

CHAPTER V

TRICHLOROETHYLENE

Trichloroethylene, $\text{Cl}_2\text{C}=\text{CHCl}$, is a clear, colorless, highly volatile, non-flammable liquid with a sweetish odor. The estimated world production capacity of trichloroethylene in 1973 was about 1 million tons per year (267). Trichloroethylene is used in large quantities as an industrial degreasing and de-fatting agent, as a solvent and extraction medium and in chemical syntheses. Trichloroethylene is also used in dry cleaning and is a frequent component of various household products (468). Trichloroethylene was introduced as an anesthetic in 1934 and it still enjoys some clinical usage as an anesthetic and analgesic (195).

TOXICITY OF TRICHLOROETHYLENE

The extensive literature on trichloroethylene pharmacology and toxicology has been reviewed by several authors (51, 90, 186, 299, 396, 468). Most reports and reviews deal with toxic effects of trichloroethylene at occupational exposure although Defalque (90) also reviews the adverse effects of clinical trichloroethylene anesthesia. As pointed out repeatedly, early reports of trichloroethylene toxicity should be viewed with caution since the trichloroethylene used might have been of low purity.

Most trichloroethylene is manufactured by dehydrochlorination of 1,1,2,2-tetrachloroethane, a powerful hepatotoxic agent, which, together with tetrachloroethylene, might have been frequent contaminants of trichloroethylene (468). In addition, trichloroethylene decomposes in the presence of light and moisture to irritating acidic products such as hydrochloric acid, in contact with hot metal or a naked flame to phosgene, a powerful lung irritant, and in the presence of strong alkali to dichloroacetylene, shown to cause encephalitis and nerve injuries (90, 186, 468).

The most prominent effects of trichloroethylene are those of a CNS depressant. The acutely narcotic action of trichloroethylene has been studied in several animal species as summarized by von Oettingen (299). Thus, a concentration of 5000 ppm trichloroethylene produced signs of CNS depression in mice in 8-11 minutes with narcosis apparent in 44 minutes. The same concentration produced CNS depression in guinea pigs and rabbits in 30 minutes. Exposure to higher concentrations shortens the time for the onset of CNS depression and narcosis and may lead to death in respiratory failure. Prolonged exposure to relatively low concentrations, about 3000 ppm, may also be fatal. Little is known about the neuropathological changes due to acute trichloroethylene poisoning. In dogs receiving four intravenous doses of 0.8 ml/kg trichloroethylene the most pronounced changes were observed in the cerebellum with swelling and chromatolysis of Purkinje cells and in the spinal chord with swelling of the myelin sheaths (28). The only consistent complaint of human volunteers exposed 7 hours daily to 200 ppm trichloroethylene was a feeling of fatigue appearing

on the fourth day of exposure (424). Irish (196) states that beginning anesthetic effects in humans are seen at exposure to 300-400 ppm but Stewart *et al.* (427) found no signs of nervous impairment in humans at exposure to 350-400 ppm except some lightheadedness. Acute occupational exposure to high concentrations of trichloroethylene with prenarcotic and narcotic symptoms and even with fatal outcome are not uncommon in the early literature (51, 299, 396). It is believed that a fairly low concentration, 5000 ppm, can cause rapid unconsciousness (255). The prenarcotic symptoms may include euphoria, which is the reason for the many observed cases of trichloroethylene addiction (90, 468). The cause of death due to trichloroethylene over-exposure may not always be of CNS origin since trichloroethylene also has cardiotoxic properties causing death in ventricular fibrillation and other kinds of cardiac arrhythmias probably due to sensitization of the myocardium to the effects of endogenous catecholamines (166). Severe over-exposure to trichloroethylene is unusual in the occupational settings of today, but adverse psychological and behavioral effects have been noted recently at acute exposure of humans (359) and animals (368) to low concentrations of trichloroethylene. The results of chronic exposure to trichloroethylene are also dominated by its neurotoxic properties. Tabershaw (436) states that long-term occupational exposure may cause headaches, dizziness, lassitude, irritability and mental confusion. Defalque (90) includes psychic disturbances, autonomic dysfunctions, lesions of cranial nerves (especially the trigeminal and optic nerves), polyneuropathy with muscle paralysis and loss of sensation and cerebellar syndromes such as tremor, ataxia and vertigo. Smith

(396) cites numerous studies reporting chronic trichloroethylene induced neurotoxic effects such as fatigue, headaches, loss of memory, depression, difficulties of attention, emotional changes and peripheral neuropathy. Thus, there seems to be little doubt that trichloroethylene is a powerful chronically neurotoxic agent affecting both the peripheral and central nervous systems with the possible exception of the sometimes reported specific injury to the trigeminal nerve, which, as pointed out by Huff (186) may be caused by the decomposition product dichloroacetylene.

As for the ability of trichloroethylene to cause other specific organ injuries, the results of both early and more recent studies are conflicting. Notable are the numerous studies devoted to reveal possible hepato-renal toxic effects of trichloroethylene. Among the causes of death after acute human exposure to trichloroethylene are also included liver and/or kidney injury. These are more characteristic of cases of accidental or suicidal oral intake of large amounts of trichloroethylene than of occupational inhalational exposure to high concentrations (51). Von Oettingen (299) lists several reports of severe liver and kidney injuries at acute occupational exposure, however, as stressed by Smith (396), contaminants and unassociated predisposing medical conditions may have contributed. Acute exposure of humans to 200 ppm trichloroethylene 7h/day for up to 5 days did not result in changes in liver function as evidenced by several clinical and laboratory tests (424). There seems to be little evidence in favor of severe hepato-renal damage at chronic exposure. Bardodej and Vyskocil (32) failed to discover any signs of hepatic or renal functional impairment in a study

of 75 persons engaged in trichloroethylene degreasing or dry cleaning for up to 25 years. Schüttmann (375) stated after examination of 14 trichloroethylene exposed workers that chronic exposure is connected with liver injury the earliest sign of which is fatty infiltration. Among 30 workers exposed for up to 10 years to low (<100 ppm) trichloroethylene concentrations only 2 definite cases of slight elevation of serum transaminase levels were found (13). Lachnit and Pietschmann (239) found a slight temporary increase of serum glutamic oxaloacetic transaminase in 6 out of 31 chronically exposed workers. Serum protein changes, induced by trichloroethylene and probably evoked by liver damage, have been reported by several authors cited by Waters *et al.* (468).

Numerous animal experimental studies have been performed with the aim to reveal adverse hepato-renal effects of trichloroethylene. Hunter (187) exposed mice to the maximal amount of trichloroethylene in air they could tolerate (1-1.5% v/v) for 40-60 minutes daily on up to 12 occasions and found no evidence of kidney or liver injury except some disappearance of liver glycogen in animals which had died during the exposures. Kylin *et al.* (238) performed single 4 hour vapor exposures of mice to up to 3200 ppm trichloroethylene and found no evidence of liver injury as assessed by serum ornithine carbamoyl transferase activity, extractable liver fat or microscopic examination. Intraperitoneal injection of trichloroethylene even at 1 g/kg did not cause any elevation of serum ornithine carbamoyl transferase activity in guinea pigs (103). Liver histopathology was also negative except for a slight fat deposition. A single subcutaneous dose of 0.004 mol/kg trichloroethylene to rats

produced a slight elevation of serum transaminase levels between 12 and 16 hours after injection concomitant with mild, degenerative parenchymatous liver changes but no lipid infiltration (473). Serum transaminase and ornithine carbamoyl transferase levels were within normal limits in rabbits exposed for 4 hours to 5000 ppm trichloroethylene on up to 3 occasions (448). Jones *et al.* (211) evaluated the hepatotoxic potency of trichloroethylene administered orally to mice. The dose causing minimal liver injury, characterized by slight fatty infiltration, was equal to the narcotic dose (0.72 g/kg). A dose of 1.46 g/kg produced moderate liver injury with massive fatty infiltration. Severe liver injury, also including necrosis, was not observed even at administration of lethal doses. Gehring (143) found that the duration of exposure of mice to trichloroethylene that caused a significant elevation of serum glutamic-pyruvic transaminase was considerably larger than that required to produce anesthesia. Trichloroethylene was a very weak hepatotoxic agent compared to chloroform or carbon tetrachloride. The same observation was made by Plaa and co-workers (316), who used several indices of trichloroethylene hepatotoxicity in mice such as prolongation of barbiturate hypnosis, sulfobromophthalein retention and elevation of serum transaminase activity. Single intraperitoneal injections of trichloroethylene failed to cause impairment of kidney function or microscopic kidney changes in mice and dogs (222, 223, 317).

Early investigators of subchronic or chronic trichloroethylene toxicity in animals tend to the conclusion that trichloroethylene resembles other chlorinated hydrocarbon solvents in exerting a toxic effect on the liver and/or kidneys whereas

later investigators state the opposite opinion. Seifter (386) noted increased bromosulfophthalein retention, liver glycogen depletion and degeneration of parenchymatous liver cells but no decreased kidney function or microscopic kidney changes in dogs exposed to 500-750 ppm trichloroethylene 4-8 h/day, 5-6 days/week for 3-8 weeks. Cats exposed to 20 ppm trichloroethylene for 1-1.5 h/day for 4-6 months developed centrilobular liver necrosis and nephritis in addition to lymphoid gland hypertrophy and splenomegaly (283). Ninety days exposure of 1 dog, 3 rabbits and 3 rats to 0.05-0.1% (v/v) trichloroethylene 18 h/day produced no tissue lesions or adverse effects on growth rate or hepato-renal and hemopoietic functions (297). Adams *et al.* (3) exposing rats and rabbits to 3000 ppm trichloroethylene 7 h/day on 27 occasions during 36 days or rats, guinea pigs, rabbits and monkeys to 100-400 ppm on up to 178 occasions noted mainly signs of nervous system effects but also some growth depression and liver fat infiltration in rats. Bartonicek and Soucek (37) reported 2 deaths attributed to renal failure among 6 rabbits given a total amount of 33-55 g trichloroethylene intramuscularly during 55-100 days. A relatively recent study by Prendergast *et al.* (329) where rats, dogs, guinea pigs, rabbits and monkeys were exposed to trichloroethylene repeatedly (3825 mg/m³, 8 h/day, 5 days/week for 30 exposures over 6 weeks) or continuously (90 days to 189 mg/m³) reports normal hematological values and no signs of liver or kidney injury. No mortality occurred but slight growth depression was noted. Exposure of rats to 50 ppm trichloroethylene 8 h/day, 5 days/week for 14 weeks caused a slight elevation of liver weights but no abnormal hematological values, decreased liver and kidney function or gross pathologi-

cal changes of several examined organs (218). Early studies revealed no carcinogenic potential of trichloroethylene in animals (3, 283, 386). Renewed interest was however focused on trichloroethylene in 1975-76 when the U.S. National Cancer Institute reported a relatively high incidence of hepatocellular carcinoma in mice given from 900 mg/kg to 2400 mg/kg trichloroethylene orally 5 times weekly for 78 weeks (468). Similar experiments with rats were negative. Trichloroethylene oxide, suggested as early as 1945 to be formed initially during trichloroethylene biotransformation (325), has been implicated as the carcinogenic agent. However, technical grade trichloroethylene contains considerable amounts of compounds known to be mutagenic and possibly carcinogenic (177). Pure trichloroethylene was slightly mutagenic to *Escherichia coli* K12 after metabolic activation (161). Radioactivity from ¹⁴C-labeled trichloroethylene has been shown to become covalently bound to rat and mouse liver proteins both *in vitro* and *in vivo* in several studies (15, 44, 451, 459). Induction of the hepatic microsomal mixed function oxidase system with phenobarbital increased the covalent binding of radioactivity to liver proteins both *in vitro* (44) and *in vivo* (15). Pretreatment of rats with phenobarbital and other stimulators of hepatic microsomal enzyme activity also transformed trichloroethylene to a powerful hepatotoxic agent as evidenced by centrilobular and midzonal necrosis as well as elevations of serum transaminase activities (15, 62, 285). There is no evidence for or against trichloroethylene carcinogenicity in humans due to the lack of epidemiological studies. A Swedish study failed to reveal any increase of tumor incidence after occupational exposure (27).

UPTAKE, DISTRIBUTION, BIOTRANSFORMATION AND ELIMINATION OF TRICHLOROETHYLENE

Trichloroethylene is rapidly absorbed through the lungs and may also be absorbed from the gastro-intestinal tract as illustrated by cases of oral poisoning (299, 468). Stewart and Dodd (422) showed that trichloroethylene may penetrate intact human skin but concluded that cutaneous exposure to trichloroethylene would not result in absorption of toxic amounts. Ahlmark and Forssman (5) calculated a retention of about 50% at inhalation of 20 mg/l trichloroethylene. Soucek *et al.* (410) found an average retention of about 60% at exposure of humans to 0.54-1.31 mg/l trichloroethylene for 5 hours. Human subjects inhaling 0.50-0.85 mg/l for 5 hours retained 58-70% (411). An average retention of 58% was obtained by Bartonicek (36) who exposed humans to about 1 mg/l trichloroethylene for 5 hours. Fernandez *et al.* (129) report a higher retention, 74.3%, at 8 hours exposure of men to 54 or 97 ppm whereas Nomiyama and Nomiyama (294) report a lower retention, 35.4%, at 2.7 hours exposure to 252-380 ppm trichloroethylene. The elimination of unchanged trichloroethylene in the expired air after cessation of exposure, an initially very rapid process which is largely complete in 24-48 hours, often accompanied by a comment about its exponential character, has been observed in several studies in animals (5, 88, 218) and in man (129, 219, 294, 295, 325, 410, 424, 427, 429) but only rarely has it been subject to quantitative measurement or mathematical analysis. Soucek *et al.* (410) recovered in 7 hours an average of 19%, Fernandez *et al.* (129) an average of 8.4% and Nomiyama and Nomiyama (295) an average of 23.1% of the amount of trichloroethylene retained by humans

in the exhaled air. Rats dosed orally with high doses (1.9-4.2 g) ^{36}Cl -trichloroethylene exhaled 72.1-84.8% of the dose (88). Three-compartment pharmacokinetic models, including the excretion pattern of trichloroethylene in the expired air and sometimes also the formation and excretion of its metabolites, have been constructed for the transfer of trichloroethylene and its metabolites in the body (128, 129, 163, 364).

Very few distribution studies of trichloroethylene and its metabolites, most of them relying upon early unspecific chemical analysis, may be found in the literature. Rabbits and dogs anesthetized with trichloroethylene showed high fat concentrations, which were about twice as high as the blood, lung and heart concentrations and three times higher than the liver and kidney concentrations (34). Further experiments showed that trichloroethylene tissue concentrations decreased rapidly after anesthesia. Fabre and Truhaut (121) exposed guinea pigs to 6-9 mg/l trichloroethylene, 4-5 h/day for 5-23 days and found the highest concentrations of trichloroethylene in body fat but also quite high concentrations in the adrenals, spleen, ovaries and lung. The brain, liver and kidney contained lower amounts. Analysis of tissue trichloroacetic acid levels revealed that these were all higher than tissue trichloroethylene levels with the highest concentrations found in the adrenals, spleen and ovaries followed by fat, lung, kidney, brain and liver. A recent investigation showed that trichloroethylene accumulated in body fat of rats but not in the brain, lung or liver at 4 days exposure to 200 ppm 6 h/day (368).

The biotransformation of trichloroethylene (Fig.V:1) has

been the subject of numerous studies both in animals and in man. The conversion of trichloroethylene to trichloroacetic acid excreted over a long period of time in the urine of dogs and humans after inhalation of trichloroethylene was described in 1939 (34, 35). Powell (325) noted the excretion of trichloroacetic acid for at least 10 days in the urine of patients undergoing trichloroethylene anesthesia. In 1949, Butler (56) identified trichloroethanol as a second metabolite of trichloroethylene in dogs. Most of the trichloroethanol appeared in the urine as a glucuronic acid conjugate and was produced in a larger amount than trichloroacetic acid. On the basis of his earlier work (55) he suggested the formation of the two metabolites from initially formed chloral hydrate, which would be either oxidized to trichloroacetic acid or reduced to trichloroethanol, although chloral hydrate was not found in plasma of dogs anesthetized with trichloroethylene. Chloral hydrate was found to be reduced by NADH and alcohol dehydrogenase to trichloroethanol and oxidized by a NAD dependent enzyme (chloral hydrate dehydrogenase) to trichloroacetic acid (85, 129). Trichloroacetic acid may also arise through the oxidation of trichloroethanol (265). The actual formation of chloral hydrate from trichloroethylene has been shown to occur in a NADPH and O_2 dependent reaction in liver microsomes (58, 247) and chloral hydrate has been identified in the blood of rats inhaling trichloroethylene (218). Trichloroethylene has also been shown to be biotransformed in the isolated perfused rat and guinea pig lung (87). Using ^{36}Cl -labeled trichloroethylene administered to rats, Daniel (88) showed that no exchange of chlorine with the body chloride pool took place during the

biotransformation of trichloroethylene but instead a migration of chlorine within the molecule since the metabolically formed trichloroacetic acid and trichloroethanol had the same specific activities as the administered trichloroethylene. The possible mechanisms of chlorine migration *in vivo* have been outlined by Bonsche and Henschler (45). The mechanisms would include the initial formation of trichloroethylene oxide, as suggested by Powell (325) and for which spectral evidence has recently been obtained (452). Daniel (88) suggested the spontaneous rearrangement of trichloroethylene oxide to trichloroacetaldehyde and subsequent hydrolysis to chloral hydrate. The biotransformation of trichloroethylene to trichloroacetic acid and trichloroethanol has been shown to occur in several both animal (37, 88, 218) and human (36, 129, 219, 286, 411, 424) experiments. Quantitatively, the formation of trichloroacetic acid and trichloroethanol may vary between species and individuals but two characteristic features are: 1/ a larger amount of trichloroethanol than trichloroacetic acid is formed and 2/ the elimination of trichloroacetic acid in urine is slower than that of trichloroethanol, probably due to a high rate of plasma protein binding of trichloroacetic acid (286). The literature on trichloroethylene biotransformation also contains scattered reports on the formation of additional metabolites. Humans inhaling 0.50-0.85 mg/l trichloroethylene for 5 hours excreted over the next 7-14 days 4% of the retained amount as monochloroacetic acid in the urine in addition to 19% and 40% of the retained amount as trichloroacetic acid and trichloroethanol respectively (411). Bardodej and Krivucova (cited by Bardodej and Vyskocil (32))

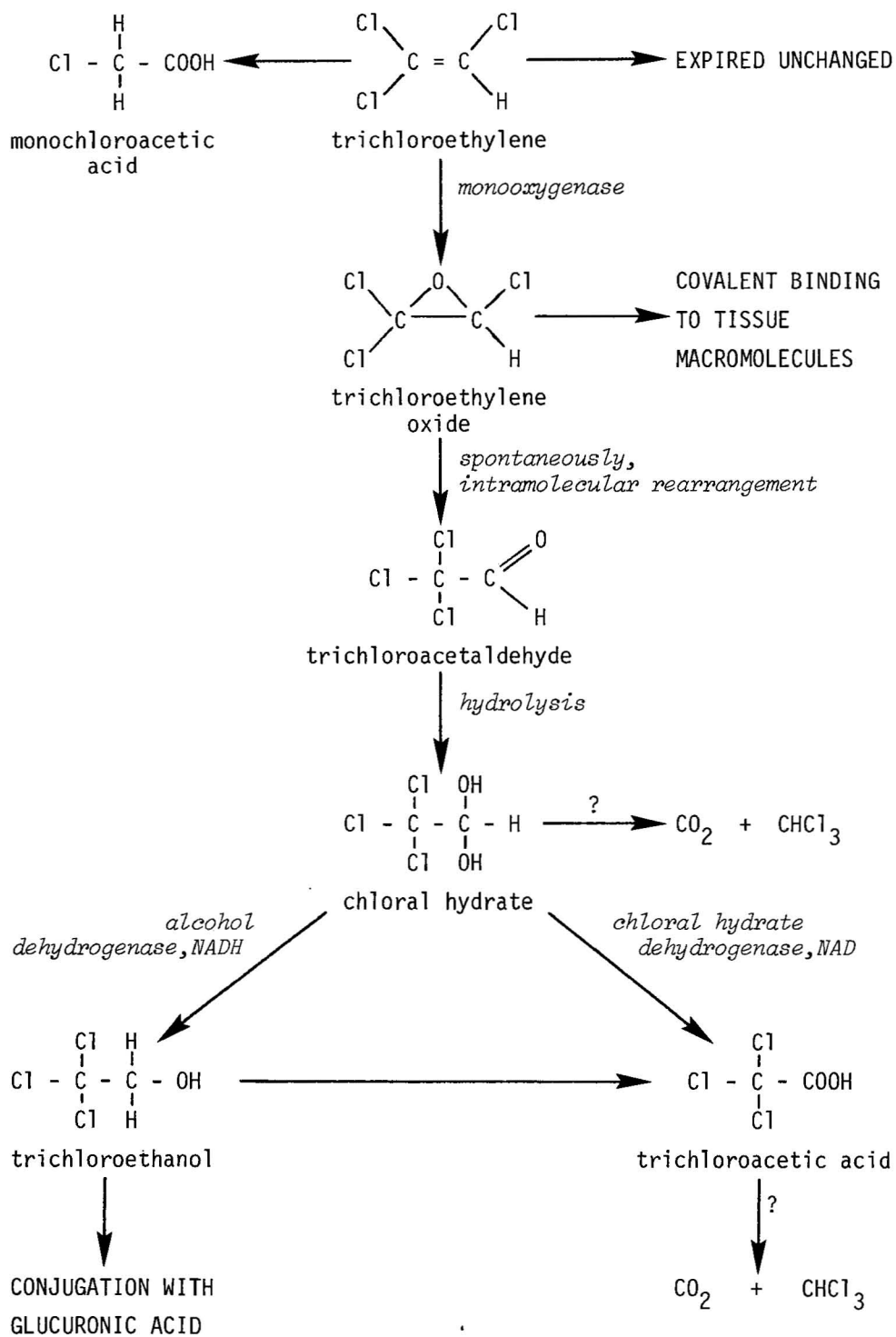


Fig.V:1. The biotransformation of trichloroethylene.

considered the spontaneous decarboxylation of trichloroacetic acid to chloroform and CO_2 and Soucek and Vlachova (cited by Bartonicek (36)) described the occurrence of small amounts of chloroform in the expired air and believed that it might arise through splitting of trichloroacetic acid or chloral hydrate. Recently, the cytochrome P450, NADPH and O_2 dependent conversion of trichloroethylene to CO was reported to take place in liver microsomes of rats pretreated with phenobarbital or 3,4-benzp(a)pyrene (447). The biotransformation of trichloroethylene is unique in that products with hypnotic properties, trichloroethanol and/or chloral hydrate, are formed, which may contribute to the nervous system effects observable at exposure to trichloroethylene. As mentioned above, the initially formed trichloroethylene oxide may be involved in mutagenesis and carcinogenesis. Metabolically formed CO was not considered to play a significant role in trichloroethylene toxicity (447).