

General Description

1,2-Dichloroethane (C₂H₄Cl₂) (DCE, ethylene dichloride) is a flammable, colourless liquid with a sweet taste. The compound has a boiling-point of 83 °C and a freezing-point of -35 °C. The solubility in water at 20 °C is 8.7 g/litre. The vapour pressure is 64 mmHg at 20 °C.

Sources

1,2-Dichloroethane is not reported to occur as a natural product (1). World production in 1979 was estimated to be 23 130 kilotonnes (2). In the countries of the European Community an estimated 5290 kilotonnes was produced in 1977 (3). In the United States production increased from 4160 kilotonnes in 1974 to 4750 kilotonnes in 1977 (4). Actual production figures may be higher, since a part of it (used as intermediate) is not separated and therefore is not always reported by some producers (1). In the manufacturing process, DCE is derived from ethene via (catalyzed) reaction with chlorine or with oxygen and hydrogen chloride (1).

The major industrial use of DCE is in the synthesis of other chemicals, among which vinyl chloride is the most important (80-90% of the DCE produced is used for production of this compound). A less important use is the production of ethylene diamines. 1,2-Dichloroethane is also used as a lead scavenger in petrol. A minor use is as a solvent and a fumigant (2,5,6).

Major sources of DCE emission to the environment include industrial use, manufacture of the compound, and inappropriate disposal of "EDC-tars", the heavy ends in vinyl chloride production. Emissions occur directly to the atmosphere both during the production process and during handling and storage. In addition, fugitive emissions contribute significantly. Emission of DCE also occurs when the compound is used for extraction purposes in the pharmaceutical industry or for crystallization in the chemical industry (5).

Besemer et al. (5) give, as a first approximation, an emission factor of 10 kg DCE per tonne production for western Europe. This value applies for controlled emissions. For uncontrolled emissions the estimated emission factor is 40 kg/tonne. Thus, total emissions of 61 000 and 11 0000 tonnes DCE have been estimated for western and eastern Europe respectively (5).

Occurrence in air

Rural or "background" levels of DCE in the USA have been reported to be up to 0.20 µg/m³ (7). Similar values were estimated for the Netherlands (5).

In the air of seven cities in the USA average DCE levels were between 0.5 and 6.1 µg/m³ (the median level was 1.0 and the maximum concentration 30.0 µg/m³) (7). 1,2-Dichloroethane concentrations near sites of production and in dispersive use are higher: at 12 locations near production facilities in each of three areas in the USA average levels gradually decreased from 61 µg/m³ at about 1 km distance to 2 µg/m³ at 3-4 km distance (8,9). Near petrol stations concentrations may also be elevated (10). In Sweden an average of 4.0 µg/m³ was measured in the air of petrol stations. In parking garages and car repair shops average concentrations were between 2.0 and 6.5 µg/m³. Inside cars, averages of 0.4-1.2 µg/m³ were found. It is noteworthy that, besides being directly volatilized from petrol, DCE is also released via engine exhaust (11). The few indoor measurement data available indicate that indoor levels of DCE are not higher than outdoor levels (12).

Degradation of DCE in the atmosphere proceeds mainly by reaction with hydroxyl radicals, a reaction that presumably will ultimately lead to carbon monoxide and hydrogen chloride. The degradation process is relatively slow (half-time = 29 days), as a consequence of which the compound will be ubiquitous. Dry deposition (half-time = 1 year) and wet deposition (half-time = 390 years), when compared with degradation via hydroxyl radicals (half-time = 29 days), are negligible (5).

Conversion factors

$$\begin{aligned} 1 \text{ ppm} &= 4.12 \text{ mg/m}^3 \text{ (20 }^\circ\text{C, 101.3 kPa)} \\ 1 \text{ mg/m}^3 &= 0.242 \text{ ppm} \end{aligned}$$

Routes of Exposure

Air

The intake from urban air in the USA was estimated to be between 8 and 80 μg per day (13), with an average of about 20 μg per day.

On the basis of model calculations an estimate of DCE exposure among the Dutch population was made. According to this, out of a total population of 14 million, 1000 are exposed to levels of about 1.5 $\mu\text{g/m}^3$, 35 000 to 1 $\mu\text{g/m}^3$, 300 000 to 0.5 $\mu\text{g/m}^3$, and the remainder to below 0.2 $\mu\text{g/m}^3$ (5).

No data were available concerning occupational exposure in DCE- and vinyl chloride-synthesizing industries (1). During use of the compound as a solvent in several industries, concentrations of between 11 and 800 mg/m^3 were measured (data from before 1960) (14,15). More recently, time-weighted averages of 0.1 and 1.0 mg/m^3 were reported for two different occupational categories in an anti-knock blending plant in the USA. The maximum exposure measured was 8.9 mg/m^3 (16).

Drinking-water

Average levels found in drinking-water were generally below 1 $\mu\text{g/litre}$ (17-19).

Food

Reports on DCE residues in food are scarce. Bauer (17) found that levels were generally low in foods in the Federal Republic of Germany and reported an average of 0.8 $\mu\text{g/kg}$ for milk products with added fruits. Significant residues of DCE in food (spice, grains) are possible when the compound has been used as an extractant or fumigant (1,5).

Relative significance of different routes of exposure

The scarcity of data on concentrations of DCE in foodstuffs does not allow a meaningful estimate of the total daily intake via this route. If a conservative upper level of 1 $\mu\text{g/litre}$ is taken for the concentration of DCE in drinking-water, the daily intake from water would be 2 μg per person (assuming a water intake of 2 litres/day).

The average daily intake of DCE from urban air in the USA is estimated at about 20 μg (13). The intake via ambient air in the Netherlands is reckoned to be 30 $\mu\text{g/day}$ for the 1000 subjects estimated to be exposed to 1.5 $\mu\text{g/m}^3$, 20 $\mu\text{g/day}$ for 35 000 exposed to 1 $\mu\text{g/m}^3$, 10 $\mu\text{g/day}$ for the 300 000 exposed to 0.5 $\mu\text{g/m}^3$ and 4 $\mu\text{g/day}$ for the 13 million exposed to concentrations below 0.2 $\mu\text{g/m}^3$ (5).

Kinetics and Metabolism

Absorption

In guinea pigs, mice and rats it was shown that the absorption of DCE is a rapid process: almost immediately after exposure the compound is found in the blood (20-23). During inhalation, steady-state levels in the blood were reached within 2-3 hours. A comparison of blood concentrations in rats indicates that at doses of 113-150 mg/kg body weight, peak levels after oral dosing are markedly higher than those observed after inhalation, a finding that indicates a difference in absorption dynamics between the two routes (21,22,24). A similar rapid rate of absorption would be expected in people exposed to DCE.

Distribution

After oral and inhalatory dosing of rats, the amount of DCE found in adipose tissue exceeded the levels present in liver, brain, spleen, kidneys and lungs (24). In one rat study in which radiolabelled DCE was used, residual radioactivity was highest in liver and kidneys (21).

Vosovaja (25) found accumulation of DCE in placental and fetal tissues of rats after inhalation of 1000 mg/m³ for 7 days. It has also been found in breast-milk and cows' milk (26,27).

Elimination and biotransformation

The excretion of DCE from rodents was rapid. In mice and rats, after oral or inhalatory treatment with radiolabelled compound, 90% or more was excreted within 48 hours (21,28). Excretion occurred mainly via the lungs and urine. About 90% of the body-burden was excreted via the lungs and urine within 24 hours in intraperitoneally injected mice and within 48 hours in orally dosed mice. Little radioactivity was found in the faeces. The elimination rate from blood and tissues was inversely related to exposure levels: the higher the dose, the longer the half-time for clearance from the blood. After oral dosing in rats the half-time ranged from 20 to 90 minutes and after inhalation the values ranged from 13 to 22 minutes (21,24). The rates of elimination from tissues after oral dosing were comparable to that for blood, with the exception of the liver, where the elimination rate was higher. After inhalation of DCE, elimination was most rapid via the lungs and slowest in adipose tissue (24).

At increased exposure levels the concentrations of unmetabolized DCE in the blood increased hyperproportionally, a phenomenon that can be assumed to be due to the saturation of metabolic pathways. At high levels the exhalation of unchanged DCE markedly increased (21,24,28). In the biotransformation of DCE two major pathways are oxidation to chloroethanol and chloroacetic acid, and conjugation with glutathione, directly or after microsomal oxidation. This has been shown to lead to the formation of carboxymethylcysteine and thiodiacetic acid (and its sulfoxide), compounds that have been identified in the urine of rats. Other urinary metabolites found in rodents *in vivo* could result from direct glutathione conjugation (21,28-30). Biotransformation to urinary metabolites ranges from 55% to 90% in rats and mice after oral, parenteral or inhalation exposure or dosing (1).

Health Effects

Effects on experimental animals and *in vitro* test systems

Toxicological effects

LC₅₀ values (6-hour exposure) were reported to be 5100 and 6666 mg/m³ in rats and 1060 mg/m³ in mice (31-35). Oral LD₅₀ values of 680 and 450 mg/kg were found in rats and mice respectively.

Several inhalation studies involving exposure of rats, mice and guinea pigs to DCE at various exposure levels ranging from 400 to 3900 mg/m³, for several weeks to 36 weeks, have been conducted (35-37). At levels above 1420 mg/m³ high mortality rates were observed in all the studies. However, in one study mortality also occurred in all three species at levels of 730 mg/m³. All studies demonstrated histological changes (fatty degeneration, cloudy swelling and necrosis) in the liver at the highest levels. The lowest level at which some of these effects were reported was 730 mg/m³. Similar effects, of varying degrees of severity, were found at levels of 730 mg/m³ and above in the kidneys. Furthermore, histological changes were observed in the myocardium, adrenals and lungs (oedema) of moribund and dead animals.

In each of the above-mentioned studies, a few animals of other species (cats, rabbits, dogs and monkeys) were also exposed to similar levels. Although only a few animals were exposed, the results, when evaluated collectively, are not inconsistent with the observations in rats and guinea pigs, in that no adverse histological changes were observed at an exposure level of about 400 mg/m³. Of all the species studied, mice and rats appear to be more sensitive than other species. Signs of central nervous system (CNS) depression observed in these studies (35-37) included apathy in guinea pigs at 1980 mg/m³ (37) and 3900 mg/m³ (36) and coma in dogs and monkeys at 3900 mg/m³ (36).

Spreafico et al. (24) exposed rats in a long-term inhalation study (3-18 months) to 0, 5, 40, 202 or 1012 mg/m³ for 7 hours per day, 5 days per week. Animals of each sex were exposed, starting at 3 months of age, for 3, 6 or 18 months. In addition, animals that were 14 months old when the study started were exposed for 12 months. The highest exposure level was reduced to 607 mg/m³ after a few weeks because of high mortality. Slight changes in SGOT, SGPT and γ -glutamyltranspeptidase activities were observed in the older animals exposed for 12 months, but not in those exposed for 18 months at levels of 202 and 607 mg/m³. Serum uric acid and blood urea nitrogen increased in the females exposed for 12 months, but not in animals exposed for 18 months. In addition, the animals exposed for 12 months, but not those exposed for 18 months, displayed decreases in serum cholesterol. The authors suggested that DCE in this exposure regimen lacks significant toxicity in spite of the changes in the biochemical parameters observed. The effects of DCE at the same exposure levels on older animals, compared with the absence of effects on younger animals exposed for a longer duration, make the results of this study inconclusive.

Fatty degeneration in the liver was also observed when DCE was administered orally, in oil. This effect was prominent at a dose of 300 mg/kg when administered daily for 5 days, but not at 150 mg/kg administered for 2 weeks (21,38). In a 90-day study, increases in the weight of kidneys, liver and brain were observed at 90 mg/kg, but not at 30 and 10 mg/kg. These weight increases were not accompanied by consistent haematological, clinicochemical or histopathological abnormalities (38). After oral administration of doses up to 35 mg/kg body weight per day for 2 years there were no effects on mortality rates, growth or serum biochemistry (39).

The effects of DCE on reproduction, teratogenicity and related endpoints have been investigated in several published studies. In a one-generation inhalation study, male and female rats were exposed for 60 days (6 hours per day, 5 days per week) to DCE up to a level of 615 mg/m³ and then bred to produce two litters. No effects on reproduction were reported and there was no evidence of fetal or maternal toxicity (40). In contrast, Vosovaja (25,41) reported a variety of adverse effects (e.g. fetal toxicity and estrous cycle prolongation) in a two-generation study of rats exposed to 15 mg/m³ and 57 mg/m³. However, the lack of data concerning the protocol, test results and statistical tests employed makes it difficult to evaluate these findings.

In a two-generation reproduction study of mice given oral doses of 5, 15 and 50 mg/kg,

no adverse effects were reported (42). Maternal toxicity was not observed.

Mutagenic and carcinogenic effects

1,2-Dichloroethane mutagenicity has been studied in several test species and in *in vitro* tests using mammalian cells. It was weakly mutagenic in *Salmonella typhimurium* in the presence and absence of microsomal activation systems (1). In the presence of cytosolic glutathione S-transferase, a stronger positive response was obtained. Glutathione conjugates of DCE consistently showed mutagenic activity in *S. typhimurium* strains TA 100 and TA 1535. Forward mutation tests in fungi were positive. In *Drosophila melanogaster* DCE induced both sex-linked recessive lethal mutations and somatic mutations. Mutagenicity tests in mammalian cells *in vitro* also showed a positive result, particularly in a cell line with high levels of glutathione S-transferase. *In vivo* mutagenicity tests (dominant lethal assay, micronucleus test), however, were mostly negative. A weak effect was reported in a spot test for somatic mutations in mice. DNA damage has been observed in bacteria, in mammalian cells *in vitro*, and in mammals *in vivo* (1,5).

On the basis of the above evidence DCE must be considered a mutagenic agent.

Inhalation carcinogenicity studies were performed in Swiss mice and Sprague-Dawley rats at exposure levels of 20, 40, 202 and 1012 mg/m³ for 7 hours per day, 5 days per week over a period of 78 weeks. Thereafter the animals were maintained until spontaneous death. The 1012 mg/m³ dose level was reduced to 607 mg/m³ because of the high mortality in the first weeks of the test. The only effect was a nonstatistically significant increased incidence of fibromas and fibroadenomas in the mammary gland of female rats at 20, 202 and 607 mg/m³. A dose-response relationship was not apparent (43).

Oral tests, performed in mice and rats, involved the dosing of DCE in corn oil by intragastric intubation. B6C3F1 mice were dosed with time-weighted average doses of 97 and 195 mg/kg body weight (males) and 149 and 299 mg/kg body weight (females) over a period of 78 weeks. After this the animals were observed for a further 12-13 weeks. Survival rates were decreased in a dose-related manner in females. There were dose-related increases in the incidence of alveolar or bronchiolar adenomas (both sexes), hepatocellular carcinomas (males), adenocarcinomas of the mammary gland (females), endometrial stromal polyps or stromal sarcomas (females) and squamous-cell carcinomas of the forestomach (females; in males hyperplastic changes at this site). Seven mice developed metastatic tumours (44,45). A similar test was conducted in Osborne-Mendel rats. The average dose levels were 47 and 95 mg/kg body weight for both males and females. The test period was 78 weeks and the post-dosing observation period lasted 15-32 weeks. A dose-related increase in mortality occurred. The incidence of squamous-cell carcinoma in the forestomach was increased in males only (incidences 0/60, 3/50 and 9/50 in control, 47 mg/kg and 95 mg/kg groups respectively); the incidence of subcutaneous fibroma was also elevated in males only (control: 0/60; 47 mg/kg: 5/50; 95 mg/kg: 6/50). The incidence of adenocarcinoma in the mammary gland was increased in females (control: 1/59; 47 mg/kg: 1/50; 95 mg/kg: 18/50). The haemangiosarcoma incidence was elevated both in males (control: 1/60; 47 mg/kg: 9/50; 95 mg/kg: 7/59) and in females (control: 0/59; 47 mg/kg: 4/50; 95 mg/kg: 4/50). In addition, treated females showed hyperplastic lesions in the fore-stomach. Nine rats developed metastatic tumours (44,45).

A dermal carcinogenicity test was performed in Ha:ICR mice. The animals were treated 3 times per week with 42 or 146 mg DCE (dissolved in acetone) for 440-594 days. At the highest dose level, DCE induced lung papillomas. The study also included a dermal test for tumour-initiating properties; phorbol myristate acetate was used as a tumour promoter. No initiating effect was observed (46).

Effects on humans

Toxicological effects

Inhalation of DCE adversely affects the CNS. Symptoms of intoxication include headache, dizziness, weakness, spasms, muscular hypotonia, vomiting and unconsciousness. Death often follows. Autopsy reports frequently mention damage to lungs, liver and kidneys. Heart rhythm disturbances have also been observed. A number of case studies related to accidental oral ingestion of DCE and resulting in fatalities have been reported. After acute oral ingestion, symptoms include CNS depression, gastroenteritis, functional disorders of liver and kidneys and cardiovascular insufficiency (1,47). Accidental ingestion of 10-250g of DCE resulted in death in all instances (1).

Only two limited studies on long-term occupational exposure, both dating back to the 1950s, are available. In one study workers exposed to DCE concentrations of 40-800 mg/m³ for 2-8 months were examined. In particular, workers exposed to the higher concentrations complained of a burning sensation of the eyes, lacrimation, dizziness, nausea, vomiting and constipation; abnormalities in liver, CNS, gastrointestinal tract and haematological parameters were also found (14). The second study involved workers who were exposed to a time-weighted average DCE concentration of 114 mg/m³ during 20% of their worktime. Morbidity among these workers in comparison with nonexposed workers was elevated for all disease categories. Upon closer examination of a group of 83 of the exposed workers, neurotic conditions, autonomic dystonia, hyperthyroidism, goitre, visual-motor reaction impairment, neuromyalgia and/or tenovaginitis were found (15). These latter conditions were stated by the authors to be unlikely to be related to DCE exposure.

No epidemiological studies are available regarding carcinogenicity.

Evaluation of Human Health Risks

Exposure

Rural or background atmospheric concentrations in western Europe and North America are approximately 0.2 µg/m³, and the limited data available on indoor concentrations show that they are about the same. Average levels in cities vary from 0.4 µg/m³ to 1.0 µg/m³, increasing to 6.1 µg/m³ near petrol stations, parking garages and production facilities.

Health risk evaluation

Human studies point to effects on the CNS and the liver, but the limited data do not allow a definitive conclusion regarding a lowest-observed-adverse-effect level or no-observed-effect level. In animals, long-term inhalation exposure (>6 months) to DCE levels of approximately 700 mg/m³ and above has been shown to result in histological changes in the liver (35-37). The same animal studies reported no adverse histological changes in the liver and kidneys of guinea pigs and rats at levels of about 400 mg/m³. Findings concerning effects on reproduction are contradictory.

Animal data suggest a no-observed-effect level in laboratory animals of 400 mg/m³ and a lowest-observed-adverse-effect level of 700 mg/m³.

With regard to mutagenicity as an endpoint and to the causal connections between DNA damage and the initiation of carcinogenicity, DCE has been shown to be weakly mutagenic in *Salmonella typhimurium*, both in the absence and in the presence of microsomal activation systems. It has also been demonstrated to be mutagenic in other test species and in *in vitro* tests using mammalian cells.

In a lifetime study in rats and mice in which DCE was administered by gavage, it caused tumours at multiple sites in both species. In the only inhalation study performed (24), DCE

exposure did not result in an increased tumour incidence. The negative results obtained in this study, however, do not detract from the positive findings of the oral study (44,45) when differences in total dose, exposure time and pharmacokinetics are considered.

1,2-Dichloroethane was evaluated in 1979 by IARC as a chemical for which there is sufficient evidence of carcinogenicity in experimental animals and inadequate evidence in humans (6). To date there are two publications giving quantitative carcinogenic risk estimates based on animal data. One, developed by the National Institute of Public Health in the Netherlands on the basis of oral exposure of rats by gavage (45), indicates a lifetime risk of one in a million from exposure to $0.48 \mu\text{g}/\text{m}^3$ (5), which corresponds to a unit risk of about 2×10^{-6} . The US Environmental Protection Agency (48) has estimated an incremental unit risk of 2.6×10^{-5} on the basis of data from gavage studies and of 1×10^{-6} on the basis of a negative inhalation study.

Guidelines

Evidence of carcinogenicity in animals is sufficient on the basis of oral ingestion data. However, animal inhalation data do not at present provide positive evidence. Because of deficiencies in extrapolation from oral data to inhalation, the two risk estimates available are not used in the guidelines.

For noncarcinogenic endpoints, data from animal studies imply a no-observed-adverse-effect level of about $400 \text{ mg}/\text{m}^3$ and suggest a lowest-observed-adverse-effect level of about $700 \text{ mg}/\text{m}^3$. A protection (safety) factor of 1000 is considered appropriate in extrapolation of animal data to the general population. In selecting such a large protection factor, variations in exposure time, the limitation of the database and the fact that a no-effect level in man cannot be established are of decisive importance. The resulting value of $0.7 \text{ mg}/\text{m}^3$ for continuous exposure (averaging time 24 hours) is recommended as a guideline value. Since this value is above current environmental levels and present exposures are not of concern to health, this guideline relates only to accidental release episodes or specific indoor pollution problems.

References

1. *1,2-Dichloroethane*. Geneva, World Health Organization (in press) (Environmental Health Criteria, No. 62).
2. **Gold, L.S.** Human exposures to ethylene dichloride. *Banbury reports*, 5: 209-225 (1980).
3. **Atri, F.R.** *Studie zur Bewertung der Toxizität wassergefährdender Stoffe. Band III. 1,2-Dichlorethan* [Studies on evaluating the toxicity of water pollutants. Vol. III. 1,2-Dichloroethane]. Berlin, Umweltbundesamtes, 1984 (Forschungsbericht 106 07 047).
4. **Drury, J.S. & Hammons, A.S.** *Investigations of selected environmental pollutants: 1,2-dichloroethane*. Washington, DC, US Environmental Protection Agency, Office of Toxic Substances, 1979 (Report No. EPA-560/2-78-006, PB 295865).
5. **Besemer, A.C. et al.** *Criteriadocument over 1,2-dichloorethaan* [1,2-Dichloroethane criteria document]. The Hague, Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer, 1984 (Publikatiereeks Lucht, No. 30).
6. 1,2-Dichloroethane. *In: Some halogenated hydrocarbons*. Lyon, International Agency for Research on Cancer, 1979, pp. 429-448 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 20).
7. **Singh, H. B. et al.** Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. *Environmental science and technology*, 16: 872-880 (1982).
8. **Elfers, L.A.** *Monitoring of ambient levels of ethylene dichloride (EDC) in the vicinity of EDC production and user facilities*. Research Triangle Park, NC, US Environmental Protection Agency, 1979 (Report No. EPA-600/4-79-029, PB 298303).

9. **Kellam, R.G. & Dusetzina, M.G.** Human exposure to ethylene dichloride: potential for regulation via EPA's proposed airborne carcinogen policy. *Banbury reports*, 5: 265-276 (1980).
10. **Tsani-Bazaca, E. et al.** Ambient concentrations and correlations of hydrocarbons and halocarbons in the vicinity of an airport. *Chemosphere*, 11: 11-23 (1982).
11. **Jonsson, A. & Berg, S.** Determination of 1,2-dibromoethane, 1,2-dichloroethane and benzene in ambient air using porous polymer traps and gas chromatographic-mass spectrometric analysis with selected ion monitoring. *Journal of chromatography*, 190: 97-106 (1980).
12. **Hartwell, T.D. et al.** Comparative statistical analysis for volatile halo-carbons in indoor and outdoor air. In: Berglund, B. et al., ed. *Indoor air: chemical characterization and personal exposure*. Stockholm, Swedish Council for Building Research, 1984, Vol. 4, pp. 57-61.
13. **Singh, H.B. et al.** Measurements of some potentially hazardous organic chemicals in urban environments. *Atmospheric environment*, 15: 601-612 (1981).
14. **Cetnarowicz, J.** Badania eksperymentalne i Kliniczne nad Azialaniem dwuchloroetanu [Experimental and clinical investigations on the action of dichloroethane]. *Folia medica cracoviensia*, 1: 169-192 (1959).
15. **Kozik, I.V.** [Some problems of occupational hygiene in the use of dichloroethane in the aircraft industry]. *Gigiena truda i professional'nye zabojevanija*, 1: 31-38 (1957) (in Russian).
16. **Jacobs, E.S.** Use and air quality impact of ethylene dichloride and ethylene dibromide scavengers in leaded gasoline. *Banbury reports*, 5: 239-255 (1980).
17. **Bauer, U.** Belastung des Menschen durch Schadstoffe in der Umwelt. Untersuchungen über leicht flüchtige organische Halogen-Verbindungen in Wasser, Luft, Lebensmitteln und im menschlichen Gewebe. I & IV Mitteilung [Human exposure to environmental chemicals - investigations on volatile organic halogenated compounds in studies on water, air, food and human tissues. I & IV]. *Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene. I Abt. Orig. B*, 174: 15-56, 556-583 (1981).
18. **Fujii, T.** Direct aqueous injection gas chromatography-mass spectrometry for analysis of organohalides in water at concentrations below the parts per billion level. *Journal of chromatography*, 139: 297-302 (1977).
19. **Symmons, J.M. et al.** National organics reconnaissance survey for halogenated organics. *Journal of the American Water Works Association*, 67: 634-648 (1975).
20. **Jakobson, I. et al.** Uptake via blood and elimination of 10 organic solvents following epicutaneous exposures of anaesthetized guinea pigs. *Toxicology and applied pharmacology*, 63: 181-187 (1982).
21. **Reitz, R.H. et al.** Pharmacokinetics and macromolecular interactions of ethylene dichloride in rats after inhalation or gavage. *Toxicology and applied pharmacology*, 62: 190-204 (1982).
22. **Sopikov, N.F. & Goršunova, A.I.** [Investigation of the intake, distribution and excretion of ethylene dichloride in rats]. *Gigiena truda i professional'nye zabojevanija*, 4: 36-40 (1979) (in Russian).
23. **Tsuruta, H.** Percutaneous absorption of organic solvents I. Comparative study of the *in vivo* percutaneous absorption of chlorinated solvents in mice. *Industrial health*, 13: 217-236 (1975).
24. **Spreafico, F. et al.** Pharmacokinetics of ethylene dichloride in rats treated by different routes and its long-term inhalatory toxicity. *Banbury reports*, 5: 107-129 (1980).
25. **Vozovaja, M.A.** [Effect of dichloroethane on the reproductive cycle and embryogenesis in experimental animals]. *Akušerstvo i ginekologija*, 2: 57-59 (1977) (in Russian).

26. **Urusova, T.P.** [The possibility of dichloroethane contaminating the milk of breastfeeding women following industrial exposure]. *Gigiena i sanitarija*, 3: 36-37 (1953) (in Russian).
27. **Sykes, J.F. & Klein, A.K.** Chloro-organic residues in milk of cows orally administered ethylene dichloride. *Journal of the Association of Official Agricultural Chemists*, 40: 203-209 (1957).
28. **Yllner, S.** Metabolism of 1,2-dichloroethane-146 in the mouse. *Acta pharmacologica et toxicologica*, 30: 257-265 (1971).
29. **Johnson, M.K.** Metabolism of chloroethanol in the rat. *Biochemical pharmacology*, 16: 185-199 (1967).
30. **Kokarovceva, M.G. & Kiseleva, N.** [Chloroethanol, a toxic metabolite of 1,2-dichloroethane]. *Farmakologija i toksikologija*, 41: 118-120 (1978) (in Russian).
31. **Bonnet, P.** Détermination de la concentration léthale 50 des principaux hydrocarbures aliphatiques chlorés chez le rat [Determination of the lethal dose 50 of the principal chlorinated aliphatic hydrocarbons in the rat]. *Archives des maladies professionnelles, de médecine du travail et de sécurité sociale*, 41: 3 17-321 (1980).
32. **Gradiski, D. et al.** Toxicité aiguë comparée par inhalation des principaux solvants aliphatiques chlorés [Comparative acute toxicity by inhalation of the principal chlorinated aliphatic solvents]. *Archives des maladies professionnelles, de médecine du travail et de sécurité sociale*, 39: 249-257 (1978).
33. **McCullister, D.D. et al.** Comparative inhalation toxicity of fumigant mixtures. Individual and joint effects of ethylene dichloride, carbon tetrachloride and ethylene dibromide. *Archives of industrial health*, 13: 1-7 (1956).
34. **Munson, A.E. et al.** *In vivo* assessment of immunotoxicity. *Environmental health perspectives*, 43: 41-52 (1982).
35. **Spencer, H.C. et al.** Vapour toxicity of ethylene dichloride determined by experiments on laboratory animals. *Archives of industrial hygiene and occupational medicine*, 4: 482-493 (1951).
36. **Heppel, L.A. et al.** The toxicology of 1,2-dichloroethane (ethylene dichloride). V. The effect of daily inhalations. *Journal of industrial hygiene and toxicology*, 28: 113-120 (1946).
37. **Hofmann, H.T. et al.** Zur Inhalationstoxizität von 1,1- und 1,2-Dichloräthan [On the inhalation toxicity of 1,1-and 1,2-dichloroethane]. *Archiv für Toxikologie*, 27: 248-265 (1971).
38. **van Esch, G.J. et al.** *Ninety-day toxicity study with 1,2-dichloroethane (DCE) in rats.* Bilthoven, National Institute of Public Health and Environmental Hygiene, 1977 (Report 195/77 Alg.Tox).
39. **Alumot, E. et al.** Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. *Food and cosmetics toxicology*, 14: 105-110 (1976).
40. **Rao, K.S. et al.** Teratogenicity and reproduction studies in animals inhaling ethylene dichloride. *Banbury reports*, 5: 149-161(1980).
41. **Vozovaja, M.A.** [Development of progeny of two generations obtained from females subjected to the action of dichloroethane]. *Gigiena i sanitarija*, 7: 25-28 (1974) (in Russian).
42. **Lane, R.W. et al.** Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. *Toxicology and applied pharmacology*, 63: 409-421 (1982).
43. **Maltoni, C. et al.** Long-term carcinogenic bioassays on ethylene dichloride administered by inhalation to rats and mice. *Banbury reports*, 5: 3-29 (1980).
44. **US National Cancer Institute.** *Bioassay of 1,2-dichloroethane for possible carcinogenicity.* Bethesda, MD, US Department of Health, Education and Welfare, 1978

- (DHEW Publication No. (NIH) 78-1305).
45. **Ward, J.M.** The carcinogenicity of ethylene dichloride in Osborne-Mendel rats and B6C3F1 mice. *Banbury reports*, 5: 35-53 (1980).
 46. **Van Dunren, B.L. et al.** Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *Journal of the National Cancer Institute*, 63: 1433-1439 (1979).
 47. **National Institute for Occupational Safety and Health.** *Criteria for a recommended standard occupational exposure to ethylene dichloride (1,2-dichloroethane)*. Washington, DC, US Government Printing Office, 1976 (DHEW Publication No. (NIOSH) 76-139).
 48. *Health assessment document for 1, 2-dichloroethane (ethylene dichloride)*. Washington, DC, US Environmental Protection Agency, 1985 (Report No. EPA-600/8-84-0067).