrophilia was observed which was maximum at 6-8 weeks. No significant excretion of albumin nor urobilinogen was seen in the urine. In animals sacrificed at 10 or 16 wks macroscopic examination revealed marked discoloration of the liver and kidneys and the spleen possessed a hard consistency. Microscopic examination revealed no substantial lesions of the hepatic parenchyma, the architecture of the trabeculae was normal and only a small amount of cellular alteration (cells without nuclei and granular or vascular degeneration) was visible. In the kidneys fairly well marked alternations were seen including lesions of almost fibrous glomerulitis, granular or vascular degeneration of the cells of the convoluted tubules and extensive lesions of the renal parenchyma. It is not clear from the data presented whether the effects occurred at all dose levels, nor whether they were dose-related. It is difficult to assess the significance of these observations.
Cat ¹⁰¹	5450 ppm, 1-1.5 hrs day for 4-6 mths	Signs of intoxication were difficulty in balancing, minor facial muscular spasms and a tendency to fall. Animals were removed prior to collapse. At autopsy gross examination revealed pronounced splenomegaly and haemorrhagic infarct of the spleen. All animals revealed major lesions of the liver, kidneys, spleen and lymph nodes on histological examination. In the liver diffuse fatty lesions with swollen cells and centrilobular fatty lesions were noted. The branches of the portal vein were considerably dilated. No cirrhotic changes were noted. In the kidneys the glomeruli were swollen, due to congestion. The tubules were distorted and distended with the cells containing vacuolated cytoplasm. Hyaline or granular casts were frequently found. In some cases infiltrating foci containing necrotic fragments were seen. The lymph nodes contained reactive and hypertrophic follicles. Large germinal centres with pale, granulated histiocytes giving the appearance of giantocytic centrilobulosis were also seen. In the spleen diffuse haemorrhage of the red pulp was noted. The Bilioth cords and venous sinuses had disappeared and the Malpighian corpuscles were hypertrophic. Massive hypertrophy and histiocytic proliferation were also evident.
Dog ⁹⁹	150-750 ppm, 4-8 hrs/day, 5-6 days/wk for 2-16 wks	Lethargy, anorexia, nausea, loss of weight, diarrhoea and vomiting were noted following exposure to 500 ppm and above for two or more weeks. A maximum decrease in red cell count of 10% was noted in most animals. No other haematological changes were noted. A dose-related decrease in bromosulphophtalein clearance was noted following 500 ppm and above for three or more weeks. This impairment in liver function returned to normal within 5 weeks after exposure had ceased. Kidney function remained normal throughout the exposure period as did the blood glucose and serum chloride levels. Histological examination of the livers of animals which died or were killed whilst intoxicated revealed glycogen depletion and hydropic parenchymatous degeneration. In animals allowed to recover no liver lesions were noted. No pathological changes were noted in the intestines, adrenals, kidneys or heart of intoxicated animals.

Table 3 Continued

Species	Concentration/dose and duration	Observations
<i>Studies to investigate effects on liver and kidneys</i>		
Rat ⁹⁶ male	2 mg/l (370 ppm) 30 mins/day for 40-120 days	Decreases in the serum albumin/globulin ratio and in the esterified/free cholesterol ratio were noted at 40, 80 and 120 days. Progressive increases in the positive results in the flocculation tests and in the levels of serum AST and ALT were also noted at 40, 80 and 120 days. Histopathologically, the liver showed moderate hyperaemia and signs of oedema at 40 days, progressing to diffuse hyperaemia, oedema and signs of turbid swelling of hepatocytes at 80 days. At 120 days marked hyperaemia and oedema with degenerative changes of hepatocytes were noted.
Rat ²⁴³ Wistar females and newborn animals	2000 ppm, 8 hrs/day, 5 days/wk for 4-10 wks	Study limited to effect on nucleoside-5-triphosphatase in the liver. Histochemical staining revealed no enzyme deficient foci.
Rat ⁹⁷ Wistar SPF male	50-2300 ppm, 5 hrs/day for 10-28 days	Study limited to the effects on hepatic microsomal enzymes. No histological liver changes were noted after exposure to 50 ppm for 28 days. Increases in aminopyrine demethylase activity after exposure to 470 ppm for 10 days ($p < 0.02$) and in cytochrome P-450 activity after exposure to 50 ppm for 28 days ($p < 0.05$) were noted in the liver.
Mouse ²⁴⁴ female	1600 ppm, 4 hrs/day, 6 days/wk for 1-8 wks	Study limited to studying effects on the liver and kidneys. No changes in serum OCT levels were observed during the exposure period. At autopsy, slight fatty degeneration of the liver was noted which decreased after 2 wks even when exposure was continued. No changes in the kidneys were seen. A significant increase in extractable liver lipid was noted after exposure for 1 wk ($p < 0.01$).
Rabbit ²⁴⁵ Fauve de Bourgogne	5000 ppm, 4 hrs/day for 1-3 days	Study limited to effects on serum ALT, AST and OCT levels. No marked effects were noted.
<i>Study to investigate effects on the lungs</i>		
Rat ^{246, 247} Wistar female	48500 mg/m ³ (9000 ppm) 30 mins/day for 5-15 days	Study limited to the effects on the lungs. Electron microscopic examination revealed degenerative changes in Type 1 pneumocytes, characterised by hydropic vacuolation of the endoplasmic reticulum and formation of clear vacuoles. Only minor morphological changes were noted in Type 2 pneumocytes with condensation, decreased numbers of microvilli and cytoplasmic surfactant lamellae. Accumulation of partly degranulated platelets in foci where blebbing of the basement membrane occurred was noted. A significant reduction in pulmonary surfactant yield was noted after 5 and 15 days ($p < 0.05$). No significant changes in RNA or DNA synthesis in lung tissue were noted.
<i>Studies to investigate brain biochemistry and behaviour</i>		
Rat ²⁴⁸ Albino SD male	200-800 ppm for 1 mth (no lengths of times of exposures given)	Study limited to the effects on the monoamine content of brain immediately post-exposure. There was a dose-dependent decrease in the acetylcholine content of the striatum which was statistically significant after exposure to 800 ppm ($p < 0.05$). No statistically significant changes were noted in the levels of dopamine, noradrenaline or 5-hydroxytryptamine in the various regions of the brain.

Table 3 Continued

Species	Concentration/dose and duration	Observations
Rat ²⁴⁹ Albino SD male	200-800 ppm for 1 mth (no lengths of times of exposures given)	Study limited to effects on free amino acid content of mid-brain immediately post-exposure. There were significant increases in the levels of serine and glycine after exposure to 800 and 400 ppm respectively ($p < 0.05$), and a significant decrease in the level of glutamate after exposure to 800 ppm ($p < 0.05$). No statistically significant changes were noted in the levels of taurine, γ -aminobutyric acid, aspartate and alanine.
Rat ¹⁰⁴ Sprague-Dawley male	200 ppm, 6 hrs/day for 4 days and 0-6 hrs on day 5	Study limited to effects on behaviour and on brain biochemistry. Significant increases in ambulation frequency ($p < 0.05$), preening and rearing frequency ($p < 0.0025$) and preening time ($p < 0.005$) were noted 1 hr post-exposure on day 4. Sixteen hrs later a significant decrease in defaecation frequency was noted ($p < 0.05$). Transient increases in brain RNA and glutathione were found after a 2-hr exposure on day 5 with the levels dropping below control levels with continued exposure. Increases in brain acid proteinase were noted after a 2- or 6-hr exposure on day 5. No change in brain protein levels was noted.
Rat ²⁵⁰ male	400 ppm, 8 hrs/day, 5 days/wk for 44 wks	No increase in mortality or decrease in weight gain was noted. Neuromuscular efficiency as measured by swimming tests was reduced significantly when measured immediately following exposure and also 16 hrs following exposure. TCE increased the exploratory behaviour of the animals The capacity to learn in the Hebb test and in the conditioned avoidance test was not affected by TCE.
Rat ¹⁰³ Carworth Farms Elias female	200-4380 ppm, 4 hrs/day, 5 days/wk for 1-2 wks	Study limited to effects on avoidance behaviour and learning ability measured daily. Slight ataxia was noted at 1568 ppm which became severe at 4380 ppm. Tolerance occurred within a few days. A reversible inhibition of the avoidance response was noted in several animals at all dose levels from day 2 of exposure. Exposure to 4380 ppm severely decreased learning ability at all times.
Rat ¹⁰² Carworth Farms Elias male	125 ppm, 4 hrs/day, 5 days/wk for 5 wks	Study limited primarily to effects on avoidance behaviour. No signs of toxicity were noted. A significant reduction in avoidance behaviour was observed on 22/25 days ($p < 0.01$). No effect was noted on the first day of each of the first 3 wks of study.
Rat ⁷¹	600 ppm for 3-4 hrs, twice a day for 5 days	Study limited to effects on conditioned avoidance behaviour. No effect on the learning of conditioned avoidance behaviour was noted.
	400 ppm for 40 wks	No significant effect on the learning of conditioned avoidance behaviour was noted.
	800 ppm for 4 wks	The time to respond to the conditioned avoidance stimulus increased significantly after 1 wk ($p < 0.001$) and after 3 and 4 wks exposure ($p < 0.01$).
Rat ²⁵¹	400 μ g/l (74 ppm) 7 hrs/day, 46 exposures in 8 wks	Study limited to effects on conditioned reflexes. A statistically significant decrease in the ability to differentiate positive and negative auditory and visual stimuli was noted ($p < 0.01$). A reduction in the latent period of the response to both stimuli was also seen.
Rat ²⁵² Wistar, Alderly Park strain male	100 ppm 6-7 hrs/day, 5 days/wk for 24 days	No decrease in body weight was noted. Behavioural pattern as a whole not significantly altered by exposure to trichloroethylene. Exploratory activity reduced on days 1, 3 and 10 but not at later periods.
Rat ²⁵³ Wistar male	2600-8000 ppm, 30 mins/day, 6 days/wk for 93 days (a total of 80 exposures)	Study limited to effects on behaviour for up to 72 days post-exposure and on the pathology of selected organs at c. 3 mths post-exposure. There was no effect on final body weight nor on food uptake during the experiment.

Table 3 Continued

Species	Concentration/dose and duration	Observations
		Signs of toxicity noted during the exposure period were a lack of response to external stimuli at 2600 ppm, and sniffing, head turning and abnormal movements at 5000 ppm. Exposure to 8000 ppm for 5-10 mins resulted in slight body trembling and abnormal leg movements, progressing to the eyes being closed and directed upwards; the abnormal leg movements ceased on prolonged exposure. The signs of toxicity became more marked after the seventh exposure but all groups recovered 5-10 mins post-exposure. No effects could be detected on the animals' emotional state nor on their general activity 10-17 days post-exposure, apart from an increase in activity at 2600 ppm as measured by an open field test ($p < 0.05$). Relearning was significantly impaired in all exposure groups at some stage 30-60 days post-exposure when compared to the controls ($p < 0.05$). At autopsy no gross changes were noted in the brain, lungs, liver or kidneys. On microscopic examination, lesions were noted in the cerebral cortex, but no pathological changes in the brain stem or cerebellum were seen. In some animals bronchial fibrosis was noted, but no pathological changes in the liver or kidneys were found.
Rabbit ²⁴	1860 ppm continuously for 20-30 days	Study limited to effects on eyes and brain. 5/5 animals died. Paresis of anterior and posterior limbs was observed. Ophthalmoscopic observations made throughout the exposure period revealed no changes in the fundus. At autopsy, microscopic examination revealed vascular lesions and massive hyperaemia in the cerebral and cerebellar cortex, as well as in the brain stem. The lesions included repletion of the arterioles, diapedesis in the capillaries and, at some points, rhexis.
Mongolian gerbil ²⁴	320 ppm continuously for 2-8 wks	Nerve cell regression was observed mainly near vessels. The changes consisted either of cytoplasmic fading with diffuse nuclear staining, or cytoplasmic hyperchromia. No changes in the neuroglia were observed. Study limited to effects on the brain. No significant changes in brain weight or body weight were noted. Significant decreases in the soluble protein content of certain areas of the brain including the anterior cerebellar hemispheres and hippocampus after 2 wks ($p < 0.05$) and of the frontal cerebral cortex and posterior vermis of the cerebellum after 8 wks were seen ($p < 0.01$ and $p < 0.05$ respectively). Transient increases in the soluble protein content of the sensory-motor cerebral cortex ($p < 0.01$ after 4 wks) and the brain stem ($p < 0.05$ after 2 wks) were also noted. Significant increases in the amount of S 100 protein (a glial cytoplasmic protein) were found in the visual cerebral cortex after 2 wks ($p < 0.05$), and the hippocampus, posterior cerebellar hemispheres and brain stem after 4 wks ($p < 0.05$). Also transient increases noted in the S 100 level in the frontal cerebral cortex and the sensory-motor cerebral cortex after 2-4 wks ($p < 0.05$ and $p < 0.001$, respectively), and both the anterior and posterior vermis of the cerebellum after 4 wks ($p < 0.001$). No change was detected in the S 100 content of the anterior cerebellar hemisphere.
Mongolian gerbil ²⁵	320 ppm continuously for 9 mths	Study limited to effects on spatial memory. There were no marked differences between the experimental and control animals.
Dog ²²¹	500-30 000 ppm, 2-8 hrs/day for up to 5 days wkly	Signs of intoxication at 3000 ppm and above consisted of head tremor, teeth gnashing, glazed eyes, extension of and subsequent bicycling movements of all extremities. Only slight and transient effects were noted below 3000 ppm. Autopsies limited to the brain revealed lesions in the Purkinje cell layer of the cerebellum where many cells had disintegrated. Scattered and often severe nerve cell lesions occurred throughout the cerebral cortex. Moderate changes to the myelin sheaths of the neurones of the white matter were also noted.

Table 3 Continued

Species	Concentration/dose and duration	Observations
ORAL		
Rat ⁸⁰ Osborne-Mendel	0.56-5.62 g/kg in corn oil by gavage 5 days/wk for 6 wks. Animals observed for 2 further wks	All animals died following dosage with 5.62 g/kg but no animals died at 3.1 g/kg or below. Decreases in body weight gain of >20% were noted in females at 1.78 g/kg and above and in males at 3.16 g/kg and above. Other signs of toxicity noted at 3.16 g/kg and above were hunching, urine-stained fur, alopecia and laboured breathing. Gross examination at autopsy revealed a dilated renal pelvis in one male and a dark red kidney medulla in another at 1.78 g/kg. Incidental findings of large abscessed regions in all lung lobes of 2 test animals were noted. No histopathology was performed.
Mouse ⁸⁰ B6C3F1	1-10 g/kg in corn oil by gavage 5 days/wk for 6 wks. Animals observed for 2 further wks	All animals died following dosage with 10 000 mg/kg but no males died at 3160 mg/kg or below, or females at 1780 mg/kg or below. No significant dose-response effects on body weight gain occurred and no other signs of toxicity were noted. No gross lesions were observed at autopsy. No histopathology was performed.
Rabbit ¹⁰⁰	74 mg/kg, 3 days/wk for 1-5 mths	No effect on weight gain was noted. No other signs of toxicity were seen apart from a fairly marked transient diarrhoea in some animals after 1-2 mths exposure. Periodic examination of the urine throughout the study revealed the presence of urobilinogen from wk 5 and also a transient albuminuria in some animals. No marked haematological changes were observed during the study. At autopsy the gross appearance of the organs was normal. On microscopic examination liver lesions (unspecified) were observed. In the kidneys subacute glomerulitis was always seen and also some degenerative lesions of the convoluted tubules could be observed.
Rat ^{105, 256, 257} Alderley Park (Wistar-derived) male	1 g/kg in corn oil by gavage for 5 or 10 consecutive days	Study limited primarily to effects on the liver. No effect on body weight was noted after 10 days. No significant changes were seen in the serum activity of AST or ALT measured 24 hrs after the tenth dose. A significant increase in the liver/body weight ratio was noted after dosing for 10 days ($p<0.05$) but no change in the water content of the liver was seen at this time. Light microscopy revealed slight centrilobular eosinophilia but no TCE-induced damage after dosing for 5 or 10 days. Electron microscopy demonstrated a 15% increase in hepatic smooth endoplasmic reticulum after dosing for 10 days. Hepatic DNA content was significantly decreased ($p<0.05$) after dosing for 10 days, but no change in the rate of incorporation of tritiated thymidine into DNA was seen 1 day after the tenth dose. No significant effect on the non-protein sulphhydryl content (NPSC) was noted after dosing for 10 days. Significant increases were noted in hepatic ethoxyresorufin-O-deethylase after 10 days ($p<0.05$), ethoxycoumarin-O-deethylase after 5 and 10 days ($p<0.001$), and both cytochrome b₅ and NADPH-cytochrome-c-reductase after 5 days ($p<0.05$, $p<0.01$) and 10 days ($p<0.01$, $p<0.02$), respectively. No effects were noted in hepatic benzphetamine-N-demethylase and total haemoprotein P-450 after 5 and 10 days. These studies have only been briefly reported and few data are given. The significance is thus difficult to assess.
Mouse ¹⁰⁸ CD-1	0.1, 1.0 and 2.0 mg/ml, as an emulsion in drinking water, for 120 days	Study limited to the effects on the cell-mediated and humoral immune response at the end of the exposure period.

Table 3 *Continued*

<i>Species</i>	<i>Concentration/dose and duration</i>	<i>Observations</i>
Mouse ^{105, 256, 257} Alderley Park (Swiss-derived) male	0.5 g/kg in corn oil by gavage for 10 consecutive days	Female mice exhibited a dose-dependent suppression of humoral immunity (as indicated by a decreased haemagglutinin titre and decreased number of antibody forming cells following sensitisation to sheep erythrocytes). An inhibition of the delayed-type hypersensitivity response (cell-mediated) to the sheep cells was also noted in female mice. No effect on either the cell-mediated or humoral immunity was noted in male mice. Study limited primarily to effects on the liver. No effect on body weight was noted. No significant changes were seen in the serum activity of AST or ALT measured 24 hrs after the tenth dose. A significant increase in the liver/body weight ratio was noted ($p < 0.05$), but no change in the water content of the liver was seen. No TCE-induced liver damage was detected by light or electron microscopy. Hepatic DNA content was significantly decreased ($p < 0.05$), but a 82-138% increase in the rate of incorporation of tritiated thymidine into DNA was seen 1 day after the tenth dose. Hepatic NPSC was increased by 33-46%. Significant increases were noted in hepatic ethoxycoumarin-O-deethylase, total cytochrome P-450, cytochrome b_5 and NADPH-cytochrome-c-reductase ($p < 0.05$). The level of ethoxyresorufin-O-deethylase in the liver was significantly reduced ($p < 0.05$). No effect was noted in hepatic benzphetamine-N-demethylase.
Mouse ¹⁰⁷ CD-1	0.1-5 mg/ml (0.5-27 ppm) of drinking water (with 1% emulphor) for 4 or 6 mths	Study limited to investigating effect on hepatic mixed function oxidase activity. No effects were noted apart from an increase in liver/body weight ratio at the highest dose (23% increase in males after 4 mths).
Mouse ¹⁰⁶ Swiss-Cox	100-1600 mg/kg in corn oil daily for 6 wks	Study limited to investigating effects on the liver. Increases in liver weights were noted. Induction of the mixed function oxidase system was noted as seen by increased cytochrome P-450 levels. No changes in triglyceride or glucose 6-phosphatase levels were noted.
Calf ²⁵⁸	c. 0.25 g/day for 346 days in milk or c. 0.25 g/day for 100 days and then c. 10 g/day for 246 days in milk	No clinical effects nor changes in haematological parameters were noted. No gross changes were observed at necropsy.
INTRAPERITONEAL Rat ²³⁰ Sprague-Dawley male	1 mmol/kg (0.13 g/kg) in methanol (0.5 ml/kg) for 1-3 days	Study limited to the effects on the liver. Levels of serum ALT 24 hrs post-dose were unchanged after 1 or 3 doses. Histopathology revealed no hepatic necrosis. Hepatic cytochrome P-450 was significantly reduced 24 hrs after 3 doses ($p < 0.05$). Hepatic glutathione levels 4 and 24 hrs post-dose were unchanged after 1 or 3 doses. A fourth administration resulted in the death of most animals with severe peritonitis and intestinal perforations but no liver or kidney necrosis.
Rat ²⁵⁹ Wistar	1.5 ml/kg (2.2 g/kg) daily on 3 alternate days	Study limited to the effects on the liver 24 hrs after the last dose. The amount of glycogen in the liver was significantly reduced ($p < 0.05$) but hepatic lipid levels were unaffected.

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Table 3 Continued

Species	Concentration/dose and duration	Observations
Rat ²²⁹ Sprague-Dawley male	0.25 ml/kg (0.37 g/kg) twice on day 1, 0.5 ml/kg (0.73 g/kg) twice on day 2 and 1.0 ml/kg (1.47 g/kg) twice on days 3-5. Compound given as a solution in liquid paraffin	Study limited to investigating effects on hepatic metabolising enzymes in animals killed 18 hrs after the last dose. Significant increases were noted in the liver/body weight ratio and in the levels of hepatic microsomal protein, NADPH-cytochrome-c-reductase, aniline hydroxylase and p-nitrophenol glucuronyl transferase ($p < 0.05$). Significant decreases in the activities of cytochrome P-450, ethylmorphine demethylase and hexobarbital transferase were also noted ($p < 0.05$).
Rat ²⁶⁰ Sprague-Dawley female	0.2-2.0 g/kg for 5 days	Study limited to investigating effects on the lungs and liver. At autopsy, histology of the lungs revealed interstitial oedema, some bleeding into alveolar spaces and necrosis. No evidence of damage to the liver was noted. Levels of the mixed function oxidase (MFO) enzymes of liver and lungs were determined. In the lungs of the MFO activity was reduced by about 25% and 50% at the lower and higher doses respectively. The MFO activity in the liver was reduced by 15% at the higher level with no change noted at the lower levels.
Mouse ²³⁶ Swiss	0.6 ml/kg (0.9 g/kg) in corn oil on alternate days over 6 days	Study limited to effects on kidney function. No significant effects were noted on urinary protein or glucose levels 48 hrs post-dose.
INTRAMUSCULAR		
Rabbit ²⁶¹ female	4.38 g/animal 3 times a week for 28 or 29 days	Study limited primarily to investigating effects on the brain. One animal died of oil embolism. The animals lost weight and appeared thin and feeble. No marked increase in erythrocyte sedimentation rate was seen. At autopsy neuronal changes including capsular cell proliferation and round cell infiltration around vessels and in the parenchyma were noted.
	2.92 g/animal 2 days/wk for 50-247 days	4/9 animals died after injection due to oil embolism. No signs of toxicity were noted. 1/9 animals exhibited a markedly increased erythrocyte sedimentation rate after 50 days of exposure. At autopsy histological examination revealed widespread neuronal changes with eosinophilic homogenisation, shrinkage of the cytoplasm and nuclear hyperchromasia. Loss of Purkinje cells and basket cells was also seen. Capsular cell proliferation was noted in the Gasserian ganglion.
Rabbit ^{262, 263}	A total of 8.75-9.0 ml/kg (12.8-13.2 g/kg) in olive oil over a 3-wk period	Study limited to investigating the effects on the eyes. There was no morphologically or clinically detectable evidence of damage to the lens or retina. The ATP content of the retina was decreased by 26%. Decreases were also noted in the activities in the lens of ALT, aldolase, glucose 6-phosphate dehydrogenase, lactate dehydrogenase and hexokinase. Increases in malate dehydrogenase and NAD-sorbitol dehydrogenase activity of the lens were also seen. Most of the changes were reversible but ATP content, aldolase and glucose 6-phosphate dehydrogenase activity had failed to return to normal within 2 wks.
INTRAVENOUS		
Rabbit ⁶⁸	c. 0.03 g/kg daily for 13-15 days.	Study limited to effects on eyes and brain. 5/5 animals died. Paresis of anterior and posterior limbs was observed.

Table 3 Continued

Species	Concentration/dose and duration	Observations
		Ophthalmoscopic observations made throughout the exposure period yielded no changes in the fundus. At autopsy, microscopic examination revealed vascular lesions and massive hyperaemia in the cerebral and cerebellar cortex, as well as in the brain stem. The lesions included repletion of the arterioles, diapedesis in the capillaries and, at some points, rhexis. Nerve cell regression was observed mainly near vessels. The changes consisted either of cytoplasmic fading with diffuse nuclear staining, or cytoplasmic hyperchromia. No changes in the neuroglia were observed.

SL 034980

Table 4 Mutagenicity of trichloroethylene

Tester strains	Concentration	Observations
<i>Point mutations in Salmonella typhimurium</i>		
TA100 and TA1535 ²⁴⁴		
- S-9	0.1-10% vapour (TCE was epoxide and epichlorohydrin free)	Negative to both strains.
+ S-9 (rat)		Negative to both strains.
		Positive controls gave satisfactory results. No note on toxicity made but 10% showed a markedly reduced number of revertants.
TA100 ²⁴⁵		
- S-9	5-20% vapour (no detectable epoxide or epichlorohydrin present)	Negative.
+ S-9 (prepared from mice pre-treated with phenobarbitone)		Equivocal. A dose-related increase in revertants was noted with a maximum of 1.8-fold background colonies. The text states that 2-fold increases have consistently been found. Toxicity, as evidenced by the absence of a normal background lawn, was seen at 20% in the presence and absence of S-9.
TA100 ²⁴⁶		
- S-9	15 000-75 000 ppm vapour phase (purity not stated)	Negative.
+ S-9 (both rat and mouse used)		Equivocal. A dose-related increase in the number of revertants was noted using both S-9 preparations but only a maximum of 1.7-fold background revertants was noted. No note on toxicity was made but the top concentration used produced a marked decrease in the number of revertants in the presence or absence of S-9.
TA98 and TA100 ²⁴⁷		
- S-9	0.5-10% vapour (commercial trilene used)	Negative.
+ S-9 (rat)		Negative. No increase in the number of revertants above controls was noted but no figures were given. No comments on toxicity were made. Vinylidine chloride was used as a positive control.
TA100 ¹²¹		
- S-9	0.1-100 μ l/ml (0.26-260 μ l/plate) TCE purified	Negative.
+ S-9		Negative. No comment on toxicity of TCE to the bacterial strain was made, but it was seen that the number of revertants decreased markedly at 25 μ l/ml in the absence of S-9 and at 100 μ l/ml in the presence of S-9. Epichlorohydrin and epoxybutane were strongly positive with this strain.
<i>Point mutations in Escherichia coli</i>		
<i>E. coli</i> ¹⁰⁹	3.3 mM (a.g. grade reagents, no purity given or stabiliser content)	
K ₁₂		
+ S-9		
gal+		Negative.
arg+		Positive, 2.3 x background (no dose response performed).
MTR		Negative.
NAD+		Negative. No raw data were given with results expressed only as percentage of controls. Only one dose level was tested; it is, therefore, difficult to assess the significance of this study.

Table 5 Chronic toxicity/carcinogenicity of trichloroethylene

Species	Concentration/dose and duration	Observations
INHALATION		
Rat ¹²⁰ Wistar	100 and 500 ppm, 6 hrs/day, 5 days/wk for 18 mths. Animals were observed until 36 mths	The experiment was terminated after 36 mths. Gross autopsies were performed on these animals and on those that died during the experiment. Microscopic examination was limited to the spleen, liver, kidneys, lungs, heart, CNS, stomach and any tumorous tissue.
	30 animals of each sex were used at each dose level and 30 more of each sex as controls	It was stated that body weight gain was normal for all test groups but no figures were given. No details or other signs of toxicity were given.
	Purified TCE was used with triethylamine as stabiliser (epoxides were present at only $2 \times 10^{-6}\%$ of TCE concentration)	No statistically significant differences in mortality between test and control animals were noted. 90% of the male test animals survived 100 wks at each dose level, as compared with 86.6% and 76.6% of the females at 100 and 500 ppm respectively and 86.7% of controls of each sex. Of the male test animals 23.3% and 36.7% at 100 and 500 ppm respectively, survived to the end of the experiment, as compared with 13.3% and 16.7% of the female test animals and 46.7% of the male and 16.7% of the female controls.
		No details of organ weights, gross changes or non-tumorous pathological changes were given.
		Tumour incidence was reported as the total number of tumours identified during the study. No significant increase in tumour incidence was noted at any site or at either dose level. No information was given regarding the times of appearance of the tumours.
		TCE does not appear to be carcinogenic in this study. The study is, however, limited by the small number of animals used in each group.
Mice NMRI	100 and 500 ppm, 6 hrs/day, 5 days/wk for 18 mths.	The experiment was terminated after 30 mths. Gross autopsies were performed on these animals and on those which died during the experiment. Microscopic examination was limited to the spleen, liver, kidneys, lungs, heart, CNS, stomach and any tumorous tissue.
	30 animals of each sex were used at each dose level and 30 more of each sex as controls	It was stated that body weight gain was normal for all test groups but no figures were given. No details on any other signs of toxicity were given.
		A statistically significant decrease in survival rate for all test groups was noted as compared to controls. For males $p=0.0455$ and $p=0.0036$ at 100 and 500 ppm respectively and for females $p=0.009$ and $p=0.012$ at 100 and 500 ppm respectively. 16 of the males and 6 of the females in the high dose group had died before $1\frac{1}{2}$ yrs. 12 of both males and females exposed to the lower concentration had also died by this time.
		No details of organ weights, gross changes or non-tumorous pathological changes were given.
		Tumour incidence was reported as the total number of tumours identified during the study.
		The only significant increase in tumour incidence was in lymphomas in female mice. These were identified in 18/28 (64%) of animals exposed to 500 ppm, as compared with 17/30 (57%) at 100 ppm and 9/29 (31%) of control animals. The increase was dose-related and was more marked if age-adjustment was performed. The first lymphomas were observed at 36 wks and 65 wks in females exposed to 100 and 500 ppm respectively, as compared with 80 wks in controls.
		These results suggest that TCE produced a dose-related increase in the incidence of lymphomas in female mice, with effects at both dose levels. However, this type of tumour appears to have a fairly high spontaneous incidence in female mice of this strain, although no historic data were given, and interpretation of the significance of the result is difficult.
		The value of this study is severely limited by the small number of animals surviving for more than $1\frac{1}{2}$ yrs. No conclusions can therefore be drawn regarding the carcinogenicity of trichloroethylene from this work.
Hamsters ¹²⁰ Syrian	100 and 500 ppm 6 hrs/day, 5 days/wk for 18 mths. Animals were observed for 30 mths	The experiment was terminated after 30 mths. Gross autopsies were performed on these animals and any that had died during the experiment. Microscopic examination was limited to the spleen, liver, kidneys, lungs, heart, CNS, stomach and any tumorous tissue.

Table 5 Continued

Species	Concentration/dose and duration	Observations
	30 animals of each sex were used at each dose level and 30 more of each sex as controls	It was stated that the body weight gain for all test groups was normal but no figures were given. No details of any other signs of toxicity were given. No statistically significant decrease in survival rate was noted as compared to control animals. In males 70% and 63.3% exposed to 500 ppm and 100 ppm respectively survived 100 wks, as compared with 56.7% of controls. A much lower survival rate was noted in females with only 30% and 20.7% surviving 100 wks at 500 ppm and 100 ppm, as compared with 23.3% of controls. No females survived to the end of the experiment, as compared with 6.7% and 26.7% of the males in the low and high dose groups and 13.3% of male control animals. All males survived 18 mths as compared with 83.3% of control females and 76.6% and 89.7% of females in the high and low dose groups. No details of organ weights were given. Liver cysts were a very common finding in both male and female hamsters of control and exposed groups, with 16/30 (53%) male and 22/30 (73%) female controls exhibiting such changes, as compared with 12-16/30 (40-53%) animals in the test group. No significant increase in the incidence of tumours of any type was noted at either dose level. The value of this study is, however, severely limited by the small group size and the low 2-yr survival rate (especially of the females). No conclusions can be drawn from this study regarding the carcinogenicity of TCE.
ORAL		
Rat ¹⁰		
Osborne-Mendel	TCE was given as a solution in corn oil (60% w/v), by gavage, two dose levels being investigated The low-dose group were given 650 mg/kg, 5 days/wk for 7 wks; then 750 mg/kg, 5 days/wk for 9 wks; then 500 mg/kg, 5 days/wk in a cycle of 1 wk no treatment and 4 wks treatment, for 48 wks The high-dose group were given exactly double the concentrations of TCE for an identical time pattern The animals were observed for a further 32 wks The TCE used was >99% pure and contained 1, 2 epoxybutane (0.19%) and epichlorohydrin (0.09%) 50 animals of each sex were used at each dose together with 20 rats of each sex as vehicle-treated controls. 99 males and 98 females were also used as colony controls	The experiment was terminated after 110 weeks and autopsies performed on all animals that had died during the experiment or had been killed at wk 110. Signs of toxicity were noted at both dose levels; these occurred with increasing frequency during the second year of the experiment. These included hunched appearance, rough coat, eyes squinted and showing a reddish discharge, localised alopecia on extremities or body, sores particularly on the tail and stains on the coat. A dose-related decrease in body weight gain was noted but was complicated by the mortality of the test groups. In male rats a dose-related increase in mortality was noted with the survival time for animals in the high-dose group being significantly shorter than the low dose and control groups ($p < 0.001$). Only 12/50 (24%) of the high-dose group survived 78 wks, as compared to 31/50 (62%) and 16/20 (80%) of the low-dose and control groups respectively. At 110 wks only 3/50 (6%), 8/50 (16%) and 3/20 (15%) of the high-dose, low-dose and control groups respectively remained alive. A statistically significant increase in mortality of the female animals was noted with 23/50 (46%), 20/50 (40%) and 16/20 (80%) of the high, low and control groups surviving 78 wks; and 13/50 (26%), 13/48 (27%) and 8/20 (40%) of the high, low and control groups surviving to the end of the experiment ($p < 0.05$). The only non-tumorous toxic effect noted at autopsy was stated to be in the kidney, i.e. toxic nephrosis. This was seen in 45/50 (90%) of the males and 36/48 (75%) of the females in the low-dose group, and in 46/50 (92%) of the male and 47/50 (94%) of the females in the high-dose group. No toxic nephrosis was noted in control animals. The nephropathy was different to that commonly encountered due to ageing, and was characterised by degenerative and regenerative changes in tubular epithelium. Dose-related lesions were, however, also noted in the heart with inflammation of the myocardium or pericardium in 7/50 (14%) males and 6/50 (12%) females in the high-dose group, as compared with 2/50 (4%) males and 3/48 (6%) females in the low-dose group and 0/20 males and 1/20 (5%) females in the control group. No significant increase was noted in the occurrence of tumours at any site in the test groups, as compared to the controls. Trichloroethylene does not appear to be carcinogenic to this strain of rat in this study.

Table 5 Continued

Species	Concentration/dose and duration	Observations
Mice B6C3F1		The study was severely limited by the low survival of the test animals.
		No definite conclusion can be drawn regarding the carcinogenicity of trichloroethylene from this study.
	TCE was dosed as a 10-24% solution in corn oil, two dose levels being investigated. In the low-dose group males were given 1000 mg/kg, 5 days/wk for 12 wks and then 1200 mg/kg, 5 days/wk for a further 66 wks. The females were dosed with 700 mg/kg, 5 days/wk for 12 wks and then 900 mg/kg, 5 days/wk for a further 66 wks. In the high-dose group male and female animals were dosed with double the quantities of the respective low-dose groups for identical time periods	The experiment was terminated at wk 90. Autopsies were performed on all animals that had died during the experiment or were killed at wk 90.
	50 animals of each sex were used at each dose level and 20 mice of each sex were used as vehicle-treated controls. 77 male and 80 females were also used as colony controls	No treatment-related signs of toxicity were noted during the first year. After 50 weeks bloating and abdominal distention was predominant in the high-dose males. By week 74, 50% of all treated males appeared bloated; this persisted until the animals died or were killed. A few treated females also exhibited abdominal distention prior to termination. No significant change in body-weight gain was noted in any of the treated groups.
Mouse ¹²² non-inbred Ha:JCR	All animals were observed for a further 12 wks following the end of the treatment period	A large number of the male control animals died before 1½ yrs, 12/20 (60%), as compared with 10/50 (20%) and 26/50 (52%) of the low and high-dose groups respectively. Of the female animals 2/20 (10%), 9/50 (18%) and 10/50 (20%) of the control, low-dose and high-dose groups survived the 1½ yrs.
		The only significant non-tumorous lesion noted at autopsy was a toxic nephrosis which was seen in practically all the treated animals but not in any of the controls.
		Tumour incidence was based on the number and type of tumours present at autopsy, irrespective of the time of death.
		In both treated male and female mice primary hepatocellular carcinoma were seen in high numbers. In males 31/48 (64.5%) of the high-dose group exhibited the tumour, as compared with 26/50 (52%) of the low-dose group and 1/20 (5%) matched controls and 5/77 (6.5%) colony controls. The difference between the numbers of tumours in both the treated groups and matched controls were significant ($p < 0.01$). A significant increase in the number of primary hepatocellular carcinoma 11/47 (23%) was noted in the females in the high-dose group, and in the low-dose group 4/50 (8%), as compared 0/20 in the matched controls ($p = 0.09$). The colony controls exhibited 1/80 (1.25%) hepatocellular carcinoma. These tumours apparently appeared earlier in the male animals given the high dose; no such effect was noted in the females. In the males the first hepatoma was identified at wk 27 at the high-dose level, at wk 81 at the low dose and at wk 72 in the controls. No tumours were found in the female animals until the rest of the animals were killed at wk 90 by which time 3 had been found in the males in the low dose group and 4 at the high dose. Metastases of the liver tumours were found in the lungs of 7/98 male mice. An increase in the number of tumours of the lungs was seen in treated animals, as compared with controls; the increase was however not statistically significant. Such tumours were seen in 5/50 (10%) of males and 4/50 (8%) of the females at the low dose and in 2/48 (4%) and 7/47 (14%) of the males and females in the high dose groups. The majority of these tumours were classified as benign adenoma of the lung.
Mouse ¹²² non-inbred Ha:JCR	0.5 mg/animal in trioctanoin 1 day/wk for 622 days, by gavage	The trichloroethylene material used in this study markedly increased the incidence of primary hepatocellular carcinoma in both sexes of B6C3F1 mice.
	30 animals of each sex were used in each test and vehicle control group. 100 female and 60 male animals were used as untreated controls	However, it should be noted that the technical grade of TCE used contained significant quantities of 1, 2 epoxybutane (0.19%) and epichlorohydrin (0.09%) as stabilisers. Both of these chemicals have been shown to be mutagenic to bacteria and epichlorohydrin has been quoted as being carcinogenic in rat and mouse. No conclusions can therefore be made as to the carcinogenicity of TCE itself in this study.
		The experiment was terminated after 622 days for test animals and 649 days for female and 636 days for male controls. All animals which died during the experiment or were killed at the termination of the experiment were subjected to gross autopsy. Histopathology was limited to stomach, liver, lungs and any tissue of abnormal appearance.
		It was stated that no difference in weight gain between test and control animal groups occurred. No comments on signs of toxicity or mortality data were given.

Table 5 Continued

Species	Concentration/dose and duration	Observations
	The TCE used had been extracted with dilute acid, dilute alkali, and then water, followed by distillation prior to use	No data on non-tumorous pathological changes seen at autopsy were given. It was stated that no increase in tumour incidence was noted but no data, apart from the incidence of tumour of the fore-stomach were given. Insufficient data given for an assessment of this study. The single dose level used was very low for a carcinogenicity study, and the small number of animals used would preclude any firm conclusions being made regarding the non-carcinogenicity of trichloroethylene in this strain of mouse.
SKIN APPLICATION		
Mouse ¹²² non-inbred Ha:ICR female	1 mg/animal/application, 3 days/wk for 83 wks. TCE was applied to the shaved dorsal region in 0.1 ml acetone 30 females were used as the test group and another 30 females as vehicle treated controls. 100 female mice were used as untreated controls. TCE was extracted as above and distilled prior to use	The experiment was terminated after 83 wks. All animals which died during the experiment or were killed at the end of the experiment were subjected to gross autopsy. Microscopic examination was limited to the skin, liver, stomach, kidneys and any tissue of abnormal appearance. It was stated that no decrease in weight gain was noted in test animals, as compared to controls. No comments on any signs of toxicity were made. It was stated that the median survival time for TCE-treated mice was $\geq$ 581 days. No equivalent figures were given for the vehicle-treated or untreated control groups. No data on gross or non-tumorous microscopic changes observed at autopsy were given. No increase in tumour incidence in the limited tissue investigated was noted, examined, as compared to control groups. Insufficient data given for assessment of this study. The small number of animals used preclude any definite conclusions being drawn regarding the non-carcinogenicity of trichloroethylene in this strain of mouse.
SUBCUTANEOUS		
Mouse ¹²² non-inbred Ha:ICR female	0.5 mg/animal in 0.05 ml trioctanoin in left flank, 1 day/wk for 89 wks 30 females were used in the test and vehicle-treated controls. 100 females were used as untreated controls	The experiment was terminated after 89 wks. All animals which died during, or were killed at the end of the experiment were subjected to autopsy. Microscopic examination was limited to liver and tissue from the site of injection only. It was stated that no difference in weight gain occurred between test and control groups. No comments on any signs of toxicity or on animal survival were made. No data on gross or microscopic non-tumorous changes at autopsy were given. No increase in tumour incidence in the limited tissue investigated was noted. Insufficient data given to make any assessment of the study. The small number of animals used preclude any definite conclusions being drawn regarding the non-carcinogenicity of trichloroethylene in this strain of mouse.

Table 6 Teratogenicity of trichloroethylene: Animal studies

Species	Concentration/dose and duration	Observations
INHALATION		
Rat ¹²³ Sprague-Dawley	300 ppm, 7 hrs/day on days 6-15 of gestation	The pregnant females were killed on day 21, the uteri removed and the contents examined. The fetuses were weighed and examined for soft-tissue and skeletal abnormalities. It was stated that exposure to TCE was associated with a statistically significant reduction (4-5%) in mean body weights of maternal rats. No figures were, however, given. No effect on the absolute or relative liver weight in dams was noted at the time of the Caesarean section. No effect was noted on the litter size, the number of implantation sites/litter, the incidence of fetal resorption, fetal sex ratios or fetal body measurements. No malformations were noted in the fetuses There was no evidence of any teratogenic or fetotoxic effect in the rats exposed to TCE.
Mouse Swiss Webster	300 ppm, 7 hrs/day on days 6-15 of gestation	The examination was carried out as described above. No decrease in the mean body weights of maternal mice was noted, as compared to controls. No effect on the absolute or relative liver weight was observed. On gross examination it was noted that fetuses from treated animals exhibited an increased incidence of undescended testes in 2/12 (16%) males, as compared with 0/26 in controls. This increase was, however, not statistically significant. A significantly increased incidence of subcutaneous oedema was noted in fetuses of the test group, as compared with controls ($p < 0.05$). Microscopic examination of sagittal sections of whole fetuses revealed no abnormalities of organs, tissues or cells, as a result of exposure to TCE. TCE was not teratogenic in mice. Some evidence of slight fetotoxic effect and delayed development was however noted.
Rat ¹²⁴ Long Evans Hooded	1800 ppm 6 hrs/day 7 days/wk on days 0-20 of gestation	15/30 dams were killed on day 21. Blood samples and maternal livers were taken for liver and kidney function tests. The uteri were removed and examined together with their contents. Four fetuses/litter were examined for soft tissue abnormalities and a further four for skeletal abnormalities. The remaining dams were allowed to come to term and representative offspring were examined for behavioural effects, mostly at weaning but some at 100 days. No signs of toxicity noted in maternal animals during exposure nor were any adverse effects in liver or kidney function tests seen. Liver weights were normal. No significant differences in the number of corpora lutea or implantation sites/litter, the fetal body weights, the number of resorption sites/litter or in the sex ratios were noted in the treated groups, as compared to controls. No increase in soft-tissue abnormalities was noted in the treated animals but a significant increase ($p < 0.05$) in the incidence of displaced right ovary (about 2 mm down from the kidney) was noted. The left ovary was in the normal position. The incidence of total skeletal abnormalities in the treated animals was significantly elevated, as compared with controls ($p < 0.05$). The abnormalities consisted mainly of incomplete ossification of the sternum, and were considered to represent delayed development rather than teratogenic effect. Observations of the offspring revealed no significant differences in post-natal growth, total activity or ambulatory response to a novel environment. Animals were treated exactly as described above. No signs of maternal toxicity or changes in liver or body weight gain and no adverse effects on liver or kidney function tests were noted in treated dams, as compared to controls No significant differences in the number of corpora lutea, implantation sites, litter size or sex ratios were noted in the treated groups. From days 20-100, offspring of animals exposed pregestationally to TCE exhibited a significant depression in body weight ($p < 0.05$), as compared with controls. No significant behavioural effects were seen.
	Pre-mating exposure to 1800 ppm, 6 hrs/day, 5 days/wk for 2-3 wks. Followed by exposure to air or exposure to TCE as above	

Table 6 Continued

Species	Concentration/dose and duration	Observations
		In the teratogenicity study TCE produced no evidence of teratogenic effect but some fetotoxic effects (delayed development of the skeletal system) were observed. No effects on development or behaviour of offspring were observed. Pretreatment with TCE prior to mating resulted in some growth retardation of the offspring.
Rat ¹²⁵ Wistar	100 ppm, 4 hrs/ day on days 6-20 of gestation The test group contained only 2-6 animals	The dams were killed on day 20. The uterus was examined for resorption sites and each fetus examined for external, soft-tissue or skeletal abnormalities. A significant decrease in fetal body weight was noted on day 20, as compared to controls ($0.001 < p < 0.01$). An increase in the number of resorption sites was also noted ($0.001 < p < 0.01$). No other data were given. Study reported as abstract only, apparently of interim results. Insufficient data available to make an assessment of this work.

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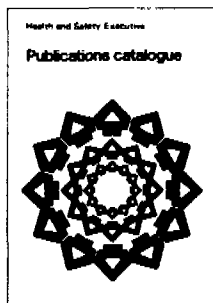
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