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Tetrachloroethylene

Guideline

The recommended maximum acceptable concentration (MAC) for tetrachloroethylene in drinking water is 0.03 mg/L (30 µg/L).

Identity, Use and Sources in the Environment

Tetrachloroethylene (C_2Cl_4) is a non-flammable, non-viscous liquid with a density of 1.62 g/mL at 20°C, a vapour pressure of 2.5 kPa at 25°C and a water solubility of 150 mg/L at 25°C. Its octanol–water partition coefficient is reported to be in the range 758–2512 (log K_{ow} = 2.9–3.4).[1]

Tetrachloroethylene is no longer produced in Canada, but it continues to be imported,[2] primarily as a solvent for use in the dry-cleaning and metal-cleaning industries. Approximately 11.4 kt of tetrachloroethylene were used for these purposes in 1990.[3] Another major industrial use of tetrachloroethylene in Canada during 1990 (2.2 kt) was the production of chlorofluorocarbons (no longer produced in Canada). Tetrachloroethylene is also used in smaller quantities in the finishing and processing of textiles, in the manufacture of paint removers and printing inks, in the formulation of adhesives and specialized cleaning fluids and as aerosols and dye carriers.[4–7]

The majority of the tetrachloroethylene used in Canada is expected to enter the environment, primarily the atmosphere, as its uses are dispersive and do not result in its transformation or destruction. However, it has been found in groundwater, primarily after improper disposal or dumping of cleaning solvents, as a result of its low propensity for adsorption to soils and consequent leaching action. Contamination of groundwater supplies occurs sporadically and can be a problem for long periods of time because of the lack of the usual mechanisms for removal that operate with surface water supplies, such as volatilization and microbial degradation. Trichloroethylene, 1,1-dichloroethylene, cis-and trans-dichloroethylene and vinyl chloride, some of which are more toxic or more soluble than tetrachloroethylene, were found in two-thirds of the Canadian wells contaminated with tetrachloroethylene, in some cases probably as a result of microbial dechlorination of the parent compound.[8,9]

Exposure

Tetrachloroethylene has been detected in some samples of drinking water across Canada and in contaminated surface water and groundwater. This substance was detected in 39 of 90 samples of potable water obtained from 30 water treatment plants across Canada in 1979; the maximum concentration was 4 µg/L.[10] In a subsequent study, it was detected (detection limit = 0.1 µg/L) in only one of 45 samples of potable water obtained (during 1982–1983) from 10 water purification plants in the Great Lakes region.[11] During the period 1985–1988, tetrachloroethylene was detected (minimum quantitation limit = 0.5 µg/L) in two of 31 samples of (treated) drinking water obtained in Newfoundland,[12] in 14 of 23 samples of drinking water obtained in Prince Edward Island,[13] in 25 of 43 samples of drinking water obtained in Nova Scotia,[14] in 14 of 37 samples of drinking water obtained in New Brunswick[15] and in 22 of 93 samples of drinking water (detection limit = 0.05 µg/L) obtained from municipalities in the province of Quebec.[16] Tetrachloroethylene was detected at trace levels (below the detection limits of 0.2 µg/L for treated water or 3.0 µg/L for raw water) in only three of 1512 samples of water taken from 215 treated and 14 raw water supplies in Alberta between 1986 and 1991.[17] In samples of drinking water obtained from 106 sites in Ontario during the period 1988–1991, the levels of tetrachloroethylene ranged from not detectable (detection limit = 0.05 µg/L) to 5.25 µg/L.[18] Similar results were obtained for the period 1990–1993; tetrachloroethylene was detected in 14 of 28 community well supplies (50%) at a maximum concentration of 5.4 µg/L and in 33 of 96 surface water supplies (34%) at a maximum concentration of 1.4 µg/L.[19]

In 1995, a national data-gathering survey[9] was undertaken to further investigate the extent of ground-water contamination by tetrachloroethylene and to

estimate, if possible, the number of people potentially exposed through consumption of contaminated drinking water. Individual wells in rural areas were excluded because of a lack of sampling data. Additionally, it was estimated that about 20% of extant data with provincial agencies and organizations were excluded because of confidentiality concerns or time constraints and that private supplies were underrepresented by about 20%. Of the 481 municipal and 215 private domestic water supplies recorded as tested for tetrachloroethylene (detection limits were not available in many cases and were variable: range 0.05–5 µg/L, with 0.5 µg/L as the most commonly reported value), 7.3% and 4.2%, respectively, contained tetrachloroethylene. These values are believed to be representative of (groundwater) municipal supplies for the country as a whole, as they were derived largely from surveillance programs carried out in three provinces. Overall, less than 4% of supplies contained tetrachloroethylene concentrations above 1 µg/L. The average of their maximum concentrations was 22 µg/L for municipal supplies and 13 380 µg/L for private supplies (the latter was heavily influenced by two or three contamination incidents). It was estimated that about 1.7 million of the 7.1 million Canadians who rely on groundwater for household use were covered by this survey and that tetrachloroethylene was detected in water supplying about 663 000 (40%) of that population. This analysis has confirmed the finding of the assessment undertaken for the *Canadian Environmental Protection Act* (CEPA)[20] that 95% of the population served by groundwater was exposed to tetrachloroethylene concentrations below 1 µg/L; viewed another way, well over a million people have been exposed to low levels of tetrachloroethylene in their drinking water, if survey coverage is taken into consideration.

Because of the volatility of tetrachloroethylene, there is also potential for exposure in the home to airborne tetrachloroethylene released from tap water during its normal use for washing, showering and bathing in addition to drinking; hence, concomitant dermal and inhalation exposure should be considered in assessing tetrachloroethylene exposure. The experimentally determined permeability constant for dermal absorption of tetrachloroethylene[21] predicts that dermal absorption for a human adult is equivalent to the amount of tetrachloroethylene contained in 2 L of water; a dermal pharmacokinetic model by Brown and Hattis[22] gives a similar prediction of the amount in 1 L of water. The average of these two predictions (1.5 L) indicates that an amount approximately equal to the amount ingested in drinking water is taken up daily via the dermal route.

Tetrachloroethylene has been detected in outdoor and indoor air in Canada. In a national survey conducted in 1990 of 22 sites in 11 Canadian cities, mean concentrations of tetrachloroethylene in outdoor urban air ranged from 0.2 to 5.0 µg/m^3, with an overall mean of 1.15 µg/m^3 (detection limit = 0.1 µg/m^3).[23] The mean concentration of tetrachloroethylene in 40 samples of air obtained at Walpole Island (a rural location in Ontario) between January and November 1990 was 0.2 µg/m^3.[23] In 757 homes randomly selected to accurately reflect the Canadian population, tetrachloroethylene was below the detection limit in 71% (n = 537) of homes. The detection limit was calculated as 3.6 µg/m^3, too high for accurate estimation of the full distribution curve. The mean, geometric mean and median were calculated to be 3.55, 0.89 and 0.96 µg/m^3, respectively, assuming that the data follow a log normal distribution. The 90th percentile value was 8.0 ± 2.0 µg/m^3; in other words, 90% of the population is considered to be exposed at or below this value.[24,25] Reliable quantitative information on the level of tetrachloroethylene in a variety of foodstuffs in Canada was not identified.

Based on a range of mean concentrations (0.1–0.9 µg/L, with the average of the means 0.5 µg/L) of tetrachloroethylene in drinking water from national and provincial surveys,[26] the mean concentration of 1.15 µg/m^3 (range 0.2–5.0 µg/m^3) of tetrachloroethylene in outdoor air from a national survey of sites across Canada[23] and the estimate (based on the log normal distribution curve) of the mean concentration of tetrachloroethylene (3.6 µg/m^3) in the indoor air of 757 randomly selected homes within Canada (range 0.1–8.0 µg/m^3 for the 10th and 90th percentiles, respectively),[24] the average daily intake* of tetrachloroethylene for an adult was estimated to be approximately 67.6 µg from air (62.2 µg from indoor air and 5.4 µg from outdoor air) and 0.75 µg from oral intake of drinking water, with an equal amount from dermal absorption. The average daily intake of tetrachloroethylene from food has been estimated (based on the levels reported in market basket surveys in the United States, according to Daft[27] and Heikes[28]) to be approximately 8.4 µg. The greatest proportion (approximately 80%) of the total daily intake of tetrachloroethylene (77.5 µg) is from indoor air.

Based on the above mean values, drinking water contributes approximately 1.0% to the total daily intake of tetrachloroethylene for the general population, or 1.9% if the contribution from incidental dermal intake is included. The direct contribution from drinking water to

* The adult is assumed to consume 1.5 L of water per day and to spend four hours per day outdoors and the rest indoors.[23] The breathing rates are assumed to be 1.17 m^3/h for moderate activity (four hours outdoors and 12 hours indoors) and 0.41 m^3/h while sleeping (eight hours).

total daily intake can be much larger for individuals whose drinking water comes from contaminated wells; for example, the contribution rises to 8.2% (or 16% if incidental dermal intake is considered) at a tetrachloroethylene concentration of 5 µg/L in drinking water.

Analytical Methods and Treatment Technology

Tetrachloroethylene may be analysed by purge-and-trap gas chromatographic methods, in which an inert gas is bubbled through the sample and the substance is trapped in an adsorbent material. The adsorbent is subsequently heated to release the tetrachloroethylene onto a gas chromatographic column. Tetrachloroethylene can be detected by mass spectroscopy (Method 6210C or D), by photoionisation (Method 6220C) or through the use of halide-sensitive electrolytic conductivity or microcoulometric detectors (Method 6230C or D). Detection limits range from 0.01 to 0.5 µg/L, and the methods are suitable for levels ranging up to 200 and 1500 µg/L, depending upon the specific protocol.[29] These methods are the same as U.S. Environmental Protection Agency Methods 524, 502.1, 502.2 and 503.1.[30]

In a national survey in the United States, the results of intra- and interlaboratory comparison tests with measures of ±40% precision and accuracy indicated that the practical quantitation limit (PQL) for tetrachloroethylene was 5 µg/L.[30] A PQL of 1 µg/L was chosen by the state of New Jersey, based on the results of a similar set of tests conducted in certified laboratories in that state for which the mean detection limit was 0.17 µg/L and the PQL was greater than 0.45 but less than 2.3 µg/L.[31]

Tetrachloroethylene may be removed from water supplies by air stripping or treatment with granular activated carbon. The former method is considered to be the most cost-effective.[32] Removal efficiencies for various air stripping techniques range from 40% for multiple tray induced air up to 90% for packed tower or diffused air, at air:water ratios up to 10:1,[32] or up to 99.8% at a ratio of 20:1 or greater.[33] A disadvantage of air stripping is that the tetrachloroethylene is transferred to ambient air, which may create a point source of pollution.

Treatment with granular activated carbon is also an effective means of removing tetrachloroethylene from drinking water supplies. Based on pilot-scale observations, the loading capacity (number of cubic metres of water that can be treated by a cubic metre of carbon before capacity is exhausted) at an influent concentration of 1000 µg/L ranged from 20 700 to 32 700 for target effluent concentrations of 1 and 100 µg/L, respectively. Loading capacity increased at lower influent concentrations of tetrachloroethylene.[33]

For individual home use, a point-of-entry home water filtration unit based on activated carbon is recommended, as it will also address concomitant exposure through inhalation and the dermal route. A point-of-use water filter may be used for drinking water only. Boiling for 3–5 minutes can also remove 99% of tetrachloroethylene from water.[33]

Health Effects

Pharmacokinetics

Quantitative data on the absorption of tetrachloroethylene in humans are limited, although this substance is likely readily taken up through the lungs.[34] Based on the levels of tetrachloroethylene in the blood and expired air of volunteers exposed (in such a way as to prevent its inhalation) to 600 ppm (4068 mg/m^3) for 3.5 hours, Riihimaki and Pfaffli[35] concluded that, compared with the amount of tetrachloroethylene that could have been absorbed via inhalation, only about 1% had been absorbed through the skin. Tetrachloroethylene is likely to be completely absorbed following ingestion, based on the results of studies conducted with rodents, in which the substance was administered orally in drinking water[36] or in a single dose dissolved in corn oil.[37,38]

The major metabolites of tetrachloroethylene in the urine of laboratory animals (rodents) are trichloroacetic acid and oxalic acid. Minor metabolites that have been detected in some, but not all, studies include trichloroethanol, dichloroacetic acid and N-oxalylaminoethanol.[34,38] Minor amounts (1–2%) of carbon dioxide (which is eliminated in the expired air) may also be produced from the metabolism of tetrachloroethylene.[37] Trichloroacetic acid has been identified as the principal metabolite of tetrachloroethylene in humans[1,34]; however, only a very small amount (1–2%) of the tetrachloroethylene absorbed by humans is metabolized and subsequently excreted in the urine as trichloroacetic acid. Most of the absorbed tetrachloroethylene is eliminated unchanged in expired air.[39–45] The available data indicate that the metabolism of tetrachloroethylene to trichloroacetic acid is greater in mice than in either rats[37,46,47] or humans.[48]

In rodents, tetrachloroethylene may also be conjugated with cellular glutathione, followed by loss of glutamine and glycine, producing 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 β-lyase enzyme, producing the (putative) highly reactive intermediate trichlorovinylthiol, which, upon rearrangement, may be capable of forming covalent links with proteins or

nucleic acids. Formation of the tetrachloroethylene–glutathione conjugate takes place in the liver, with subsequent metabolism occurring primarily in the kidney.[49] The conjugation of tetrachloroethylene with glutathione and activation of S-(1,2,2-trichlorovinyl)-L-cysteine by the renal β-lyase occur to a greater extent in rats than in mice.[38,49] Based on the results of dose–response studies in rodents, Green *et al*.[50] concluded that the glutathione conjugation pathway of tetrachloroethylene metabolism becomes quantitatively important only once the oxidative pathway is saturated.

Formation of the tetrachloroethylene–glutathione conjugate was not detected in *in vitro* enzymatic assays conducted with human hepatic extracts (number of samples not specified),[49] and the metabolism of S-(1,2,2-trichlorovinyl)-L-cysteine in male rats is approximately two-fold greater than in female rats and 30-fold higher than in mice or humans (three or four samples from either sex).[50] Thus, conjugation of tetrachloroethylene with glutathione and activation of S-(1,2,2-trichlorovinyl)-L-cysteine by the renal β-lyase, although taking place in rats and (to some extent) mice, may not be relevant to humans (or the enzymatic activities in humans are much less).[49]

Effects on Humans

The accidental (acute) exposure of humans to elevated concentrations of tetrachloroethylene produces hepatotoxic and nephrotoxic effects and death.[1,34,42,51–53] Following the short-term exposure of volunteers to concentrations of tetrachloroethylene ranging from 106 to 2000 ppm (719–13 560 mg/m^3), symptoms ranging from mild eye and nasal irritation to dizziness and anaesthesia were observed[54,55]; with increasing concentrations of tetrachloroethylene, the severity of the effects increased, while the time of onset became shorter.

The incidence of or mortality due to cancer associated with occupational exposure to tetrachloroethylene has been examined in case–control studies of laundry and dry-cleaning workers with liver or bladder cancer and in cohort studies of workers employed in the dry-cleaning and laundry industries or at an aircraft maintenance facility (see reference 56 for a review). Although increased risks of liver cancer, increased mortality due to cancer of the cervix, bladder, kidney, lung and respiratory system, skin, genitals, and oesophagus, increased mortality due to lymphosarcoma, multiple myeloma and non-Hodgkin's lymphoma, and an increased incidence of liver and pancreatic cancer have been reported in individual studies, there is little consistent evidence for increases in cancer of a specific type in these occupationally exposed populations. Moreover, workers in these industrial settings were probably exposed to other solvents in addition to tetrachloroethylene; as well, in virtually all of these epidemiological investigations, little or no quantitative information concerning the level of exposure to tetrachloroethylene was presented. Notably, in a small study of dry-cleaning workers, there was no increase in mortality due to cancer in a subcohort of 615 individuals exposed only to tetrachloroethylene. In addition, in many of the available studies, individuals who were employed in the dry-cleaning and laundry industries were analysed as a single group, although their exposure to tetrachloroethylene is likely to be quite different, and the impact of potential confounding factors such as smoking on the morbidity or mortality due to cancer was not taken into account.

The potential effects of occupational exposure to tetrachloroethylene on reproduction and development have been examined in a number of case–control, cross-sectional and cohort studies (see reference 56 for a review). An increased risk of spontaneous abortion was reported in some, but not all, studies. Occupational exposure to tetrachloroethylene was not associated with an increased risk of birth defects or significant alterations in the quality of sperm; however, in one report, there was a positive association between idiopathic infertility in females and exposure to dry-cleaning chemicals. These workers were likely exposed to other solvents, and quantitative information on exposure to tetrachloroethylene was usually not presented.

The effects of chronic exposure to tetrachloroethylene on renal function have been examined in a limited number of cross-sectional studies of workers employed in the dry-cleaning industry (see reference 56 for a review). Other than a slight increase in the level of lysozyme in the urine of workers exposed to tetrachloroethylene, there has been no evidence of renal dysfunction.

Ikeda *et al*.[57] found no significant difference in the frequency of chromosomal aberrations or sister chromatid exchange in lymphocytes from 10 workers exposed to 10–220 ppm (67.8–1492 mg/m^3) tetrachloroethylene compared with 11 unexposed individuals. Seiji *et al*.[58] reported that the frequency of sister chromatid exchange in lymphocytes obtained from 27 smoking or non-smoking workers (of either sex) employed in dry-cleaning establishments (and exposed to a geometric mean [time-weighted average] con-centration of 10 ppm [67.8 mg/m^3] for 41 months) was not significantly different from that in 26 controls; however, the frequency of sister chromatid exchange in 12 male smokers exposed to tetrachloroethylene was significantly ($p < 0.05$) greater (18%) than in three male (control) non-smokers.

Effects on Laboratory Animals

The acute toxicity of tetrachloroethylene in laboratory animals is relatively low. LC_{50}s for the four-hour inhalation exposure of rodents to tetrachloroethylene range from 2445 ppm (16 577 mg/m^3) to 5200 ppm (35 256 mg/m^3).[59–61] The LD_{50} for the oral administration of tetrachloroethylene to rodents ranges from 3.0 to 12.9 g/kg bw.[62–65]

When tetrachloroethylene was administered orally (in doses ranging from 2200 to 8850 mg/kg bw) to Sprague-Dawley rats, tremors, ataxia and central nervous system depression were observed prior to death of the animals.[62] Ambulatory (open field) behaviour was transiently increased immediately after male Sprague-Dawley rats were exposed via inhalation to 200 ppm (1356 mg/m^3) tetrachloroethylene for four days.[66]

Dose-dependent adverse effects in the liver, kidney, and haematopoietic, reproductive and central nervous systems are associated with the repeated exposure of laboratory animals to tetrachloroethylene, with mice being more sensitive than rats to the hepatotoxic effects. A lowest-observed-effect level (LOEL) of 100 mg/kg bw per day in B6C3F$_1$ mice and a no-observed-effect level (NOEL) of 500 mg/kg bw per day in Sprague-Dawley rats were derived on the basis of the results from a study in which this substance was administered (orally) to these animals for 11 consecutive days; effects observed at the LOEL were an increased liver to body weight ratio and hepatocellular hypertrophy and swelling.[46]

In a study in which the hepatotoxicity of tetrachloroethylene in mice was assessed, groups (4–26, depending upon the dose) of male (outbred) Swiss-Cox mice were administered (by gavage) tetrachloroethylene (dissolved in corn oil) at doses of 0, 20, 100, 200, 500, 1000, 1500 or 2000 mg/kg bw per day five times weekly for six weeks.[67] Mice were sacrificed after the last dose and examined; the liver was examined histopathologically. Liver to body weight ratios and hepatic triglyceride levels were significantly increased at doses of 100 mg/kg bw per day and above. Hepatic glucose-6-phosphatase activity was reduced, whereas serum glutamate–pyruvate transaminase activity was increased at doses of 500 mg/kg bw per day and above. Data on histopathological changes in the liver were presented only for the controls and mice administered tetrachloroethylene doses of 200 or 1000 mg/kg bw per day. Mice administered 200 or 1000 mg/kg bw per day had hepatic damage (degeneration, karyorrhexis, necrosis, polyploidy), the severity of which increased with dose. No histopathological or biochemical changes were found at a tetrachloroethylene dose of 20 mg/kg bw per day, although liver weights were slightly (6%) but not significantly increased (no-observed-adverse-effect level [NOAEL] = 20 mg/kg bw per day, equivalent to 14 mg/kg bw per day after conversion from a five-day to a seven-day dosing basis).

In a study conducted by Hayes *et al*.,[62] groups of 20 male and 20 female Sprague-Dawley-derived CD rats were administered tetrachloroethylene (emulsified in 4% Emulphor) at "theoretical" daily doses of 14, 400 and 1400 mg/kg bw per day in their drinking water for 90 days. Controls were administered drinking water or vehicle (4% Emulphor) in drinking water in the same fashion. Fluid consumption declined for all animals during the course of the study. Significantly lower weight gain was observed in the males receiving tetrachloroethylene at 1400 mg/kg bw per day and in the females receiving tetrachloroethylene at 400 and 1400 mg/kg bw per day. No significant changes were observed in urine chemistry. A slight increase was found in serum 5'-nucleotidase activity in the high-dose females and mid-and high-dose males. Ratios of liver or kidney to body weights were increased at the highest dose level for both sexes, as well as in mid-dose males. Animals receiving 14 mg/kg bw per day tetrachloroethylene apparently suffered no adverse health effects (NOEL = 14 mg/kg bw per day); however, tissues were not examined histopathologically, and it is not entirely clear how these "theoretical" daily doses were determined or maintained, as the daily fluid consumption of all animals declined during the course of the study.

Marth[68] reported reversible erythropoietic damage in a study in which female NMRI mice received low concentrations of tetrachloroethylene in drinking water (equivalent to 50 and 100 µg/kg bw per day) over a period of 49 days. This result has not been confirmed in other strains of mice, and no haematological effects were observed in rats administered tetrachloroethylene in drinking water at a dose of 14 mg/kg bw per day for 90 days.[52] Clear evidence of renal toxicity (increased kidney to body weight ratio; increased urinary volume and glucose level; increases in alkaline phosphatase and N-acetyl-D-glucosaminidase activities; increased size and number of protein [hyaline] droplets; tubular casts and basophilic proximal tubular regeneration) was observed in male F344 rats administered (by gavage) tetrachloroethylene (dissolved in corn oil) at a dose of 1.5 g/kg bw per day for 42 consecutive days.[50]

The toxicological effects produced by the chronic exposure of laboratory animals to tetrachloroethylene have been examined only in studies designed primarily to assess the carcinogenic potential of this substance. In a National Toxicology Program (NTP) study, the exposure (via inhalation for six hours per day, five days per week for 103 weeks) of F344/N rats or B6C3F$_1$ mice to 200 or 400 ppm (1356 or 2712 mg/m^3) tetrachloroethylene produced a small (but not statistically significant) increase in the incidence of renal tubular cell adenomas and adenocarcinomas in male rats but not

female rats or $B6C3F_1$ mice (of either sex), compared with unexposed controls.[59] The incidence of renal tubular cell adenomas and adenocarcinomas in groups of male rats exposed to 0, 200 or 400 ppm (0, 1356 or 2712 mg/m^3) tetrachloroethylene was 1/49, 3/49 and 2/50 (adenomas) and 0/49, 0/49 and 2/50 (adenocarcinomas). The incidence of testicular interstitial tumours (39/49 and 41/50) in males exposed to 200 or 400 ppm (1356 or 2712 mg/m^3) tetrachloroethylene was slightly (but significantly) increased compared with controls (35/50), although the increase was not considered to be substance related, as the incidence in both exposed groups was similar to the overall incidence (89%) observed in historical controls.[59] In male and female rats exposed to 0, 200 and 400 ppm (0, 1356 or 2712 mg/m^3) tetrachloroethylene, the incidence of mononuclear cell leukaemia was 28/50, 37/50 and 37/50 (males) and 18/50, 30/50 and 29/50 (females). However, it should be noted that in this particular study, the incidence of this type of tumour (56% and 36%) in the male and female non-exposed controls was higher than in historical controls (29% and 19%). Toxic effects produced by chronic exposure (via inhalation for six hours per day, five days per week over a period of 103 weeks) of F344/N rats to tetrachloroethylene included a significant reduction in their survival, an increased incidence of renal karyomegaly in both males and females and renal tubular cell hyperplasia in the males, an increased incidence of nasal cavity thrombosis and nasal squamous metaplasia, as well as an increased incidence of adrenal medullary (males) and cortical (females) hyperplasia (lowest-observed-adverse-effect level [LOAEL] = 200 ppm; 1356 mg/m^3).[59]

Enhanced cellular proliferation resulting from cell damage produced by the renal accumulation of α_{2u}-globulin (i.e., hyaline droplet formation resulting in hyaline droplet nephropathy) and the formation of genotoxic metabolites of tetrachloroethylene within the kidney have been proposed as mechanisms by which tetrachloroethylene induces the formation of kidney tumours in male rats exposed to this substance. The mechanism by which structurally diverse hydrocarbons (including tetrachloroethylene) induce hyaline droplet nephropathy in male rats has been well documented.[69–71] Hyaline droplet formation has been observed in the kidneys of male F344 rats exposed for short periods to concentrations of tetrachloroethylene higher than those administered in the NTP bioassay (e.g., following exposure [by inhalation for up to 10 days] to 1000 ppm [6780 mg/m^3] tetrachloroethylene).[50] Whereas hyaline droplet formation has been observed in the kidneys of male F344 rats receiving tetrachloroethylene (orally) at a dose of 1 g/kg bw per day for 10 days[69] or 1.5 g/kg bw per day for 42 days,[50] a similar effect was not observed in female F344 rats.[69]

It has also been proposed that covalent binding to nucleic acids or proteins of a reactive metabolite produced in the kidney by the glutathione conjugation pathway of tetrachloroethylene metabolism (which may become quantitatively important upon saturation of the oxidative pathway[50]) may also play a role in the induction of renal tumours in male rats.[49,50,72–75]

The exposure (via inhalation for six hours per day, five days per week for 103 weeks) of $B6C3F_1$ mice to 0, 100 or 200 ppm (0, 678 or 1356 mg/m^3) tetrachloroethylene produced an increase in the incidence of hepatocellular carcinomas in both males and females (7/49, 25/49 and 26/50 in males and 1/48, 13/50 and 36/50 in females, respectively).[59] The incidence of hepatocellular adenomas (12/49, 8/49 and 19/50) in male mice exposed to 0, 100 or 200 ppm (0, 678 and 1356 mg/m^3) tetrachloroethylene was increased only at the highest concentration.[59] Toxic effects produced by the chronic exposure (via inhalation for six hours per day, five days per week over a period of 103 weeks) of $B6C3F_1$ mice to tetrachloroethylene included diminished survival, an increased incidence of renal nephrosis and tubular cell karyomegaly, an increased number of renal casts, as well as increased lung congestion, hepatic degeneration and necrosis (LOAEL = 100 ppm; 678 mg/m^3).[59]

Available data indicate that the hepatotoxic effects of tetrachloroethylene in mice are due principally to trichloroacetic acid, a metabolite of tetrachloroethylene. Data also indicate (although it has not been proven) that peroxisomal proliferation may play an important role in the development of these tumours. Trichloroacetic acid is a potent inducer of peroxisomal proliferation in the liver of rodents; in some,[76,77] but not all,[78] studies, the effect of trichloroacetic acid on hepatic peroxisomal proliferation was greater in mice than in rats. Moreover, trichloroacetic acid inhibits gap junction-mediated intercellular communication in hepatocytes from mice but not rats.[79] Thus, the increased incidence of hepatic tumours in mice but (apparently) not rats exposed to tetrachloroethylene is consistent with the greater sensitivity of mice (compared with rats) to increases in hepatic peroxisomal proliferation and disruptions of intercellular communication induced by trichloroacetic acid. If increased peroxisomal proliferation plays a critical role in the development of hepatic tumours in rodents exposed to specific substances, the observation (based on limited available data) that trichloroacetic acid stimulates such proliferation in rodent but not human hepatocytes (n = 2) *in vitro*[78] suggests that these tumours are unlikely to be relevant to humans or, at least, that humans are likely to be much less sensitive to the induction of hepatic tumours by tetrachloroethylene.

The carcinogenicity of orally administered tetrachloroethylene was examined in a study in which

this substance (dissolved in corn oil) was administered (by gavage) to 50 Osborne-Mendel rats or 50 $B6C3F_1$ mice (of both sexes) for five days per week over a 78-week period, followed by an observation period of 32 or 12 weeks, respectively.[80] Groups of 20 rats and 20 mice (of both sexes) were given vehicle (corn oil) alone or left untreated. The time-weighted average daily doses of tetrachloroethylene for the male and female rats were 471 and 941 mg/kg bw and 474 and 949 mg/kg bw, respectively, whereas the daily doses for the male and female mice were 536 and 1072 mg/kg bw and 386 and 772 mg/kg bw, respectively.[80] Exposure to tetrachloroethylene produced a statistically significant increase in the incidence of hepatocellular carcinomas in both male and female mice; however, a number of considerations limit interpretation of the results. Survival rates of both the rats and mice were reduced in the exposed groups. Both the control and treated rats exhibited evidence of respiratory disease and pneumonia. Additionally, questions have been raised concerning the large volume of vehicle administered and the purity of the tetrachloroethylene used in this study.[1,34] Based on the results of studies in which laboratory animals were administered tetrachloroethylene orally, the evidence concerning the potential of tetrachloroethylene to act as a tumour "promoter" in a liver tumour induction assay system is equivocal.[81,82] Owing to the limitations of other carcinogenesis bioassays in which laboratory animals were administered tetrachloroethylene orally,[80–82] via inhalation,[83] via intraperitoneal injection[84,85] or via dermal exposure,[86] the results of these investigations are not useful in assessing the weight of evidence of carcinogenicity.

The weight of evidence indicates that tetrachloroethylene is not genotoxic (based on examination of a range of genetic end-points in both *in vitro* and *in vivo* bioassays) or teratogenic, although it has induced minor embryotoxic and foetotoxic effects, but only at doses or concentrations toxic to the mothers (see reference 56 for a review).

Classification and Assessment

Epidemiological studies concerning the carcinogenicity of tetrachloroethylene in humans are limited principally to investigations of workers employed in the dry-cleaning and laundry industries (usually combined) who were likely exposed to several substances in addition to tetrachloroethylene and for whom quantitative data on cumulative exposure were not available. Although increased mortality and morbidity due to various types of cancer have been observed in workers employed in this occupational setting, the available information is considered inadequate to assess the carcinogenicity of tetrachloroethylene in humans, owing to the lack of consistency of reported results and to possible confounding by concomitant exposure to other substances that may have contributed to the observed effects.

An increased incidence of renal tubular cell adenomas and adenocarcinomas (although not statistically significant) in male rats, mononuclear cell leukaemias in male and female rats and hepatocellular adenomas (males) and carcinomas (male and female) in mice exposed by the inhalation route to tetrachloroethylene has been observed in an NTP carcinogenesis bioassay.[59] Generally, a substance for which there is adequate evidence of carcinogenicity in two species of laboratory animals (as observed in the NTP carcinogenesis bioassay for tetrachloroethylene) would be categorized as being probably carcinogenic to humans. However, consideration of data on possible mechanisms of action reduces the relevance of several of the increases in tumour incidence observed in the NTP bioassay in assessing the weight of evidence for the carcinogenicity of tetrachloroethylene to humans. Owing to quantitative and qualitative differences in the metabolism of tetrachloroethylene in rats and humans, the induction of renal tumours in (specifically) male rats and liver tumours in mice exposed to tetrachloroethylene may not be relevant to humans (or, at least, humans may be much less sensitive to such effects). The results considered most pertinent in assessing the weight of evidence for carcinogenicity are the small increase in the incidence of spontaneously occurring mononuclear cell leukaemias in a single species (i.e., male and female F344 rats) in the NTP bioassay, in which the incidence of this tumour in the non-exposed (control) rats was higher than that observed in historical controls.[59] The proportions of animals with this tumour in the high-dose group of males and females were 74% and 58%, respectively, compared with 56% and 36% in the concurrent control groups and 29% and 19% in historical controls.[59]

On the basis of these observations, tetrachloroethylene has been classified as being possibly carcinogenic to humans. Generally, for compounds classified in this way, a tolerable daily intake (TDI) is derived on the basis of division of a NO(A)EL or LO(A)EL by an uncertainty factor, which, when considered appropriate, takes into account the limited evidence of carcinogenicity.

The available data derived from epidemiological and clinical studies in humans are considered inadequate to serve as a basis for development of a TDI. A TDI has therefore been derived on the basis of results from the longest-term study of adequate design in which tetrachloroethylene was administered orally to laboratory animals in the most appropriate vehicle. For tetrachloroethylene, the (oral) TDI is derived as follows:

$$\text{TDI} = \frac{14 \text{ mg/kg bw per day}}{1000} = 0.014 \text{ mg/kg bw per day}$$

where:

- 14 mg/kg bw per day is the NOEL in the longest-term adequate study in which tetrachloroethylene was administered in drinking water[62]**; the critical effects in this study were increased liver and kidney to body weight ratios in rats
- 1000 is the uncertainty factor (×10 for interspecies variation; ×10 for intraspecies variation; ×10 for use of a subchronic study — available chronic studies in which effects were observed at all administered doses were considered inadequate as a basis for development of meaningful effect levels or comparison with those reported in subchronic studies. An additional factor for the limited evidence of carcinogenicity has not been incorporated, as this evidence [mononuclear cell leukaemias in rats] is not related to the critical effect on which the TDI is based. Moreover, the weight of evidence from a battery of genotoxicity tests indicates that this compound is not genotoxic).

Rationale

As tetrachloroethylene has been classified as being possibly carcinogenic to humans, the maximum acceptable concentration (MAC) in drinking water is derived from the TDI as follows:

$$\text{MAC} = \frac{0.014 \text{ mg/kg bw per day} \times 70 \text{ kg bw} \times 0.1 \times 0.5}{1.5 \text{ L/d}} \approx 0.03 \text{ mg/L}$$

where:

- 0.014 mg/kg bw per day is the TDI, as derived above
- 70 kg bw is the average body weight of an adult
- 0.1 is the proportion of total tetrachloroethylene intake allocated to drinking water
- 0.5 is an additional modifying factor applied to account for dermal absorption
- 1.5 L/d is the average daily consumption of drinking water for an adult.

Available data indicate that the intake of tetrachloroethylene through ingestion in drinking water normally contributes approximately 1% of total intake. However, normal allocation factors based on average exposures are not meaningful for developing guidelines for chemicals, such as tetrachloroethylene, that occur sporadically in drinking water as a consequence of gross pollution, at concentrations at least one order of magnitude above the average (in which case intake through drinking water is more likely to approach 10% of total intake). Moreover, such contamination is likely to persist for years.

** A TDI of approximately 0.014 mg/kg bw per day could also be derived based on the NOAEL of 20 mg/kg bw per day (equivalent to 14 mg/kg bw per day after conversion from a five-day to a seven-day dosing basis) from the study in which mice were administered this substance (by gavage in corn oil) five days per week for six weeks.[67]

As household water supplies are normally used for washing, showering and bathing in addition to drinking, concomitant dermal and inhalation exposure should also be considered for highly volatile organics such as tetrachloroethylene, when data are available. A modifying factor of 0.5 was applied to the allocation factor to account for dermal absorption from bathing or showering, giving an overall allocation factor of 0.05.

No quantitative estimate of concomitant inhalation exposure in terms of the equivalent number of litres of water was attempted. One approach to allowing for this contribution from inhalation exposure is to take the 90th percentile (8.0 µg/m^3) of the randomized national indoor air survey[24] as the indoor air concentration, based on the assumption that a person with 30 µg/L (the MAC) of tetrachloroethylene in drinking water would be near the top end of the distribution curve for indoor air levels. This would result in a daily intake of about 138.2 µg/d from indoor air. Using the average food intake and average outdoor value for tetrachloroethylene in ambient air as before, the total daily intake for a person with 30 µg/L in drinking water is estimated to be 242 µg, or 25% of the adult daily intake of 980 µg, as indicated by the oral TDI of 0.014 mg/kg bw per day. The allocation factor of 10% thus gives ample allowance for the additional unquantified exposure that will come from inhalation of volatilized tetrachloroethylene during household and personal use of water, such as showering.

The documentation and assessment for this guideline were based primarily on information presented previously in the CEPA assessment report on tetrachloroethylene[56] and accompanying unpublished supporting documentation.[20] The CEPA assessment on tetrachloroethylene was based on data identified prior to April 1992.

References

1. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for tetrachloroethylene (update, April 1993). U.S. Public Health Service (1993).

2. Chen, E.C. Tetrachloroethylene: background document for “The strategic options report” [draft]. Chemical Industries Division, Industrial Programs Branch, Environment Canada, March (1993).

3. Corpus Information Services (CIS). CPI product profile, perchloroethylene. Don Mills, Ontario (1990).

4. International Agency for Research on Cancer (IARC). Some halogenated hydrocarbons. Monogr. Eval. Carcinog. Risk Chem. Man, 20: 491–514 (1979).

5. Verschueren, K. Handbook of environmental data on organic chemicals. 2nd edition. Van Nostrand Reinhold Co., New York, NY. pp. 1076–1080 (1983).

6. World Health Organization (WHO). Tetrachloroethylene. Environmental Health Criteria 31, Geneva (1984).

7. Environment Canada. Chlorinated hydrocarbons use pattern update 1989. Commercial Chemicals Branch (1990).

8. Boyle, C.D. Interpretation of literature dealing with microbial metabolization of PERC, TCE, and related compounds in groundwater. Report prepared for Monitoring and Criteria Division, Health Canada. Research and Productivity Council, Fredericton (1995).

9. Raven Beck Environmental Ltd. Survey of tetrachloroethylene and trichloroethylene occurrences in Canadian groundwater. Report prepared for Monitoring and Criteria Division, Health Canada, Ottawa (1995).

10. Otson, R., Williams, D.T. and Bothwell, P.D. Volatile organic compounds in water at thirty Canadian potable water treatment facilities. J. Assoc. Off. Anal. Chem., 65: 1370–1374 (1982).

11. Otson, R. Purgeable organics in Great Lakes raw and treated water. Int. J. Environ. Anal. Chem., 31: 41–53 (1987).

12. Environment Canada. Atlantic Region Federal–Provincial Toxic Chemical Survey of Municipal Drinking Water Sources. Data summary report 1985–1988, Province of Newfoundland. Publication No. IWD-AR-WQB-89-157, Inland Waters Directorate, Moncton (1989).

13. Environment Canada. Atlantic Region Federal–Provincial Toxic Chemical Survey of Municipal Drinking Water Sources. Data summary report 1985–1988, Province of Prince Edward Island. Publication No. IWD-AR-WQB-89-156, Inland Waters Directorate, Moncton (1989).

14. Environment Canada. Atlantic Region Federal–Provincial Toxic Chemical Survey of Municipal Drinking Water Sources. Data summary report 1985–1988, Province of Nova Scotia. Publication No. IWD-AR-WQB-89-154, Inland Waters Directorate, Moncton (1989).

15. Environment Canada. Atlantic Region Federal–Provincial Toxic Chemical Survey of Municipal Drinking Water Sources. Data summary report 1985–1988, Province of New Brunswick. Publication No. IWD-AR-WQB-89-155, Inland Waters Directorate, Moncton (1989).

16. Quebec Ministry of the Environment. Data collected under the Programme de Surveillance des Micro-polluants (1990).

17. Halina, G.P. Personal communication. Municipal Branch, Environmental Protection Services, Alberta Environment (1991).

18. Ontario Ministry of the Environment. Information provided under the Drinking Water Surveillance Program (1991).

19. Ontario Ministry of Environment and Energy. Information provided under the Drinking Water Surveillance Program (1993).

20. Health and Welfare Canada. Tetrachloroethylene. Supporting documentation, health-related sections for the priority substance assessment report. Unpublished (1993).

21. Bogen, K.T., Colston, B.W., Jr. and Machicao, L.K. Dermal absorption of dilute aqueous chloroform, trichloroethylene, and tetrachloroethylene in hairless guinea pigs. Fundam. Appl. Toxicol., 18: 30–39 (1992).

22. Brown, H.S. and Hattis, D. The role of skin absorption as a route of exposure to volatile organic compounds in household tap water: a simulated kinetic approach. J. Am. Coll. Toxicol., 8: 839–851 (1989).

23. Dann, T. and Wang, D. Measurement of volatile organic compounds in Canada 1987–1990. Pollution Measurement Division Report 923, River Road Environmental Technology Centre, Conservation and Protection, Environment Canada (1992).

24. Otson, R., Fellin, P. and Whitmore, R. A national pilot study on occurrence of airborne VOCs in residences. Proceedings of the U.S. Environmental Protection Agency/Air & Waste Management Association Symposium on Measurement of Toxic and Related Air Pollutants, May 1992, Durham, NC (1992).

25. Otson, R. Volatile organic chemical (VOC) concentrations in Canadian homes. Unpublished study with statistical analysis by M. Walker, Biostatistics Division, Environmental Health Directorate, Health Canada (1993).

26. Health Canada. Human health risk assessment for priority substances. Supply and Services Canada, Ottawa (1994).

27. Daft, J.L. Rapid determination of fumigant and industrial chemical residues in food. J. Assoc. Off. Anal. Chem., 71: 748–760 (1988).

28. Heikes, D.L. Purge and trap method for determination of volatile halocarbons and carbon disulfide in table-ready food. J. Assoc. Off. Anal. Chem., 70: 215–226 (1987).

29. American Water Works Association, American Public Health Association and Water Pollution Control Federation. Standard methods for the examination of water and wastewater. 18th edition. American Public Health Association, Washington, DC. pp. 6-26 to 6-30, 6-42 to 6-46, 6-51 to 6-57 (1992).

30. U.S. Environmental Protection Agency. National primary drinking water regulations; volatile synthetic organic chemicals, proposed rules. Fed. Regist., 50 (Nov. 13): 46905–46908 (1985).

31. Oxenford, J.L., McGeorge, L.J. and Jenniss, S.W. Determination of practical quantitation levels for organic compounds in drinking water. J. Am. Water Works Assoc., 81: 149–154 (1989).

32. Health and Welfare Canada. Guidelines for Canadian drinking water quality, water treatment principles and applications, a manual for production of drinking water. Canadian Water and Wastewater Association, Ottawa (1993).

33. Love, O.T., Jr. and Eilers, R.G. Treatment of drinking water containing trichloroethylene and related industrial solvents. J. Am. Water Works Assoc., 74: 413–425 (1982).

34. U.S. Environmental Protection Agency. Health assessment report for tetrachloroethylene (perchloroethylene). Final report. PB85-249707, Office of Environmental Health and Assessment, Washington, DC (1985).

35. Riihimaki, V. and Pfaffli, P. Percutaneous absorption of solvent vapors in man. Scand. J. Work Environ. Health, 4: 73–85 (1978).

36. Frantz, S.W. and Watanabe, P.G. Tetrachloroethylene: balance and tissue distribution in male Sprague-Dawley rats by drinking water administration. Toxicol. Appl. Pharmacol., 69: 66–72 (1983).

37. Pegg, D.G., Zempel, J.A., Braun, W.H. and Watanabe, P.G. Disposition of tetrachloro(^{14}C)ethylene following oral and inhalation exposure in rats. Toxicol. Appl. Pharmacol., 51: 465–474 (1979).

38. Dekant, W., Metzler, M. and Henschler, D. Identification of S-1,2,2-trichlorovinyl-N-acetylcysteine as a urinary metabolite of tetrachloroethylene: bioactivation through glutathionine conjugation as a possible explanation of its nephrocarcinogenicity. J. Biochem. Toxicol., 1: 57–72 (1986).

39. Monster, A.C., Boersma, G. and Steenweg, H. Kinetics of tetrachloroethylene in volunteers: influence of exposure concentration and work load. Int. Arch. Occup. Environ. Health, 42: 303–309 (1979).

40. Monster, A.C. Difference in uptake, elimination and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. Int. Arch. Occup. Environ. Health, 42: 311–317 (1979).

41. Ohtsuki, T., Sato, K., Koizumi, A., Kumai, M. and Ikeda, M. Limited capacity of humans to metabolize tetrachloroethylene. Int. Arch. Occup. Environ. Health, 51: 381–390 (1983).

42. Koppel, C., Arndt, I., Arendt, U. and Koeppe, P. Acute tetrachloroethylene poisoning — blood elimination kinetics during hyperventilation therapy. Clin. Toxicol., 23: 103–115 (1985).

43. Riihimaki, V. Metabolism and excretion of organic solvents. In: Safety and health aspects of organic solvents. V. Riihimaki and U. Uflvarson (eds.). Alan R. Liss, New York, NY. pp. 61–71 (1985).

44. Fernandez, J., Guberan, E. and Caperos, J. Experimental human exposures to tetrachloroethylene vapor and elimination in breath after inhalation. Am. Ind. Hyg. Assoc. J., 37: 143–150 (1976).

45. Ogata, M., Takasuka, Y. and Tomokuni, K. Excretion of organic chlorine compounds in the urine of persons exposed to vapours of trichloroethylene and tetrachloroethylene. Br. J. Ind. Med., 28: 386–391 (1971).

46. Schumann, A.M., Quast, J.F. and Watanabe, P.G. The pharmacokinetics and macromolecular interactions of perchloroethylene in mice and rats as related to oncogenicity. Toxicol. Appl. Pharmacol., 55: 207–219 (1980).

47. Odum, J., Green, T., Foster, J.R. and Hext, P.M. The role of trichloroacetic acid and peroxisome proliferation in the differences in carcinogenicity of perchloroethylene in the mouse and rat. Toxicol. Appl. Pharmacol., 92: 103–112 (1988).

48. Ikeda, M. and Ohtsuji, H. A comparative study of the excretion of Fujiwara reaction-positive substances in urine of humans and rodents given trichloro-or tetrachloro-derivatives of ethane and ethylene. Br. J. Ind. Med., 29: 99–104 (1972).

49. Green, T. Species differences in carcinogenicity. The role of metabolism in human risk evaluation. Teratogen. Carcinogen. Mutagen., 10: 103–113 (1990).

50. Green, T., Odum, J., Nash, J.A. and Foster, J.R. Perchloroethylene-induced rat kidney tumors: an investigation of the mechanisms involved and their relevance to humans. Toxicol. Appl. Pharmacol., 103: 77–89 (1990).

51. Stewart, R.D. Acute tetrachloroethylene intoxication. J. Am. Med. Assoc., 208: 1490–1492 (1969).

52. Levine, B., Fierro, M.F., Goza, S.W. and Valentour, J.C. A tetrachloroethylene fatality. J. Forensic Sci., 26: 206–209 (1981).

53. Hake, C.L. and Stewart, R.D. Human exposure to tetrachloroethylene: inhalation and skin contact. Environ. Health Perspect., 21: 231–238 (1977).

54. Carpenter, C.P. The chronic toxicity of tetrachloroethylene. J. Ind. Hyg. Toxicol., 19: 323–326 (1937).

55. Rowe, V.K., McCollister, D.D., Spencer, H.C., Adams, E.M. and Irish, D.D. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. Arch. Ind. Hyg. Occup. Health, 5: 566–579 (1952).

56. Environment Canada and Health Canada. Tetrachloroethylene, priority substances list assessment report. Supply and Services Canada, Ottawa (1993).

57. Ikeda, M., Koizumi, A., Watanabe, T., Endo, A. and Sato, K. Cytogenetic and cytokinetic investigations on lymphocytes from workers occupationally exposed to tetrachloroethylene. Toxicol. Lett., 5: 251–256 (1980).

58. Seiji, K., Jin, C., Watanabe, T., Nakatsuka, H. and Ikeda, M. Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene, or tetrachloroethylene, with reference to smoking habits. Int. Arch. Occup. Environ. Health, 62: 171–176 (1990).

59. National Toxicology Program (NTP). Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344/N rats and B6C3F_1 mice (inhalation studies). NTP TR 311, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC (1986).

60. Friberg, L., Kylin, B. and Nystrom, A. Toxicities of trichloroethylene and tetrachloroethylene and Fujiwara's pyridine–alkali reactions. Acta Pharmacol. Toxicol., 9: 303–312 (1953).

61. Bonnet, P., Francin, J.M., Gradinski, D., Raoult, G. and Zissu, D. Détermination de la concentration léthale$_{50}$ des principaux hydrocarbures aliphatiques chlorés chez le rat. Arch. Mal. Prof., 41: 317–321 (1980).

62. Hayes, J.R., Condie, L.W. and Borzelleca, J.F. The subchronic toxicity of tetrachloroethylene (perchloroethylene) administered in the drinking water of rats. Fundam. Appl. Toxicol., 7: 119–125 (1986).

63. Withey, R.J. and Hall, J.W. The joint action of perchloroethylene with benzene or toluene in rats. Toxicology, 4: 5–15 (1975).

64. Smyth, H.F., Weil, C.S., West, J.S. and Carpenter, C.P. An exploration of joint action: twenty-seven industrial chemicals intubated in rats in all possible pairs. Toxicol. Appl. Pharmacol., 14: 340–347 (1969).

65. Wenzel, D.G. and Gibson, R.D. A study of the toxicity and antihelminthic activity of n-butylidene chloride. J. Pharm. Pharmacol., 3: 169–176 (1951).

66. Savolainen, H., Pfaffli, P., Tengen, M. and Vainio, H. Biochemical and behavioural effects of inhalation exposure to tetrachloroethylene and dichloromethane. J. Neuropathol. Exp. Neurol., 36: 941–949 (1977).

67. Buben, J.A. and O'Flaherty, E.J. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose–effect study. Toxicol. Appl. Pharmacol., 78: 105–122 (1985).

68. Marth, E. Metabolic changes following oral exposure to tetrachloroethylene in subtoxic concentrations. Arch. Toxicol., 60: 293–299 (1987).

69. Goldsworthy, T.L., Lyght, O., Burnett, V.L. and Popp, J.A. Potential role of ∝-2μ-globulin, protein droplet accumulation and cell replication in the renal carcinogenicity of rats exposed to trichloroethylene, perchloroethylene and pentachloroethane. Toxicol. Appl. Pharmacol., 96: 367–379 (1988).

70. Swenberg, J.A., Short, B., Borghoff, S., Strasser, J. and Charboneau, M. The comparative pathobiology of α_{2u}-globulin nephropathy. Toxicol. Appl. Pharmacol., 97: 35–46 (1989).

71. Olson, M.J., Johnson, J.T. and Reidy, C.A. A comparison of male rat and human urinary droplet proteins: implications for human resistance to hyaline droplet nephropathy. Toxicol. Appl. Pharmacol., 102: 524–536 (1990).

72. Green, T. Chloroethylenes: a mechanistic approach to human risk evaluation. Annu. Rev. Pharmacol. Toxicol., 30: 73–89 (1990).

73. Dekant, W., Vamvakas, S., Koob, M., Kochling, A., Kanhai, W., Muller, D. and Henschler, D. A mechanism of haloalkene-induced renal carcinogenesis. Environ. Health Perspect., 88: 107–110 (1990).

74. Dekant, W., Vamvakas, S. and Anders, M.W. Biosynthesis, bioactivation and mutagenicity of S-conjugates. Toxicol. Lett., 53: 53–58 (1990).

75. Vamvakas, S., Herkenoff, M., Dekant, W. and Henschler, D. Mutagenicity of tetrachloroethylene in the Ames test — metabolic activation by conjugation with glutathione. J. Biochem. Toxicol., 4: 21–27 (1989).

76. DeAngelo, A.B., Daniel, F.B., McMillan, L., Wernsing, P. and Savage, R.E. Species and strain sensitivity to the induction of peroxisome proliferation by chloroacetic acids. Toxicol. Appl. Pharmacol., 101: 285–298 (1989).

77. Goldsworthy, T.L. and Popp, J.A. Chlorinated hydrocarbon-induced peroxisomal enzyme activity in relation to species and organ carcinogenicity. Toxicol. Appl. Pharmacol., 88: 225–233 (1987).

78. Elcombe, C.R. Species differences in carcinogenicity and peroxisome proliferation due to trichloroethylene: a biochemical human hazard assessment. Arch. Toxicol. Suppl., 8: 6–17 (1985).

79. Klaunig, J.E., Ruch, R.J. and Lin, E.L.C. Effects of trichloroethylene and its metabolites on rodent hepatocyte intercellular communication. Toxicol. Appl. Pharmacol., 99: 454–465 (1989).

80. National Cancer Institute (NCI). Bioassay of tetrachloroethylene for possible carcinogenicity. NIH 77-813, National Institutes of Health, Public Health Service, U.S. Department of Health, Education and Welfare, Bethesda, MD (1977).

81. Milman, H.A., Story, D.A., Riccio, E.S., Sivak, A., Tu, A.S., Williams, G.M., Tong, C. and Tyson, C.A. Rat liver foci and *in vitro* assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Ann. N.Y. Acad. Sci., 534: 521–530 (1988).

82. Lundberg, I., Hogberg, J., Kronevi, T. and Holmberg, B. Three industrial solvents investigated for tumor promoting activity in the rat liver. Cancer Lett., 36: 29–33 (1987).

83. Rampy, L.W., Quast, J.F., Balmer, M.F., Leong, B.K.J. and Gehring, P.J. Results of a long-term inhalation toxicology study in mice and rats of perchloroethylene (tetrachloroethylene) formulation. Unpublished report, Toxicology Research Laboratory, DOW Chemical Co., Midland, MI (1978), cited in references 1 and 34.

84. Theiss, J.C., Stoner, G.D., Shimkin, M.B. and Weisberger, E.K. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res., 37: 2717–2720 (1977).

85. Maronpot, R.R., Shimkin, M.B., Witschi, H.P., Smith, L.H. and Cline, J.M. Strain A mouse pulmonary tumor test results for chemicals previously tested in the National Cancer Institute carcinogenicity tests. J. Natl. Cancer Inst., 76: 1101–1112 (1986).

86. Van Duuren, B.L., Goldschmidt, B.M., Loewengart, G., Smith, A.C., Melchionne, S., Seldman, I. and Roth, D. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst., 63: 1433–1439 (1979).