Chapter 5.15 Trichloroethylene

General description

Physical and chemical properties

Trichloroethylene is a widely used industrial solvent. It is a readily volatile, colourless liquid with a sweet ethereal (chloroform-like) smell. Other physical and chemical properties include:

Density	1.4 g/ml at 25 °C
Boiling point	86.7 °C
Water solubility	3400 mg/litre at 20 °C
Vapour pressure	77 mmHg at 25 °C
Henry law constant	0.83 kPa.m^3/mol at 20 °C

Sources

There are no known natural sources of trichloroethylene. Estimated production in 1990 was 131 kilotonnes in western Europe, 79 kilotonnes in the United States of America and 57 kilotonnes in Japan, compared to 210, 121 and 82 kilotonnes, respectively, in 1980. The estimated annual consumption in these areas is 65–103% of the production levels. No estimates of the levels of production and use are available for other parts of the world *(1)*.

Trichloroethylene is mainly used for the vapour degreasing and cold cleaning of manufactured metal parts (80–95% of consumption). Other applications include industrial dry cleaning, printing, the production of printing ink, extraction processes, paint production and textile printing. Consumer products that contain trichloroethylene include typewriter correction fluids, paint removers/strippers, adhesives, stain removers, and rug-cleaning fluids *(1–3)*.

Most trichloroethylene (99%) is emitted to the environment as a result of use. Practically all of it enters the atmosphere unchanged. A small proportion enters water and waste water. Trichloroethylene can volatilize rapidly from surface water *(2,4)*.

Occurrence in air

Concentrations of trichloroethylene 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 worldwide background levels vary from <17 to 109 ng/m^3. In rural areas levels of 0.10–0.68 µg/m^3 have been reported *(4,5)*. In urban areas levels are higher. In European cities, the reported range is 0.04–64.1 µg/m^3 (mean concentrations 0.8–18.5 µg/m^3). For Germany, 5–15 µg/m^3 is reported as the typical concentration range for urban areas *(4)*. In the United States, concentrations in municipal areas ranged from 0.03 to 13.5 µg/m^3 (mean concentrations 0.5–2.1 µg/m^3) *(4);* the average for urban areas of 2.5 µg/m^3 (0.46 ppb) that resulted from a compilation of data in 1982, is in agreement with more recent measurements

(3). Mean concentrations (24-hour composite samples averaged over 1–12 months) in 11 Canadian cities ranged from 0.7 to 0.96 μg/m^3 *(5)*.

The median value for indoor air from the 2031 entries in the United States Environmental Protection Agency (EPA) data base on volatile organic contaminants (VOC-AMBI) is 0.68 μg/m^3 (0.125 ppb); the average value was 7.36 μg/m^3 (1.347 ppb) *(6)*. In Canada, mean indoor air concentrations of up to 165 μg/m^3 with an overall mean value of 1.4 μg/m^3 have been reported *(5)*. Concentrations measured in several western European countries varied from 0.76 to 1200 μg/m^3. Concentrations are generally higher in indoor air than outdoors *(4)*. An important source for trichloroethylene in indoor air is volatilization from contaminated water *(7)*.

In the atmosphere, trichloroethylene may react with photochemically produced hydroxyl radicals yielding phosgene, dichloroacetyl chloride, formyl chloride and other degradation products. Half-life in the atmosphere varies with latitude, season and concentration of hydroxyl radicals. Reported half-lives for the reaction with hydroxyl radicals vary from 1 day to 2½ weeks (in regions very far to the north, half-life may be as long as several months in winter) *(4,5)*.

Conversion factors

1 ppm = 5.4 mg/m^3
1 mg/m^3 = 0.18 ppm

Analytical methods in air

The primary method for determination of trichloroethylene 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 trichloroethylene 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 1.5–75 pg/m^3 *(3)*.

Routes of exposure

Air

Presence of trichloroethylene in ambient air will result in exposure of the general population, especially in urban areas. A route of possible additional exposure is through indoor air where concentrations may be higher than in outdoor air owing to use of consumer products containing trichloroethylene or of water (for showering, dish washing, cleaning) that is contaminated with trichloroethylene. Groups with higher than usual exposure levels are workers using trichloroethylene in their professional tasks and people living in the vicinity of plants emitting trichloroethylene to the air. A further group with increased exposure through air is constituted by people living at sites where trichloroethylene is present as a soil contaminant.

It has been estimated that in the Netherlands 0.1% of the population is exposed to an average concentration of 10 μg/m^3, 2.5% to 4 μg/m^3 and the remainder to 0.8 μg/m^3 *(8)*. The average concentrations for urban areas in Canada (0.07–0.96 μg/m^3) and the United States (0.5–2.5 μg/m^3) are of the same order of magnitude.

In occupational settings exposure levels are higher. In the United States, metal degreasers were found to be exposed to trichloroethylene; 60% of the measured concentrations were less than 270 mg/m^3 and 93% less than 540 mg/m^3. Data from 1980 For western Europe show similar exposure levels for metal degreasers *(8)*. More recent measurements (biomonitoring) from Sweden pertaining to vapour degreasing in specially designed equipment with exhaust ventilation, showed considerably lower exposure concentrations of well below 50 mg/m^3 *(9)*.

Drinking-water

In a survey carried out in Germany it was found that trichloroethylene was detectable in about 40% of the tested drinking-water samples with a concentration of more than 1 µg/litre for 5.5% of the supplied residents (concentration range <0.001–21 µg/litre) *(4)*. In the United States, trichloroethylene is not detectable in drinking-water in most cases. The EPA Groundwater Supply Survey of 945 drinking water systems nationwide found trichloroethylene in 91 out of 945 water systems in 1984. The median level of the positive samples was about 15 µg/litre, with a maximum level of 650 µg/litre *(3)*. In Canada, trichloroethylene is usually not detectable in drinking-water; mean concentrations were ≤1.0 µg/litre at 30 drinking-water treatment facilities across the country surveyed in 1979 *(5)*.

Food

The presence of trichloroethylene has been demonstrated in a wide range of foodstuffs and in some exceptional cases high concentrations have been observed. In some countries, the use of trichloroethylene as a solvent in the production of foodstuffs has been banned. In total diet studies carried out in the United States, trichloroethylene was detected in only a small proportion of the samples *(3,5)*. From determinations of trichloroethylene in food items in Germany carried out in the early 1980s, total daily intakes of 1–7 µg/day have been calculated *(8)*. Individual products in which high concentrations of trichloroethylene have been observed are decaffeinated coffee, butter, margarine and tea *(4)*.

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, and average daily intake from foods at 1–7 µg/day. In countries where the use of trichloroethylene in food production has been banned, the average intake is probably below this range. The average concentration in air is less than 1 µg/m^3 in rural areas and up to 10 µg/m^3 in urban areas. Concentrations in indoor air are in the same range. In general, inhalation is the major route of exposure.

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 trichloroethylene was found to be 1.2 µg/m^3 . The 95th percentile was 8 µg/m^3 *(10)*.

Toxicokinetics

Absorption

Trichloroethylene is readily absorbed in the gastrointestinal tract and the lungs. In humans and animals, initial uptake following inhalation is rapid, with rates levelling off after a few hours of exposure. In an inhalation experiment in rats, uptake was found to exceed 90% during the first 5 minutes of exposure and to decrease over the next 30 minutes to near steady-state levels of about 70% *(11)*. The systemic uptake of trichloroethylene was time- but not concentration-dependent *(8)*. Uptake of trichloroethylene in the lungs in humans was 27–

64% *(3,5)*. Absorption via the oral route is extensive, with proportions of 80–98% observed in mice and rats following a single dose *(3)*.

Dermal absorption of significant amounts of trichloroethylene is possible in some situations. Some observations in humans with short exposure periods suggest a low absorption level only, but longer exposure periods may well lead to higher absorption, in part due to defatting and disruption of the outer skin layer through the action of trichloroethylene. The results of experiments in hairless guinea pigs have shown substantial dermal absorption from dilute aqueous solutions *(12)*.

Distribution

Limited data in humans and animals show that, following absorption, trichloroethylene is distributed to all body tissues and that it crosses the blood–brain barrier and the placenta. Highest concentrations occur in adipose tissues *(2,3,8)*. In lactating rats, it was shown that trichloroethylene and its metabolite trichloroacetic acid are excreted in milk *(13)*. In goats, trichloroethylene and its metabolite trichloroethanol were found to be transferred to milk to a slight degree only (about 0.06% of the dose following a single intraruminal application) *(14)*.

Biotransformation

In humans, 40–75% of the retained dose of inhaled trichloroethylene is metabolized. The principal site of biotransformation is the liver; biotransformation also occurs in the Clara cells of the lungs. The major metabolic route is oxidation (by cytochrome P-450 mixed-function oxygenases) giving trichloroethanol, tricholoroethanol-glucuronide and trichloroacetic acid as the major metabolites (identified in both humans and animals). Chloral hydrate is an intermediate in this oxidative biotransformation and its formation is probably preceded by the conversion of trichloroethylene to its epoxide. Oxidative metabolism of trichloroethylene occurs to a greater extent in mice than in rats, especially at high dose levels.

Several minor metabolites of trichloroethylene have also been identified, including the mercapturic acid *N*-acetyl-*S*-(dichlorovinyl)-*L*-cysteine (DCVC), which is formed in the kidneys from the glutathione conjugate of trichloroethylene (previously formed in the liver as a minor biotransformation product). The presence of the potentially nephrocarcinogenic metabolite DCVC in urine has been demonstrated in rats and also in workers exposed to trichloroethylene *(3–5,15)*.

Interspecies differences in biotransformation

Mice metabolize trichloroethylene to a greater extent than rats; in mice saturation of trichloroethylene metabolism was not observed at dose levels at which it was evident in rats (2700–3240 mg/m^3). Several strains of mice (e.g. B6C3F1 and Swiss) metabolize trichloroethylene more readily and this leads to higher concentrations of trichloroacetic acid in the blood, especially at higher dose levels. In humans, oxidative metabolism of trichloroethylene to trichloroacetic acid is not limited by saturation but nevertheless, humans metabolize about 60 times less trichloroethylene on a body weight basis than do mice.

There is inconclusive evidence to suggest that the glutathione biotransformation route (leading to formation of the potentially nephrocarcinogenic metabolite DCVC) is more important in humans than in rodents *(15–17)*.

Elimination
In humans and animals, part of the absorbed amount of trichloroethylene is exhaled unchanged (11–40%) *(3,8)*. Following intravenous administration, elimination from the blood was fairly rapid with a half-time of 0.3–1 hours. Elimination from fat is slower, with a half-time of 3.5 hours *(8)*. Metabolites are excreted primarily in the urine. In humans, the half-times for renal elimination of trichloroethanol and trichloroethanol-glucuronide is about 10 hours. Urinary excretion of trichloroacetic acid is slower with reported half-times of about 52 hours *(3)*.

Biomarkers of exposure
Several studies have demonstrated a correlation between trichloroethylene concentrations in ambient air and those in human breath. Other methods are the determination of trichloroethylene and its major metabolites trichloroethanol and trichloroacetic acid in blood and urine. Exposure levels were found to correlate with concentrations of these metabolites in urine. However, concentrations of trichloroacetic acid in urine show great interindividual variation even between individuals with equal exposure; urinary excretion of this compound may also be due to exposure to other compounds like tetrachloroethane, tetrachloroethylene and 1,1,1-trichloroethane *(3)*. Elimination rates suggest that measurement of trichloroethanol in urine is best suited for detecting recent exposure to trichloroethylene, while trichloroacetic acid is the best indicator for long-term exposures *(9)*. Adducts to haemoglobin and serum albumin may provide alternative biomarkers for exposure to trichloroethylene *(18)*.

Physiologically based pharmacokinetic modelling
Physiologically based pharmacokinetic (PBPK) models have been developed to describe the kinetics of trichloroethylene and its metabolite trichloroacetic acid in pregnant and lactating rats and nursing pups following oral and inhalation exposure. The model predictions were in agreement with the data points obtained experimentally in dams and fetuses/pups *(13,19)*. Another PBPK model simulated the time-course of trichloroethylene concentrations in exhaled breath and blood in rats during and after exposure to two inhalation dose levels *(11)*. A model for description of the uptake and plasma clearance of trichloroethylene and its metabolite trichloroacetic acid in rats and mice following inhalation exposure, was successful in rats only *(20)*.

Several PBPK models for humans are available for the parent compound and the metabolite trichloroacetic acid *(21,22)*. With a model based on experimental data on concentrations of trichloro-compounds in the blood of workers exposed to trichloroethylene, the average proportion of the retained dose being metabolized in humans, as observed in a number of published studies, could be adequately simulated *(23)*. Model parameters were obtained from the published literature and subsequently optimized using data on trichloroethylene concentrations in blood and exhaled breath, trichloroacetic acid concentrations in plasma and excretion in urine. Each of the available models for humans has been applied for cancer risk estimation using results from animal bioassays. These estimates were based on liver tumours in mice *(23,24)*, lymphomas in mice and kidney tumours in rats *(23)* and the non-tumorigenic dose level in rats *(21)*.

Health effects

Effects on experimental animals and *in vitro* test systems

Toxicological effects
Trichloroethylene has a low acute inhalation toxicity (LC_{50} in rodents, $\geq$ 45 mg/litre). Acute oral toxicity is also low (LD_{50} in rodents, $\geq$ 2400 mg/kg body weight (bw)) *(2)*.

Liver, kidneys and the central nervous system (CNS) are the target organs for systemic effects. In short-term toxicity studies (oral, inhalation) hepatic effects were seen 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 200, 405, 810 or 1620 mg/m^3 produced a dose-related increase in liver weight at all dose levels. Plasma butyrylcholinesterase activity, an indication of the early stages of liver toxicity, showed a dose-related increase in males only. Morphological changes in the liver were observed at all dose levels; these changes were reversible. At 120 days after cessation of exposure, liver weight was normal and only a slight degree of histological changes could be detected (observations only made for the 810 mg/m^3 dose level) *(25)*. Increased liver weights were also found in rats and gerbils (810 mg/m^3, 30 days of continuous exposure), but this increase was smaller than in mice *(26)*. Renal effects caused by trichloroethylene are of mild nature and only occur at higher doses than the liver effects *(3,4)*.

CNS effects have been reported in a number of studies, mostly in rats. In a 16-week study in rats, brainstem auditory-evoked response potentials were depressed at test concentrations as high as 8640 and 17 280 mg/m^3 *(27)*. Another inhalation study in rats showed increased latency in visual discrimination tasks; the no-observed-adverse-effect level (NOAEL) in this study was 2700 mg/m^3 (exposure: 18 weeks, 5 days/week, 16 hours/day) *(28)*. In rabbits neuro-ophthalmological modifications (determined by electroretinogram) were observed during a 12-week period of inhalation exposure (4 hours/day, 4 days/week) to test concentrations of 1890 and 3780 mg/m^3. Following cessation of treatment, the changes were reversed, baseline values being attained within 6 weeks *(29)*.

In teratogenicity studies in rats and mice, fetotoxicity and embryotoxocity were observed at inhalation levels of $\geq$450 mg/m^3. In reproduction studies in rats and mice, adverse effects on reproductive performance were observed at high oral dose levels only ($\geq$1000 mg/kg bw) *(3)*.

Carcinogenic effects
Data on trichloroethylene carcinogenicity have been evaluated in several health assessment documents *(1, 3–5)*. Table 1 gives an overview of the relevant studies and their outcome *(30–37)*. Several of the studies showed limitations in study design, reducing their value for the evaluation of trichloroethylene carcinogenicity. In the older studies, the test samples contained impurities that are known to produce carcinogenicity in animals and the positive results were attributed to the action of the impurities and not that of trichloroethylene. However, in studies with purified trichloroethylene similar results were found.

The significance of the increase in malignant lymphomas in the study in NMRI mice is questionable in view of the lack of a clear dose–response, the high spontaneous incidence in this particular strain of mice, and the absence of a similar effect in all other studies. The increase in liver tumours in mice, consistently and exclusively observed in virtually all mouse

studies, has been ascribed to the action of the species-specific high levels of trichloroacetic acid formed following exposure to trichloroethylene. Peroxisome proliferation is thought to play a role. There is substantial experimental evidence to support the hypothesis that the high trichloroacetic acid levels in mice are responsible for the liver tumours in this species. This effect is probably not relevant for humans because they are much less sensitive.

The mechanism for the pulmonary tumours observed in mice is insufficiently known, although it has been argued that the high level of oxidative metabolism in Clara cells in lungs of mice (in contrast to that in humans) may be an important factor. The few kidney tumours observed in male rats provide weak evidence only and may well be related to the toxic effect in this organ. The testes tumours observed in two rat studies were seen in strains not known to be excessively sensitive to this type of tumour. There is no convincing evidence that would show that these findings are not relevant for humans.

IARC concluded that the results of the available animal bioassays provide sufficient evidence for carcinogenicity to animals *(1)*.

Unit risk values have been estimated using the linearized multistage model on carcinogenicity data from mice and rats, using the most sensitive tumour type for which there was sufficient evidence of an effect. Unit risk values were 9.3×10^{-7} for pulmonary adenomas/carcinomas in Swiss mice *(30)* and 4.3×10^{-7} for Leydig cell testicular tumours in Sprague-Dawley rats *(33)*, respectively.

Mutagenicity and related endpoints

Several comprehensive reviews on the mutagenicity of trichloroethylene are available *(3,8,16,38)*. For many assays, the interpretation of the results is hampered by the presence in the test samples of impurities known to be mutagenic. In a number of studies in bacteria, purified trichloroethylene was weakly mutagenic in the presence of metabolic activation. In other studies, however, purified trichloroethylene produced no such response. In fungi and yeasts, a weak positive response was found when the purified compound was tested with metabolic activation, but negative results were also observed.

In mammalian cells *in vitro*, tests for gene mutations have shown a weak positive response with activation. A single test for chromosome aberrations in mammalian cells *in vitro* did not show an effect.

In vivo mutagenicity studies include several host-mediated assays in mice with yeasts as test organisms. In these limited tests (mostly only one dose level tested) both positive and negative results were found, but no information on trichloroethylene purity was provided. Micronucleus tests and cytogenetic tests for chromosome aberrations have been carried out in mice and rats.

Table 1. Results of carcinogenicity assays

Species and strain	Treatment[a]	Observed increase in tumour incidence[b]	Reference
Inhalation studies			
Mouse (m, f) B6C3F1	0, 540, 1620 and 3240 mg/m^3, 7 hours/day, 5 days/week for 78 weeks; observation for rest of lifespan; TCE purity 99.9%, epoxide-free	Pulmonary adenomas in females only (4/90, 6/90 10/90 and 15/90); hepatomas in females (3/90, 4/90, 4/90 and 9/90) and males (14/90, 19/90, 27/90 and 21/90)	*(30)*
Mouse (m, f) Swiss	0, 540, 1620 and 3240 mg/m^3, 7 hours/day, 5 days/week for 78 weeks; observation for rest of lifespan; TCE purity 99.9%,.epoxide-free	Pulmonary adenomas and carcinomas in males only (10/90, 11/90, 23/90 and 27/90); hepatomas in males only (4/90, 2/90, 8/90 and 13/90)	*(30)*
Mouse (m, f) NMRI	0, 540 and 2700 mg/m^3, 7 hours/day, 5 days/week for 78 weeks; observation until week 130; TCE purified, epoxide-free	Lymphomas in females only (9/29, 18/28 and 17/30)	*(31)*
Hamster (m, f) Syrian	0, 540 and 2700 mg/m^3, 7 hours/day, 5 days/week for 78 weeks; observation until week 130; TCE purified, epoxide-free	No increase observed	*(31)*
Mouse (f) ICR	0, 270, 810 and 430 mg/m^3, 7 hours/day, 5 days/week for 104 weeks; observation until week 107; TCE purity 99.8% + 0.02% benzene + 0.02% epichlorohydrin	Pulmonary adenocarcinomas (1/49, 3/50, 8/50 and 7/46)	*(32)*
Rat (m, f) Wistar	0, 540 and 2700 mg/m^3, 6 hours/day, 5 days/week for 78 weeks; observation until week 156; TCE purified, epoxide-free	No increase observed	*(31)*
Rat (m, f) Sprague-Dawley	0, 270, 810 and 430 mg/m^3, 7 hours/day, 5 days/week for 104 weeks; observation until week 107; TCE purity 99.8% + 0.02% benzene + 0.02% epichlorohydrin	No increase observed	*(32)*
Rat (m, f) Sprague-Dawley	0, 540, 1620 and 3240 mg/m^3 7 hours/day, 5 days/week for 104 weeks; observation for rest of lifespan; TCE purity 99.9% epoxide-free	Renal adenocarcinomas in males and at high dose only (4/130 versus 1/130 in controls); Leydig cell tumours in testis (1/135, 16/130, 30/130 and 31/130)	*(33)*
Hamster (m, f) Syrian	0, 540 and 2700 mg/m^3, 6 hours/day, 5 days/week for 78 weeks; observation until week 130; TCE purified, epoxide-free	No increase observed	*(31)*
Oral studies (administration by gavage)			
Mouse (m, f) B6C3F1	1169 and 2339 mg/kg bw (m), 869 and 1739 mg/kg bw (f) 5 days/week for 78 weeks; killed after 90 weeks; TCE + 0.09% epichlorohydrin and 0.19% epoxybutane	Hepatocellular carcinomas in males (1/20, 26/50 and 31/48) and females (0/20, 4/50 and 11/40); lung adenomas in males (0/20, 5/50 and 2/48) and females (1/20, 4/50 and 7/47)	*(34)*

Mouse (m, f) B6C3F1	0 and 1000 mg/kg bw, 5 days/week for 103 weeks; TCE epichlorohydrin-free	Hepatocellular carcinomas in males (8/48 and 30/50) and females (2/48 and 13/49) (toxic effects: renal cytomegaly in all TCE-treated males and females)	*(35)*
Mouse (m, f) Ha:ICR	0, TWA 1900 mg/kg bw (m), TWA 1400 mg/kg bw (f), 5 days/week for 78 wks; TCE with or without epichlorohydrin and epoxybutane	Papillomas and carcinomas in forestomach in groups given TCE + epichlorohydrin + epoxy- butane; no increase observed in groups that received pure TCE	*(36)*
Rat (m, f) Osborne Mendel	549 and1098 mg/kg bw, 5 days/week for 78 weeks with observation until week 110	No increase observed but value of study reduced because survival was decreased owing to toxic nephropathy (both sexes, both dose levels)	*(34)*
Rat (m, f) F344/N	0, 500 and 1000 mg/kg bw, 5 days/week for 104 weeks; TCE purity >99.9%, epoxide-free	Renal tubular adenocarcinomas in males only(0/33, 0/20 and 3/16); nephropathy in all treated groups (m and f); NTP considers study inadequate (survival too low)	*(35)*
Rat (m, f) Sprague - Dawley	0, 50 and 250 mg/kg, 5 days/week for 52 weeks; observation for rest of lifespan; TCE purity >99.9%, epoxide-free	No increase observed (karyomegaly in renaltubular cells at 250 mg/kg, males only)	*(33)*
Rat (m, f) ACI, August, Osborne Mendel and Marshall	0, 500 and 1000 mg/kg bw, 5 days/week for 104 weeks; TCE purity >99.9%, epoxide-free	Study judged inadequate by NTP;[c] nevertheless to be noted: in Osborne Mendel rats: renal tubular cell adenomas in males only (0/50, 6/50 and 1/50); in male Marshall rats: interstitial cell tumours (17/46, 21/48 and 32/48)	*(37)*

[a] For all inhalation studies, test concentrations originally reported in ppm, have been converted to mg/m^3.

[b] The presentation of numbers of tumours: control incidence followed by low- to high-dose incidences.

[c] Owing to reduced survival, chemical toxicity and deficiencies in the conduct of the study. The tumour incidences given for this study are considered relevant despite the general qualification that the study is inadequate. The testes tumours gain significance in the light of the results of the other rat studies.

No chromosome aberrations were found in bone marrow cells, lymphocytes or splenocytes. Conflicting results were observed in inhalation studies with mice and rats concerning the effects of trichloroethylene on micronuclei in bone marrow and on chromosomal aberrations. In one study micronuclei were observed in the bone marrow of rats without an increase in chromosomal aberrations, whereas mice did not show effects *(39)*. In another study, similar alterations were seen in mice *(40)*. It is suggested that the induction of micronuclei without concomitant chromosomal aberrations is an indication for spindle effects.

The results of a limited number of *in vivo* tests for effects on germ cells in mice and rats were inconclusive, and no effects were found in the *Drosophila* sex-linked recessive lethal assay *(16)*.

Conflicting results have also been observed for DNA damage (single-strand breaks in liver DNA) in mice and rats *in vivo (3,16)*. An observation relevant to the evaluation of the hepatocarcinomas found in mice is the increased rate of hepatic DNA synthesis observed in mice but not in rats *(3)*. In addition, both mice and rats have shown a very low level of binding of trichloroethylene to DNA in all tissues examined *(8,16)*.

The available data on mutagenicity do not show a consistent pattern, but the results indicate that trichloroethylene has a weak mutagenic action, causing numerical chromosomal aberrations (aneuploidy) *in vivo*, an effect that may be ascribed to the metabolite chloral hydrate, a known aneugen. There is evidence that the minor mutagenic trichloroethylene metabolite DCVC is excreted in the urine following occupational trichloroethylene exposure *(1,15)*.

Interactions with other chemicals
Rat studies have shown that, depending on the dose level and the interval between exposure to ethanol and trichloroethylene, ethanol either increases or decreases the formation of metabolites of trichloroethylene. Several liver enzyme inducers have been shown to potentiate the hepatotoxicity of trichloroethylene as a result of increased formation of cytotoxic metabolites. Decreased metabolism occurs when there is competition between ethanol and trichloroethylene for enzymatic sites. This effect has also been demonstrated for other low-molecular-weight alcohols *(3)*.

Trichloroethylene lowers the threshold for epinephrine-induced cardiac arrhythmias, an effect attributable to trichloroethylene itself, and not to the metabolites. In humans, levels of metabolites in urine were lower when there was simultaneous exposure to other solvents (tetrachloethene, carbon tetrachloride), indicating depression of trichloroethylene metabolism *(3)*. A study on the combined effects of styrene and trichloroethylene on the rat auditory system did not show synergism *(41)*. In mice, no synergism was observed for induction of micronuclei in bone marrow following intraperitoneal administration of trichloroethylene together with the fungicide fenarimol *(42)*.

Effects on humans

Toxicological effects
The main target organ for trichloroethylene toxicity in humans is the CNS. Acute inhalation exposure to very high concentrations produces narcotic effects. The available controlled acute or short-term neurobehavioural studies in volunteers have been reviewed *(43)*. At concentrations of $\geq$1080 mg/m^3, decreased psychomotor performance, visuomotor disturbances and subjective complaints were observed. In the range 594–810 mg/m^3, performance in tests for perceptivity, memory, reaction time, manual ability and dexterity was decreased. At lower levels, the results did not show a consistent pattern. At exposure levels of 270–540 mg/m^3 (exposure for 3.5 and 7 hours), the visual and auditory potentials were affected.

In studies on long-term occuptional exposure, effects on the CNS and liver were found *(44)*. Exposure concentrations varied widely in these studies. These fluctuations have led to attempts to relate the concentrations of the metabolite trichloroacetic acid in urine to the observed health effects. It was suggested that at levels in urine of 50 mg/litre (group average, determined at end of the working day) and higher, adverse effects (mainly on the nervous system) may occur. On the basis of this conclusion, an occupational exposure limit of 135 mg/m^3 was proposed *(44)*.

In a cross-sectional study in Japanese workers, levels of total cholesterol and high-density-lipoprotein cholesterol slightly increased with increasing exposure levels. Serum enzyme activities did not increase. It was concluded that exposure to low levels of trichloroethylene

influences hepatic function, affecting cholesterol metabolism rather than causing hepatic cell damage *(45)*.

Mutagenic and carcinogenic effects
A few studies to test for genetic effects in occupationally exposed workers have been performed. In two studies of imperfect design, increased incidences of chromosome aberrations and hypoploid cells have been observed in lymphocytes of workers exposed to technical trichloroethylene. The results of other studies suggest the absence of sister chromatid exchanges when the subjects are exposed to trichloroethylene only *(3,16)*.

Three cohort studies were considered to be particularly relevant for the evaluation of trichloroethylene. Two of these studies, conducted in Sweden and Finland, involved people who had been monitored for exposure to trichloroethylene by measurement of trichloroacetic acid in urine. The levels in samples from most of the people in the two cohorts indicated relatively low levels of exposure. The third study, from the United States, covered workers, some of whom were also exposed to other solvents. The results of these studies consistently indicate an excess relative risk for cancer of the liver and biliary tract, with a total of 23 observed cases, whereas 12.87 were expected. Results for liver cancer were given separately in the studies from Finland and the United States. A total of seven cases were observed, whereas 4.00 were expected. Three case–control studies of primary liver cancer indicated elevated relative risks for people exposed to solvents, but only a few of the subjects in each study reported exposure to trichloroethylene.

With regard to non-Hodgkin lymphoma, the results of these cohort studies were also consistent; the data indicated a modest excess relative risk, with 27 cases observed and 18.9 expected. In a case–control study covering all malignant lymphomas, an elevated odds ratio for exposure to trichloroethylene was indicated on the basis of seven exposed cases. The risk for non-Hodgkin lymphoma was not increased among people assumed to have been exposed to trichloroethylene in a study in Montreal.

IARC concluded that there is limited evidence in humans for the carcinogenicity of trichloroethylene *(1)*.

Since that evaluation, a case–control study conducted in Germany has found elevated risks for kidney-cell tumours among workers exposed to both trichloroethylene and tetrachloroethylene. Although these tumours are different from those observed to be elevated in the cohort studies, the German MAK-Commission has taken this information in association with metabolic data to indicate that trichloroethylene is a human carcinogen *(46)*.

Sensory effects
The odour threshold in water for detection of trichloroethylene is 0.5 mg/litre. The odour threshold in air for recognition of trichloroethylene is 115 mg/m^3 (21.4 ppm) *(47)*. The threshold level for 50% detection in air was reported to be approximately 50 mg/m^3 *(8)*.

Evaluation of human health risks

Exposure evaluation

The average ambient air concentrations of trichloroethylene are less than 1 µg/m^3 in rural areas and up to 10 µg/m^3 in urban areas. Concentrations in indoor air are typically similar,

although higher concentrations can be expected in certain areas, e.g. in proximity to industrial operations. Inhalation of airborne trichloroethylene is the major route of exposure for the general population.

Health risk evaluation

The main health effects of concern with trichloroethylene are cancer, and effects on the liver and the CNS.

Studies in animals and humans show that the critical organs or systems for non-carcinogenic effects are the liver and the CNS. The dose–response relationship for these effects is insufficiently known, making health risk assessment for the occurrence of these effects in case of long-term exposure to low levels of trichloroethylene difficult.

IARC classified trichloroethylene as a group 2A carcinogen (probably carcinogenic to humans). This classification was based on sufficient evidence in animals and limited evidence in humans.

The available data suggest that trichloroethylene may have a weak genotoxic action *in vivo*. Several of the animal carcinogenicity studies show limitations in design. In mice, increased incidences of adenomas and carcinomas in lungs and liver were observed. In two rat studies, incidences of testicular tumours were increased. Evidence from mechanistic studies suggests that humans are likely to be less susceptible to the production of tumours as a result of exposure to trichloroethylene. However, the relevance of the observed increased lung tumours in mice and testicular tumours in rats for human cancer risks cannot be excluded. The results of the mechanistic studies do not provide full elucidation or guidance on this point.

Positive associations between exposure to trichloroethylene and risks for cancer of the liver and biliary tract and non-Hodgkin lymphomas were observed in epidemiological studies on cancer in humans. Confounding cannot be ruled out. A quantitative risk estimate cannot be made from these human data a. The increased tumours in lungs and testes observed in animal bioassays are considered to be the best available basis for the risk evaluation. However, it cannot be conclusively established whether a threshold with regard to carcinogenicity in the action of trichloroethylene may be assumed. Therefore, linear extrapolation from the animal tumour data is used, providing a conservative approach to the estimation of human cancer risk.

Using the data on the incidence of pulmonary adenomas in B3C6F1 mice and on pulmonary adenomas/carcinomas in Swiss mice unit risks of 9.3×10^{-8} and 1.6×10^{-7}, respectively, can be calculated by applying the linearized multistage model. Applying the same model on the incidence of Leydig-cell tumours in the testes of rats, a unit risk of 4.3×10^{-7} can be derived.

PBPK models have been developed for trichloroethylene. Use of these models for cancer risk estimate is not considered feasible because it is not known what an appropriate internal dose measure would be.

Guidelines

Because the available evidence indicates that trichloroethylene is genotoxic and carcinogenic, no safe level can be recommended. On the basis of the most sensitive endpoint, Leydig-cell tumours in rats, a unit risk estimate of 4.3×10^{-7} $(\mu g/m^3)^{-1}$ can be derived. The ranges of

ambient air concentrations of trichloroethylene corresponding to an excess lifetime risk of 1:10 000, 1:100 000 and 1:1 000 000 are 230, 23 and 2.3 μg/m^3, respectively.

References

1. *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).
2. *Trichloroethylene*. Geneva, World Health Organization, 1985 (Environmental Health Criteria, No. 50).
3. *Toxicological profile for trichloroethylene*. Atlanta, GA, Agency for Toxic Substances and Disease Registry, 1993 (US Public Health Service Report, No. TP-92/19).
4. GERMAN CHEMICAL SOCIETY. *Trichloroethene*. Stuttgart, Hirzel, 1994 (BUA Report 95 (June 1991)).
5. *Trichloroethylene*. *Priority substances assessment report for the Canadian Environmental Protection Act.* Ottawa, Government of Canada, Environment Canada/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 & technology*, **22:** 1381–1388 (1988).
7. CLARK, C.M. & FULLER, C.L. *Total exposure and risk assessment for drinking water contaminated with volatile organic compounds.* Springfield VA,1987, United States National Technical Information Services (NTIS No. PB-88-50602; Illinois Dept. of Energy and Natural Resources Report, No. ILENR/RE-AQ-87/22).
8. BESEMER, A.C. ET AL. *Criteriadocument over trichlooretheen* [Trichloroethylene criteria document]. The Hague, Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer, 1984 (Publikatiereeks Lucht, No. 33).
9. ULANDER, A. ET AL. Assessment of intermittent trichloroethylene exposure in vapor degreasing. *American journal of industrial medicine,* **53:** 742–743 (1992).
10. 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, 1996 (WaBoLu-Hefte 4/96).
11. DALLAS, C. E. ET AL. Physiological pharmacokinetic modeling of inhaled trichloroethylene in rats. *Toxicology and applied pharmacology,* **110:** 303–314 (1991).
12. 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).
13. FISHER, J.W. ET AL. Physiologically based pharmacokinetic modeling of the lactating rat and nursing pup: a multiroute exposure model for trichlooroethylene and its metabolite, trichloroacetic acid. *Toxicology and applied pharmacology,* **102:** 497–513 (1990).
14. 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).
15. BIRNER, G. ET AL. Nephrotoxic and genotoxic *N*-acetyl-*S*-dichlorovinyl-*L*-cysteine is a urinary metabolite after occupational 1,1,2-trichloroethene exposure in humans:

implications for the risk of trichloroethene exposure. *Environmental health perspectives,* **99:** 281–284 (1993).
16. *Trichloroethylene: assessment of human carcinogenic hazard*. Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals, 1994 (ECETOC Technical Report, No. 60).
17. GOEPTAR, A.R. ET AL. Metabolism and kinetics of trichloroethylene in relation to toxicity and carcinogenicity. Relvance of mercapturic acid pathway. *Chemical research toxicology,* **8:** 3–21 (1995).
18. STEVENS, D.K. ET AL. Adduction of hemoglobin and albumin *in vivo* by metabolites of trichloroethylene, trichloroacetate and dichloroacetate in rats and mice. *Fundamental and applied toxicology,* **19:** 336–342 (1992).
19. FISHER, J.W. ET AL. Physiologically based pharmacokinetic modeling of the pregnant rat: a multiroute exposure model for trichlooroethylene and its metabolite, trichloroacetic acid. *Toxicology and applied pharmacology,* **99:** 395–414 (1989).
20. FISHER, J.W. ET AL. Physiologically based pharmacokinetic modeling with trichloroethylene and its metabolite, trichloroacetic acid, in the rat and mouse. *Toxicology and applied pharmacology,* **109:** 183–195 (1991).
21. 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).
22. ALLEN, B.C. & FISHER, J.W. Pharmacokinetic modeling of trichloroethylene and trichloroacetic acid in humans. *Risk analysis,* **13:** 71–86 (1993).
23. BOGEN, K.T. Pharmacokinetics for regulatory risk analysis: the case of trichloroethylene. *Regulatory toxicology and pharmacology,* **8:** 447–466 (1988).
24. FISHER, J.W. & ALLEN, B.C. Evaluating the risk of liver cancer in humans exposed to trichlorethylene using physiological models. *Risk analysis,* **13:** 87–95 (1993).
25. KJELLSTRAND, P. ET AL. Trichlorooethylene: further studies of the effects on body and organ weights and plasma butyrylcholinesterase activity in mice. *Acta pharmacologica et toxicologica,* **53:** 375–384 (1983).
26. KJELLSTRAND, P. ET AL. Trichloroethylene: effects on body and organ weight s in mice, rats and gerbils. *Toxicology,* **21:** 105–115 (1981).
27. REBERT, C.S. ET AL. Sensory-evoked potentials in rats chronically exposed to trichloroethylene : predominant auditory dysfunction. *Neurotoxicology and teratology,* **13:** 83–90 (1991).
28. KULIG, B.M. The effects of chronic trichloroethylene exposure on neurobehavioral functioning in the rat. *Neurotoxicology and teratology*, **9:** 171–178 (1987).
29. BLAIN, L. ET AL. Electroretinal responses are modified by chronic exposure to trichloroethylene. *Neurotoxicology,* **15:** 627–632 (1994).
30. MALTONI, C. ET AL. Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss mice and $B3C6F_1$ mice. *Annals of the New York Academy of Sciences,* **534:** 316–342 (1988).
31. HENSCHLER, D. ET AL. Carcinogenicity study of trichloroethylene by long-term inhalation in three animal species. *Archives of toxicology,* **43:** 237–248 (1980).
32. FUKUDA, K. ET AL. Inhalation carcinogenicity of trichloroethylene in mice and rats. *Industrial health,* **21:** 243–254 (1983).
33. MALTONI, C. ET AL. Experimental research on trichloroethylene carcinogenesis. *In:* Maltoni, C. & Mehlman, M.A., ed. *Archives of research on industrial carcinogenesis*. Princeton, NJ, Princeton Scientific Publishing Co., 1986.

34 *Technical report on the carcinogenesis bioassay of trichloroethylene, CAS No. 79-01-6*. Bethesda, MD, US Department of Health, Education and Welfare, 1976 (DHEW Publication No. 76-802; US National Cancer Institute Technical Report, No. 2).
35. NATIONAL TOXICOLOGY PROGRAM. *Technical report on the carcinogenesis studies of trichloroethylene (without epichlorohydrin) in F344/N rats and B6C3F1 mice (gavage studies)*. Research Triangle Park, NC, US Department of Health and Human Services, 1990 (Report No. TR-243).
36. HENSCHLER, D. ET AL. Carcinogenicity study of trichloroethylene, with and without epoxide stabilisers, in mice. *Journal of cancer research and clinical oncology,* **107:** 149–156 (1984).
37. NATIONAL TOXICOLOGY PROGRAM. *Toxicology and carcinogenesis studies of trichloroethylene (CAS No. 79-01-6) in four strains of rats (ACI, August, Marshall, Osborne-Mendel) (gavage studies)*. Research Triangle Park, NC, US Department of Health and Human Services, 1988 (Report No. TR-273).
38. CREBELLI, R. & CARERE, A. Genetic toxicology of 1,1,2-trichloroehylene. *Mutation research,* **221:** 11-37 (1989).
39. KLIGERMAN, A.D. ET AL. Inhalation studies of the genotoxicity of trichloroethylene to rodents. *Mutation research,* **322:** 87–96 (1994).
40. SBRANA, I. ET AL. TCE induces micronuclei but not chromosomal aberrations in mouse bone marrow cells. *In*: *Abstracts of the Fourth International Conference on Environmental Mutagens, Stockholm, 1985*, p.163.
41. REBERT, C.S. ET AL. Combined effects of solvents on the rat's auditory system: styrene and trichloroethylene. *International journal of psychophysiology,* **14:** 49–59, (1993).
42. HRELIA, P. ET AL. Interactive effects between trichloroethylene and pesticides at metabolic and genetic level in mice. *Environmental health perspectives,* **102:** 31–34, (1994).
43. *Air quality guidelines for Europe.* Copenhagen, WHO Regional Office for Europe, 1987 (WHO Regional Publications, European Series, No. 23).
44. *Recommended health-based limit values in occupational exposure to selected organic solvents. Report of a WHO Study Group.* Geneva, World Health Organization, 1981 (WHO Technical Report Series, No. 664).
45. NAGAYA, T. ET AL. Subclinical and reversible hepatic effects of occupational exposure to trichloroethylene. *International archives environmental health,* **64:** 561–563 (1993).
46. DEUTSCHE FORSCHUNGSGEMEINSCHAFT. *MAK- und BAT werte Liste 1993* [MAK and BAT value list 1993]. Weinheim, VCH Verlagsgesellschaft, 1993 (Report No. 29).
47. *Hazardous Substances Data Bank*. Bethesda, MD, National Toxicology Information Program, 1995.

