Chapter 5.13 Tetrachloroethylene

General description

Physical and chemical properties

Tetrachloroethylene (also known as perchloroethylene) is widely used as an industrial solvent. It is a readily volatile, colourless liquid with an ethereal smell. Other physical and chemical properties include:

Density	1.6227 g/ml at 20 °C
Boiling point	121 °C
Water solubility	150 mg/litre at 25 °C
Vapour pressure	18.47 mmHg at 25 °C
Henry law constant	1.8 kPa.m^3/mol at 25 °C *(1)*.

Sources

There are no known natural sources of tetrachloroethylene. The estimated production volume in the United States of America in 1990 was 137 kilotonnes, compared to 282 kilotonnes in 1980 *(1)*. The corresponding figures for western Europe and Japan for 1990 were 280 and 83 kilotonnes, respectively *(2)*. For eastern Europe an estimate of 50–100 kilotonnes has been reported *(3)*. The estimated annual consumption in western Europe for 1990 was 235 kilotonnes; for the United States and Japan it was 178 and 102 kilotonnes, respectively *(4)*. In Canada, where tetrachloroethylene is no longer produced, the demand in 1990 was estimated at 14 kilotonnes *(5)*. No estimates of consumption levels are available for other parts of the world.

The major industrial uses of tetrachloroethylene are as a solvent in dry-cleaning, as a degreasing agent for manufactured metal parts and as a precursor in the production of chlorofluorocarbons. Other applications include the finishing and processing of textiles, the production of paint removers and printing ink, and the formulation of adhesives and specialized cleaning fluids. Consumer products that contain tetrachloroethylene include motor vehicle cleaners, stain removers, adhesives and wood cleaners *(2,5)*.

About 75–85% of the amount used annually is emitted to air *(1,2)*. Practically all tetrachloroethylene enters the atmosphere unchanged. A small proportion enters water and waste water. From surface water tetrachloroethylene volatilizes owing to its relatively low water solubility and high vapour pressure.

Occurrence in air

Concentrations in ambient air may fluctuate widely over relatively short periods of time depending on the strength of the emission source, variations in wind direction and velocity, and scavenging and photodecomposition *(5)*.

Reported background levels for remote or rural regions vary from <7 to 620 ng/m^3 *(4)*. For rural areas in Canada, a mean concentration of 200 ng/m^3 has been reported *(5)*.

Concentrations in ambient air in urban areas are higher. Several studies in towns in the United States reported concentrations ranging from 0.23 to 9.0 μg/m^3 *(1)*. A survey in1990 in cities in Canada showed mean concentrations of 0.2 to 5.0 μg/m^3 *(5)*; mean concentrations in the Netherlands ranged from 0.7 to 1.4 μg/m^3 *(4)*. Concentrations in ambient air are elevated in the vicinity of dry-cleaning facilities and at waste disposal sites.

The median value for indoor air from 2195 entries in the United States Environmental Protection Agency (EPA) database on volatile organic contaminants (VOC-AMBI) was 4.9 μg/m^3 (0.737 ppb), the average value, 20.7 μg/m^3 (3.056 ppb) *(6)*. In Canada, a mean indoor air concentration of about 5.1 μg/m^3 has been reported *(5)*.

In a series of measurements in the Netherlands in the indoor air of residences located directly above dry-cleaning facilities, a median concentration of 2200 μg/m^3 was found (maximum 29 900 μg/m^3). In shops directly adjacent to these dry-cleaning facilities the median concentration was 177 μg/m^3 compared to 127 μg/m^3 in ambient air. These measurements were made after the introduction of closed-system machines in these dry-cleaning facilities *(7)*. A similar series of measurements carried out in the United States in apartments located above dry cleaners using open transfer systems showed average concentrations of 7500–13 000 μg/m^3. In the close vicinity of the apartments, mean concentrations of 580 and 1000 μg/m^3 were found. In apartments above dry cleaners using closed equipment, average concentrations of 370 and 130 μg/m^3 were measured. In another study, concentrations in air close to dry-cleaning facilities (open transfer) were reported to be as high as 50 000–197 000 μg/m^3 *(2)*. Indoor air levels in the homes of dry-cleaning workers have been found to be increased (on average 265 μg/m^3 versus 2 μg/m^3 in control houses) owing to exhalation of tetrachloroethylene by the workers when at home after working hours *(8)*. A further source of indoor exposure related to dry cleaning is off-gassing of tetrachloroethylene from dry-cleaned clothes. Keeping freshly dry-cleaned clothes in private cars has led to concentrations of up to 2100 mg/m^3 *(2)*. Another potential source for tetrachloroethylene in indoor air is the volatilization from contaminated water that is used in the home *(9)*.

In the atmosphere, tetrachloroethylene may react with photochemically produced hydroxyl radicals yielding phosgene, chloroacetyl chlorides and other degradation products. The half-life in the atmosphere varies with latitude, season and concentration of hydroxyl radicals. Reported half-lives for the reaction of tetrachloroethylene with hydroxyl radicals vary from 27 to 251 days *(1,5)*.

Conversion factors

1 ppm = 6.78 mg/m^3
1 mg/m^3 = 0.147 ppm

Analytical methods in air

The primary method for determination of tetrachloroethylene in air is gas chromatography with either mass spectrometry or electron capture detection. Air samples are usually pumped through a sample collection column from which tetrachloroethylene is then thermally desorbed and concentrated on a cryogenic trap located on the gas chromatograph. Vapours are heat-released from the trapping column directly into the gas chromatograph. The limit of detection is 2.0–12.9 pg/m^3 (0.3–1.9 ppt) *(1)*.

Routes of exposure

Air

Presence of tetrachloroethylene in ambient air will result in exposure of the general population, especially in urban areas. Additional exposure may occur in indoor air where concentrations may be higher than outdoors owing to evaporation from dry-cleaned clothes or the use of water (for showering, dish washing, cleaning) contaminated with tetrachloroethylene. Groups with higher than average exposure levels, are workers using tetrachloroethylene and people living in the vicinity of dry-cleaning facilities and industrial plants emitting tetrachloroethylene to the air.

It has been estimated that 0.1% of the population in the Netherlands is exposed to an average ambient air concentration of 40 μg/m^3, 0.5% to 20 μg/m^3, 3.3% to 6 μg/m^3, 12.5% to 2 μg/m^3 and the remainder to 1 μg/m^3. For people living in the close vicinity of dry-cleaning facilities (estimated to represent 0.08% of the population), the average exposure concentration for every working day was estimated at 1000 μg/m^3 *(4)*.

In Canada, average total daily intake from air has been estimated at 1.2–2.2 μg/kg body weight (bw) *(5)*. An analogous estimate for the United States, based on ambient air concentrations of 2.0–10.1 μg/m^3, is 0.6–2.9 μg/kg bw for a 70-kg adult *(1)*.

In occupational settings, exposure levels are higher. In dry-cleaning shops mean time-weighted average concentrations of about 150 mg/m^3 (range 10–800 mg/m^3) have been reported *(10,11)*. A recent study in the homes of dry-cleaning facility workers in Italy showed exposure concentrations (8-hour averages) of 2.6–221.5 mg/m^3 *(12)*.

In a study carried out in Germany in 1990–1991 with 113 persons selected at random over the country, the geometric mean of personal exposure to tetrachloroethylene was found to be 2.0 μg/m^3 . The 95th percentile was 22 μg/m^3 *(13)*.

Drinking-water

In the United States, tetrachloroethylene is not detectable in drinking-water in most cases. The EPA Groundwater Supply Survey of 945 drinking-water systems nationwide reported tetrachloroethylene in 75 out of 945 water systems in 1984; the median level of the positive samples was about 0.75 μg/litre, with a maximum level of 69 μg/litre *(1)*. In several studies in Canada, tetrachloroethylene was detectable in 6–60% of the tested samples. Reported mean values ranged from 0.1 to 0.9 μg/litre *(5)*. In several other countries (Germany, United Kingdom) similar results have been observed *(2,3)*. In villages in Finland, concentrations of up to 180 μg/litre were found *(14)*.

Food

Data on concentrations of tetrachloroethylene in food are scarce. In some studies from Switzerland and Germany reported in the early 1980s, relatively high total intakes of 87–170 μg/day were found *(3)*. The results of market basket surveys in the United States reported in 1987 and 1988 indicated lower levels. From the results of these surveys, total daily intake via food has been estimated at 0.12–65 μg/kg bw *(5)*. Several groups of researchers have reported elevated concentrations of tetrachloroethylene in fatty food products in residences and markets owing to contamination from dry-cleaning establishments nearby. In a supermarket near a dry-cleaning shop in Germany, concentrations were 110 μg/kg and

36 µg/kg in cheese *(2)*. In one instance in the United States, a very high tetrachloroethylene concentration was found in margarine (up to 50 mg/kg) in a shop next door to a dry cleaner *(1)*.

Relative significance of different routes of exposure
On the basis of the above data, average total intake via ingestion of drinking-water can be estimated at ≤2 µg/day, that from food at ≤45 µg/day for a 70-kg adult. The average concentration in ambient air is generally less than 5 µg/m^3 in urban areas and less than 1 µg/m^3 in rural areas. Indoor concentrations are generally less than 5 µg/m^3. In general, inhalation is the major route of exposure. Close to dry-cleaning shops, inhalation exposure may be significantly higher.

Toxicokinetics

Absorption
Tetrachloroethylene is readily absorbed in the gastrointestinal tract and the lungs. Pulmonary uptake is proportional to ventilation rate, duration of exposure and, at lower atmospheric concentrations, to the concentration in the inspired air (1). In humans and animals, initial uptake following inhalation is rapid, with rates levelling off after a few hours of exposure. The available data suggest that a high proportion is absorbed in humans, but actual percentages have not been reported. In rats, the proportion absorbed was approximately 55–70% after 1 minute, gradually declining to 40–50% after 2 hours *(15)*.

Dermal absorption of significant amounts of tetrachloroethylene is probably possible in some situations. Dermal absorption of tetrachloroethylene solutions resulted in measurable levels of the compound in breath, reaching a maximum 10 minutes after exposure *(3)*. Experiments in hairless guinea pigs have shown substantial dermal absorption from dilute aqueous solutions *(16)*.

Distribution
Limited data in humans and animals show that tetrachloroethylene is preferentially stored in fatty tissues. In rats, distribution to brain, liver and kidneys has also been demonstrated *(1,17)*. In a study in mice, transplacental transport of unchanged tetrachloroethylene has been observed *(1)*. In rats and goats, it has been shown that excretion of unchanged tetrachloroethylene in milk occurs *(18,19)*. Following inhalation exposure of lactating rats to a concentration of 4070 mg/m^3 (600 ppm) for 2 hours, total body burden for the pups was up to about 14 mg/kg body weight *(18)*.

Biotransformation
In experiments in humans and rats, it was observed that most of the absorbed amount of tetrachloroethylene is exhaled unchanged. Only a small proportion is converted into trichloroacetic acid, the principal metabolite in humans and animals. This compound is formed through oxidation (by cytochrome P-450 mixed-function oxygenases) in the liver and is subsequently excreted in urine. Metabolism in rats resembles that in humans, but in mice a much higher level of trichloroacetic acid formation occurs.

Several other, minor biotransformation pathways are known. Trichlorethanol has been identified as a minor metabolite, excreted in urine in humans. Another urinary metabolite, detected in rats only, is oxalic acid. The conjugation of tetrachloroethylene in the liver giving

trichlorovinyl glutathione has been demonstrated in rodents. In the kidneys, the latter is converted to *S*-(1,2,2-trichlorovinyl)-*L*-cysteine which may be either metabolized via the mercapturic acid pathway, producing *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-*L*-cysteine which is excreted in the urine, or activated by the renal enzyme β-lyase to produce the reactive intermediate trichlorovinylthiol, which upon rearrangement covalently leads to proteins and nucleic acids *(1,3,5,20)*.

Interspecies differences in biotransformation

Mice metabolize tetrachloroethylene to trichloroacetic acid to a greater extent than rats. In rats, saturation of the oxidative metabolism at exposure concentrations exceeding 678 mg/m^3 (100 ppm) prevents the occurrence of the high trichloroacetic acid concentrations that are observed in mice at these dose levels. The available evidence indicates that in humans too saturation of the oxidative metabolism of tetrachloroethylene occurs at $\geq$678 mg/m^3 ($\geq$100 ppm) *(20)*. In a comparative study, the urine levels of *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-*L*-cysteine, one of the final metabolites in the glutathione biotransformation pathway, were shown to be higher in rats than in mice after inhalation exposure to tetrachloroethylene. *In vitro* tests in hepatocytes and kidney fractions of rats, mice and humans suggest that the potential for this biotransformation in the kidneys is also lower in humans than in rats *(1,5,21)*.

Elimination

In humans and animals, the major part of the absorbed amount of tetrachloroethylene is exhaled unchanged. In humans, 80–100% of the uptake was exhaled as parent compound in the 7 days following a single 4-hour inhalation exposure to 72 or 144 ppm tetrachloroethylene. In rats, the proportion is somewhat lower (68%). Elimination of tetrachloroethylene from adipose tissues is relatively slow (calculated half-life 55 hours) owing to the high adipose/blood partition coefficient and the low rate of blood perfusion to this tissue *(1)*. Excretion of metabolites in urine represents only a small proportion of the inhaled dose. Following single inhalation exposure in humans, only 2% of the uptake was found as the major urinary metabolite, tetrachloroacetic acid. This compound was excreted from the blood with a half-life of 75–80 hours. In another study, its half-life in urine was estimated at 6 days *(3)*. In rat studies, high concentrations in milk have been observed, peak concentrations being one order of magnitude higher than in maternal blood *(22)*. Limited data in humans also show that tetrachloroethylene is excreted in milk *(23)*.

Biomarkers of exposure

Biological monitoring of exposure to tetrachloroethylene can be carried out by measuring levels of the parent compound in blood, urine or exhaled air or of the metabolites in blood or urine. These methods have been applied for assessing both occupational and non-occupational exposure. Measurement of the parent compound in exhaled air is considered the method of choice. Measuring of metabolites (trichloroacetic acid, trichlorethanol) in blood or urine may not necessarily represent exposure to tetrachloroethylene because some related chlorinated hydrocarbons (trichloroethylene, 1,1,1-trichloroethane) are converted to the same metabolites *(1)*.

Physiologically based pharmacokinetic modelling

Several groups of researchers have developed physiologically based pharmacokinetic (PBPK) models for tetrachloroethylene; Table 1 provides an overview of these efforts *(15,17,22–29)*.

Table 1. Physiologically based pharmacokinetic (PBPK) models for tetrachloroethylene metabolism

Species	Input parameters and calibration	Model application	Reference
Mice, humans	Data from single-dose inhalation	Human cancer risks estimated on the basis of the predicted amounts of PCE[a] metabolites in mice and humans, and using liver tumour incidences in mice	*(24)*
Humans	Partition coefficients determined *in vitro*; metabolic parameters from occupational studies	Simulation of the time-course of PCE concentration in blood for continuous inhalation exposure	*(25)*
Mice, rats	Partition coefficients determined *in vitro*; metabolic parameters from oral and/or inhalation exposure studies in rats and mice	Simulation of the amount of urinary metabolites in mice or proportion of exhaled PCE following a single inhalation exposure in rats	*(26)*
Humans	Animal data and metabolic parameters derived from data on urinary levels of trichloro compounds in urine in workers exposed to PCE	Simulation of the time-course of exhaled unchanged PCE	*(26)*
Rats, humans	Partition coefficients determined *in vitro*; metabolic parameters calculated and optimized from inhalation studies in rats and humans	Simulation of the proportion of exhaled PCE and body burden in rats and humans	*(27)*
Rats (male)	Partition coefficients and metabolic parameters from data generated by a single intra-arterial dose study in male rats	Simulation of the time-course of concentrations in tissues, blood and exhaled air	*(15,17)*
Rats (male), dogs (male)	Partition coefficents from AUCs[b] as determined *in vivo* in single-dose oral tests in rats (m) and dogs (m); metabolic parameters estimeated from blood and liver concentrations	Simulation of the time-course of the fractions exhaled and metabolized in single-dose studies in rats and dogs	*(28,29)*
Rats (lactating)	Partition coefficients determined *in vitro*; metabolic parameters from *in vivo* gas-uptake tests in lactating rats	Simulation of the time-course of PCE concentrations in maternal blood and milk and in pup tissues	*(22)*
Humans (lactating)	Existing model adjusted for prediction of excretion of PCE in mothers' milk	Concentrations in milk and infant doses predicted for inhalation exposure scenarios in and close to dry-cleaning shops	*(23)*

[a] PCE = tetrachloroethylene (perchloroethylene).
[b] AUC = area under curve.

Some of the studies focused on the evaluation of these models. In one, the key parameters and predictions for PBPK models for mice, rats and humans developed by different groups of researchers were compared. The amounts of metabolized tetrachloroethylene predicted showed considerable differences (about 12- to 14-fold for humans). Most of the differences in risk-related model predictions were due to the choice of the data sets used for calibrating metabolic parameters (V_{max}, K_m) *(30)*. A statistical approach to some of the PBPK models for tetrachloroethylene in mice, rats and humans showed that the kinetic parameters defining the metabolic rate were the most important parameters for model sensitivity *(31)*.

Health effects

Effects on experimental animals and *in vitro* test systems

Toxicological effects
Tetrachloroethylene has a low acute inhalation toxicity (LC_{50} in rodents, ≥16.6 mg/litre). Acute oral toxicity is also low (LD_{50} in rodents, ≥3000 mg/kg bw) *(5)*.

The liver, kidneys, blood and central nervous system (CNS) are the target organs for systemic effects. Hepatic effects occur at lower dose levels in mice than in rats. In a series of experiments in mice, continuous (24 hours/day) inhalation exposure for 30 days at concentrations of 61, 251, 508 or 1017 mg/m^3 produced a dose-related increase in liver weight at all dose levels. Morphological changes in the liver were observed at 251 mg/m^3 and, as is stated but not fully reported, at all other dose levels as well. Plasma butyrylcholinesterase activity showed a slight increase at ≥251 mg/m^3. The reversibility of the effects was examined at 1071 mg/m^3 only, showing that at 120 days after cessation of treatment, only a slight increase in liver weight remained *(32)*. Within the United States National Toxicology Program (NTP) subchronic inhalation studies were carried out in rats and mice. In mice, liver effects were observed at 1350 mg/m^3 (≥200 ppm) or higher. Karyomegaly of the renal tubule epithelial cells was observed at ≥1350 mg/m^3 (≥200 ppm). At 680 mg/m^3 (100 ppm) no effects were seen but at this level no histopathological examination of the liver was carried out. In rats, mild congestion of the liver was seen at ≥1350 mg/m^3 (≥200 ppm) (lower concentrations not tested), with congestion of the lungs, decreased survival and growth retardation at higher dose levels *(33)*. In chronic studies renal tubular cell karyomegaly was observed in female rats and mice at both of the dose levels (200 and 400 ppm in rats and 100 and 200 ppm in mice). In addition, in rats renal tubular hyperplasia (males), thrombosis and squamous metaplasia in the nasal cavity (males and females) and hyperlasia in the adrenal medullae (males) or cortices (females) were found. In mice only, liver cell degeneration and necrosis were seen at both concentrations *(33)*.

CNS effects have been observed at high dose levels. In the short-term NTP experiment in rats and mice neurological symptoms were observed only at the highest concentration, 11 860 mg/m^3 (1750 ppm) *(33)*. Biochemical changes in brain tissues have been observed in rats and gerbils at concentrations of ≥407 mg/m^3 (≥60 ppm). However, the toxicological significance of these changes is unclear *(1)*. In a recent short-term study in rats, decreased weight of brain regions and reductions in neuronal marker proteins were seen at 4080 mg/m^3 (600 ppm) but not at 2040 mg/m^3 (300 ppm) *(34)*. Haematotoxicity was observed in an inhalation study in mice at test concentrations of 915 and 1830 mg/m^3 (no other concentrations tested) in which the animals were exposed for 6 hours/day, 5 days/week for 7.5 or 11.5 weeks *(35)*.

Limited teratogenity studies in rats, mice and rabbits suggest that tetrachloroethylene produces fetotoxicity and embryotoxicity at high dose levels (≥2034 mg/m^3). In a behavioural teratogenicity study in rats, neuromuscular ability in pups was decreased at 6100 mg/m^3 (900 ppm) but not at 2034 mg/m^3 (300 ppm) *(1)*.

Carcinogenic effects
Data on the carcinogenicity of tetrachloroethylene have been evaluated in various health assessment documents *(1,4,5,20)*.

NTP oral and inhalation studies have been performed in mice and rats. In a gavage study in B6C3F1 mice (time-weighted average (TWA) daily dose levels of 536 and 1072 mg/kg bw in males and 386 and 772 mg/kg in females), increased incidences of hepatocellular carcinomas were found in males and females (incidences 4/37, 32/49 and 27/48 in males and 2/40, 19/48 and 19/48 in females). In Osborne Mendel rats no increase in tumour incidence was seen. This study has various limitations: numerous dose adjustments during the study, early mortality related to compound-induced toxic nephropathy and pneumonia due to intercurrent infectious disease in both rats and mice *(1,36)*. In the inhalation study in B6C3F1 mice (test concentrations 100 and 200 ppm, 6 hours/day, 5 days/week for 103 weeks, corresponding to 680 or 1360 mg/m^3), incidences of hepatocellular carcinomas were increased (incidences 7/49, 25/49 and 26/50 in males and 1/48, 13/50 and 36/50 in females). In F344/N rats (test concentrations 200 and 400 ppm, 6 hours/day, 5 days/week for 103 weeks, corresponding to 1360 or 2720 mg/m^3) tetrachloroethylene caused dose-related increases in the incidence of stage 3 mononuclear-cell leukaemia in animals of both sexes: in males, 20/50 in controls, 24/50 at the low dose and 27/50 at the high dose; in females, 10/50, 18/50 and 21/50, respectively. The historical control for mononuclear-cell leukaemia in rats in the same laboratory was 47% in males and 29% in females. Uncommonly occurring renal tubular-cell adenomas or adenocarcinomas were found in male rats (adenomas,1/49 in controls, 3/49 at the low dose and 2/50 at the high dose; adenocarcinomas, 0/49, 0/49 and 2/50, respectively).

Although induction of peroxisome proliferation as a mechanism underlying the hepatocarcinogenic effect of tetrachloroethylene in mice appears attractive, a poor quantitative correlation was seen between peroxisome proliferation and tumour formation in the liver following administration by inhalation.

The induction of kidney tumours observed in male rats provides weak evidence only. The increase in incidence is not statistically significant. In addition, two different mechanisms of action have been proposed for the induction of these tumours: alpha 2µ-globulin droplet nephropathy, an effect specific for male rats, and formation of genotoxic metabolites in the kidneys as the final step of the glutathione biotransformation pathway. Given the low incidences observed combined with the data on the mechanism of induction, it can be concluded that the result in male rats is equivocal evidence only for a risk of renal cancer in humans.

IARC *(2)* concluded that the results of the available animal bioassays provide sufficient evidence for carcinogenicity to animals.

Mutagenicity

Comprehensive reviews of the data obtained from the many studies carried out with tetrachloroethylene are available *(1,2,20)*. *In vitro* studies include tests for gene mutations in prokaryotes and eukaryotes and tests for chromosome aberrations in mammalian cell lines. *In vivo* studies include tests for chromosome aberrations in bone marrow in rats and mice and a dominant-lethal assay in rats. In addition, several studies on DNA damage *in vitro* and *in vivo* have been carried out. The body of results shows absence of mutagenicity of tetrachloroethylene in virtually all of the systems tested. The few weakly positive results may be due to the presence of mutagenic stabilizers in the test samples *(1,20)*. Binding of tetrachloroethylene *in vivo* to unpurified DNA from several organs was noted in one study, although no covalent binding to purified hepatic DNA could be demonstrated in another. In the other available *in vivo* studies, it is not known whether the test compound (or its

metabolites) reached the target tissues. This observation reduces the value of the negative results observed.

For the metabolites of tetrachloroethylene that are formed by conjugation with glutathione (a minor biotransfomation route demonstrated in rodents) positive results were obtained in *in vitro* studies in *Salmonella typhimurium* TA 100 (reverse mutation) with metabolic activation with kidney microsomes, in the presence of glutathione and glutathione transferase *(2)*.

Interactions with other chemicals
Results of studies on the influence of ethanol on the metabolism and toxicity of tetrachloroethylene in liver did not show synergism *(1,37)*. Following pretreatment with polychlorinated biphenyls, increased urinary excretion of metabolites of tetrachloroethylene and enhanced hepatotoxicity have been observed in rats *(1)*.

Effects on humans

Toxicological effects
Numerous case (accidental exposure) and occupational studies have been reported. In addition, some controlled studies in humans with acute or short-term inhalation exposure are available *(1,3,5)*.

The target organs for tetrachloroethylene toxicity in humans are the CNS, liver and kidneys. The dose–response relationship in humans for the effects on the liver and kidneys is not completely known.

In a series of controlled short-term studies in limited numbers of human volunteers, neurological symptoms (including dizziness, drowsiness and decreased functioning in motor coordination tests) and visual system dysfunction have been observed at $\geq$678 mg/m^3 ($\geq$100 ppm) and 339 mg/m^3 (50 ppm), respectively *(1,3,38,39)*.

Limited information on neurological effects following long-term exposure was obtained in occupational studies in dry-cleaning workers. In a cross-sectional study with two groups of exposed workers (exposure concentrations 83 ± 53 mg/m^3 and 364 ± 114 mg/m^3, duration of exposure 127 or 141 days), small effects on scores in psychological tests were found. However, the response did not correlate with the exposure level in this study *(1,5,40)*. In another study in female dry-cleaning workers with exposures of 6.8–408 mg/m^3 (4-hour averages, median 102 mg/m^3) and tetrachloroethylene concentrations in blood of 12–864 mg/litre (median 145 mg/litre), performance test scores in a test battery for neuromotor functions were decreased. Neither the duration of exposure nor the blood concentrations of tetrachloroethylene were significantly correlated with performance *(41)*. In cross-sectional studies in dry-cleaning workers, effects on blue-yellow colour vision were found at mean tetrachloroethylene concentrations of 42–102 mg/m^3 *(42,43)*.

In case studies of high, accidental exposures, liver effects have been reported. In limited studies in dry-cleaning workers, exposed to a TWA concentration of 143 mg/m^3 (21 ppm) over a 6-year period, serum enzymes indicative for liver function were not affected *(10,43)*. Further data for hepatic effects in humans are lacking.

Symptoms of renal dysfunction, including proteinuria and haematuria have been associated with accidental exposure to anaesthetic concentrations of tetrachloroethylene vapour *(1)*. In several cross-sectional studies in dry-cleaning workers the effect of tetrachloroethylene on renal function was examined. Female workers exposed for an average of 14 years to an estimated TWA concentration of 68 mg/m^3 (10 ppm) had increased levels of urinary levels of lysozyme and β-glucuronidase suggestive of mild renal effects *(44)*. No effects were observed in workers estimated to have been exposed to a TWA concentration of 142 mg/m^3 (21 ppm) for 6 years *(10)*. In a recent cross-sectional study, about 20 markers of early nephrotoxic effects were measured in workers in dry-cleaning facilities (n = 50). Exposure was determined by analysing air samples collected during 4-hour periods randomly selected over the working week. The median exposure concentration was 102 mg/m^3 (range, trace–580 mg/m^3). Compared to the control population, the exposed group had significantly higher frequencies of abnormal values for a number of the markers in urine, including albumin, transferrin, tissue nonspecific alkaline phosphatase and brush-border antigens. The siginificance of the findings cannot be easily assessed but may represent an early stage of clinically silent but potentially progressive renal disease *(45)*.

Mutagenic and carcinogenic effects
In two studies for genetic effects (sister chromatid exchanges and/or chromosome aberrations) in lymphocytes of occupationally exposed workers no clear-cut effects were found *(5)*.

A number of epidemiological studies on the ocurrence of cancer in tetrachloroethylene-exposed populations, mostly workers, are available. Those rated highest as to relevance are five cohort studies. In addition, six relevant case–control studies were considered. IARC concluded that there is evidence for consistently positive associations between exposure to tetrachloroethylene and the risks for oesophageal and cervical cancer and non-Hodgkin lymphoma. These associations appear unlikely to be due to chance, although confounding factors cannot be excluded and the total numbers in the cohort studies combined are relatively small. IARC therefore concluded that there is limited evidence in humans for the carcinogenicity of tetrachloroethylene *(2)*.

In other evaluations of the epidemiological studies on cancer in humans, which included most of the studies evaluated by IARC, it was concluded that the evidence is inadequate to assess the carcinogenicity of tetrachloroethylene in humans *(1,5)*.

Sensory effects
The odour threshold in air for detection of tetrachloroethylene is 8 mg/m^3. The odour threshold in air for recognition of tetrachloroethylene is three to four times higher *(46)*.

Evaluation of human health risks

Exposure evaluation

Ambient air concentrations of tetrachloroethylene are generally less than 5 μg/m^3 in urban areas and typically less than 1 μg/m^3 in rural areas. Indoor concentrations are generally less than 5 μg/m^3. Indoor tetrachloroethylene air levels may rise to more than 1 mg/m^3 in close proximity to dry-cleaning operations where tetrachloroethylene is used as a cleaning solvent or in homes where dry-cleaned clothing is often worn. Inhalation of tetrachloroethylene is the major route of exposure in the general population.

Health risk evaluation

The main health effects of concern are cancer and effects on the CNS, liver and kidneys. Tetrachloroethylene is classified by IARC as a group 2A carcinogen (probably carcinogenic to humans).

In carcinogenicity studies, an increased incidence of adenomas and carcinomas in the livers of exposed mice was observed. There is suggestive evidence from mechanistic studies that humans are likely to be less sensitive to the development of these tumours following tetrachloroethylene exposure. A low incidence of kidney tumours among male rats has been reported. It can be concluded from this small and not-statistically-significant increase, together with the data related to a possible mechanism of induction, that the result in male rats is equivocal evidence only for a risk of renal cancer in humans. The significance for humans of the increased incidences of mononuclear-cell leukaemias, as observed in a study in F344 rats, is unclear owing to the lack of understanding of the mechanism underlying the formation of this cancer type, which has a high background incidence.

Epidemiological studies in humans show positive associations between exposure to tetrachloroethylene and risks for oesophageal and cervical cancer and non-Hodgkin lymphoma. Confounding factors cannot be ruled out and the statistical power of the studies is limited. These studies therefore provide only limited evidence for the carcinogenicity of tetrachloroethylene in humans.

From the weight of the evidence from mutagenicity studies, it can be concluded that tetrachloroethylene is not genotoxic. Several *in vitro* studies indicate that conjugation of tetrachloroethylene with reduced glutathione, a minor biotransformation route demonstrated to occur in rodents, produces renal metabolites that are mutagenic in *S. typhimurium* TA 100. In the absence of further data on this point, the significance of the latter results for humans is uncertain.

Short-term exposure studies in volunteers (duration 1 or 5 days) have shown effects on the CNS at a concentration of $\geq$678 mg/m^3. A recent study of dry-cleaning workers with long-term exposure showed that renal effects may develop at lower exposure concentrations, with the reported onset of renal damage occurring following exposure to a median concentration of 102 mg/m^3 (range, trace–576 mg/m^3).

Although carcinogenicity studies in experimental animals are available, adequate long-term toxicity studies are not. A chronic lowest-observed-adverse-effect level (LOAEL) of 678 mg/m^3 (100 ppm) for the systemic toxicity (in kidney and liver) of tetrachloroethylene in mice can be derived from the NTP carcinogenicity study in this species.

Use of existing PBPK models for derivation of a guideline value based on kidney effects is not considered feasible because these models do not contain the kidney or kidney specific metabolism as a compartment. As yet it is therefore unknown what an appropriate internal dose measure would be.

Guidelines

Given the limitations of the weight of the epidemiological evidence and the uncertainty of the relevance to humans of the induction of tumours in animals exposed to tetrachloroethylene,

the derivation of a guideline value is at present based on non-neoplastic effects rather than on carcinogenicity as the critical endpoint.

On the basis of a long-term LOAEL for kidney effects of 102 mg/m^3 in dry-cleaning workers, a guideline value of 0.25 mg/m^3 is calculated. In deriving this guideline value, the LOAEL is converted to continuous exposure (dividing by a factor of 4.2, 168/40) and divided by an uncertainty factor of 100 (10 for use of an LOAEL and 10 for intraspecies variation). Recognizing that some uncertainty in the LOAEL exists because the effects observed at this level are not clear-cut and because of fluctuations in exposure levels, an alternative calculation was made, based on the LOAEL in mice of 680 mg/m^3, and using an appropriate uncertainty factor of 1000. This calculation yields a guideline value of 0.68 mg/m^3.

On the basis of the overall health risk evaluation, a guideline of 0.25 mg/m^3 is currently established. However, the concern about a possible carcinogenic effect of tetrachloroethylene exposure in humans should be addressed through an in-depth risk evaluation process in the near future.

References

1. *Toxicological profile for tetrachloroethylene*. Atlanta, GA, Agency for Toxic Substances and Disease Registry, 1993 (Public Health Service Report, No. TP-92/18).
2. *Dry cleaning, some chlorinated solvents and other industrial chemicals*. Lyon, International Agency for Research on Cancer, 1995 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 63).
3. *Tetrachloroethylene*. Geneva, World Health Organization, 1984 (Enviromental Health Criteria, No. 31).
4. BESEMER, A.C. ET AL. *Criteriadocument over Tetrachlooretheen.* [Tetrachloroethylene criteria document]. The Hague, Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer, 1984 (Publikatiereeks Lucht, No. 32).
5. *Tetrachloroethylene*. *Priority substances assessment report for the Canadian Environmental Protection Act*. Ottawa, Environment Canada and Health Canada, 1993.
6. SHAH, J.J. & SINGH, H.S. Distribution of volatile organic chemicals in outdoor and indoor air – a national VOCs data base. *Environmental science and technology,* **22:** 1381–1388 (1988).
7. FAST, T. & VAN WIJNEN, J.H. Exposure to perchloroethylene in homes nearby drycleaners using closed systems. Fourth European Meeting of Environmental Hygiene, Wageningen, Netherlands, June 9–11, 1993. *Zentralblatt für Hygiene und Umweltmedizin,* **195:** 147–148 (1994).
8. AGGAZZOTTI G. ET AL. Indoor exposure to perchloroethylene (PCE) in individuals living with dry-cleaning workers. *Science of the total environment,* **156:** 133–137 (1994).
9. CLARK, C.M. & FULLER, C.L. Total exposure and risk assessment for drinking water contaminated with volatile organic compounds. Springfield, VA, US National Technical Information Services, 1987 (NTIS No. PB-88-50602; Illinois Dept. of Energy and Natural Resources Report, No. ILENR/RE-AQ-87/22).
10. LAUWERYS, R. ET AL. Health surveillance of workers exposed to tetrachloroethylene in dry-cleaning shops. *International archives of occupational and environmental health,* **52:** 69–77 (1983).
11. VYSKOCIL, A. ET AL. Study on kidney function in female workers exposed to perchloroethylene. *Human and experimental toxicology,* **9:** 377–380 (1990).

12. AGGAZZOTTI, G. ET AL. Occupational and environmental exposure to perchloroethylene (PCE) by dry cleaners and their family members. *Archives of environmental health,* **49:** 487–493 (1994).
13. HOFFMANN, K. ET AL. *Umwelt-Survey 1990/91. Band IV: Personengebundene Exposition gegenüber flüchtigen organischen Verbindungen in den alten Bundesländern* [Personal exposure to volatile organic compounds in the "old" federal states of Germany]. Berlin, Institut für Wasser-, Boden- und Lufthygiene, Umweltbundesamt (WaBoLu-Hefte 4/96).
14. VARTIAINEN, T. ET AL. Population exposure to tri- and tetrachlororethene and cancer risk: two cases of drinking water pollution. *Chemosphere,* **27:** 1171–1181 (1993).
15. DALLAS, C.E. ET AL. Use of physiologically based model to predict systemic uptake and respiratory elimination of perchloroethylene. *Toxicology and applied pharmacology,* **128:** 60–69 (1994).
16. BOGEN, K.T. ET AL. Dermal absorption of dilute aqueous chloroform, trichloroethylene, and tetrachloroethylene in hairless guinea pigs. *Fundamental and applied toxicology,* **18:** 30–39 (1992).
17. DALLAS, C.E. ET AL. Development of a physiologically based model for perchloroethylene using tissue concentration–time data. *Toxicology and applied pharmacology*, **128:** 50–59 (1994).
18. BYCZKOWSKI, J.Z. & FISHER, J.W. Lactational transfer of tetrachlorethylene in rats. *Risk analysis,* **14:** 339–349 (1994).
19. HAMADA, T. & TANAKA, H. Transfer of methyl chloroform, trichloroethylene and tetrachloroethylene to milk, tissues and expired air following intraruminal or oral administration in lactating goats and milk-fed kids. *Environmental pollution,* **87:** 313–318 (1995).
20. *Tetrachloroethylene: assessment of human carcinogenic hazard*. Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals, 1990 (ECETOC Technical Report, No. 37).
21. GREEN, T. ET AL. Perchloroethylene-induced rat kidney tumors: an investigation of the mechanisms involved and their relevance to humans. *Toxicology and applied pharmacology,* **103:** 77–89 (1990).
22. BYCZKOWSKI, J.Z. ET AL. Computer simulation of the lactational transfer of tetrachloroethylene in rats using a physiologically based model. *Toxicology and applied pharmacology*, **125:** 228–236 (1994).
23. SCHREIBER, J.S. Predicted infant exposure to tetrachloroethylene in human breastmilk. *Risk analysis* **13:** 515–524 (1993).
24. CHEN, C.W. & BLANCATO, J.N. Role of pharmacokinetic modeling in risk assessment: perchloroethylene as an example. *In: Pharmacokinetics in risk assessment – drinking water and health,* Vol. 8. Washington DC, National Academy Press, 1987.
25. BOGEN, K.T. & MCKONE, T.E. Linking indoor air and pharmacokinetic models to assess tetrachloroethylene risk. *Risk analysis,* **8:** 509–552 (1988).
26. WARD, R.C. ET AL. Pharmacokinetics of tetrachloroethylene. *Toxicology and applied pharmacology,* **93:** 108–117 (1988).
27. KOIZUMI, A. Potential of physiologically based pharmacokinetics to amalgamate kinetic data of trichloroethylene and tetrachloroethylene obtained in rats and man. *British journal of industrial medicine,* **46:** 239–249 (1989).
28. DALLAS, C.E. ET AL. Use of tissue distribution data from rats and dogs to determine species differences in input parameters for a physiological model for perchloroethylene. *Environmental research,* **67:** 54–67 (1994).

29. DALLAS, C.E. ET AL. Physiologically based pharmacokinetic model useful in prediction of the influence of species, dose, and exposure route of perchloroethylene pharmacokinetics. *Journal of toxicology and environmental health,* **44:** 301–317 (1995).
30. HATTIS, D. ET AL. Uncertainties in pharmacokinetic modelling for perchloroethylene. I. Comparison of model structure, parameters, and predictions for low-dose metabolism rates for models derived by different authors. *Risk analysis,* **10:** 449–458 (1990).
31. BOIS, F.Y. ET AL. Precision and sensitivity of pharmacokinetic models for cancer risk assessment: tetrachloroethylene in mice, rats and humans. *Toxicology and applied pharmacology*, **102:** 300–315 (1990).
32. KJELLSTRAND, P. ET AL. Perchloroethylene: effects on body and organ weights and plasma butyrylcholinesterase activity in mice. *Acta pharmcologica et toxicologica,* **54:** 414–424 (1984).
33. *Technical report on the toxicology carcinogenesis studies of tetrachloroethylene (perchloroethylene) in F344/N rats and B6C3F1 mice (inhalation studies)*. Research Triangle Park, NC, National Toxicology Program, 1986 (NTP Technical Report, No. 311).
34. WANG, S. ET AL. Perchloroethylene-induced reduction of glial and neuronal cell marker proteins in rat brain. *Pharmacology and toxicology,* **72:** 273–278 (1993).
35. SEIDEL, H.J. ET AL. Hematological toxicity of tetrachloroethylene in mice. *Archives of toxicology,* **66:** 228–230 (1992).
36. *Technical report on the bioassay of tetrachloroethylene (CAS No. 127-18-4) for possible carcinogenesis*. Bethesda, MD, United States Department of Health, Education and Welfare, 1977 (DHEW Publication, No. 77-813; National Cancer Institute Technical Report, No. 13).
37. GIOVANNINI, L. ET AL. Effect of ethanol chronic use on hepatotoxicity in rats exposed to tetrachloroethylene. *International journal of tissue reactions,* **24:** 281–285 (1992).
38. HAKE, C.L. & STEWART, R.D. Human exposure to tetrachloroethylene: inhalation and skin contact. *Environmental health perspectives,* **21:** 231–238 (1977).
39. ALTMANN, L. ET AL. Neurophysiological and psychological measurements reveal effects of acute low-level oraganic solvent exposure in humans. *International archives of occupational and environmental health,* **62:** 493–499 (1990).
40. SEEBER, A. Neurobehavioral toxicology of long-term exposure to tetrachloroethylene. *Neurotoxicology and teratology,* **11:** 579–583 (1990).
41. FERRONI, C. ET AL. Neurobehavioral and neuroendocrine effects of occupational occupational exposure to perchloroethylene. *Neurotoxicology,* **13:** 243–248 (1992).
42. NAKATSUKA, H. ET AL. Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene mostly at levels below occupational exposure limits. *International archives of occupational and environmental health,* **64:** 113–117 (1992).
43. CAVALLERI, A. ET AL. Perchloroethylene exposure can induce color vision loss. *Neuroscience letters,* **179:** 162–166 (1994).
44. FRANCHINI, I. ET AL. Early indicators of renal damage in workers exposed to organic solvents. *International archives of occupational and environmental health,* **52:**1–9 (1983).
45. MUTTI, A. ET AL. Nephropathies and exposure to perchloroethylene in dry-cleaners. *Lancet,* **340:** 189–193 (1992).
46. *Air quality guidelines for Europe.* Copenhagen, WHO Regional Office for Europe, 1987 (WHO Regional Publications, European Series, No. 23).

