APPENDIX 4. TOXICOLOGICAL DATA FOR CLASS 1 SOLVENTS

BENZENE

Category: Human carcinogen (IARC 1)

Not teratogenic

Toxic Effects:

Benzene causes central nervous system depression and destroys bone marrow, leading to injury in the hematopoietic system.

Carcinogenesis:

There is sufficient evidence to establish that benzene is a human carcinogen (lymphatic and hematopoietic cancers). In animal studies, Zymbal gland tumors, preputial gland tumors, skin carcinomas, mammary gland tumors and leukemia are observed.

Genotoxicity:

Chromosomal aberration and DNA adducts tests are positive but other mutagenicity tests are negative.

Assessment:

From the data of human leukemia and exposure concentrations of benzene, it was calculated that a daily intake of 0.02 mg was associated with a lifetime excess cancer risk of 10^{-5} (IRIS).

The guideline value for benzene is 0.02 mg per day (2 ppm).

References

Reviews: IARC Monographs 93 (1982)

Toxicological Profile ATSDR/TP 92/03

Pharmacopieal Forum (1991) Jan-Feb

Integrated Risk Information System (IRIS). US EPA, 1990.

CARBON TETRACHLORIDE

Category

Possible human carcinogen (IARC 2B).

Genotoxicity

Not mutagenic with or without metabolic activation in bacterial (Ames) test with *S. typhimurium* or *E. coli*.

Refs. McCann J and Ames BN Proc. Natl Acad. Sci. 1976 73 950-954

Barber ED et al., Mutat. Res. 1981 90 31-48

Uehleke H et al., Mutat. Res. 1976 38 114

Uehleke H et al., Xenobiotica 1977 7 393-400

De Flora S, Carcinogenesis 1981 2 283-298

De Flora S et al., Mutat. Res. 1984 133 161-198

Negative for induction of *umu* gene expression in *S. typhimurium* TA1535/pSK1002 when tested at up to 5.3 mg/mL.

Ref. Nakamura S et al., Mutat. Res. 1987 192 239-246

Induced DNA repair in *E. coli* strains, in the absence of metabolic activation.

Ref. De Flora S et al., Mutat. Res. 1984 133 161-198

De Flora S et al., Mutat. Res. 1984 134 159-165

Induced gene convertants, recombinants and revertants at high concentrations in *S. cerevisiae* without microsomal activation (not tested with S9).

Ref. Callen DF et al., Mutat. Res. 1980 77 55-63

Positive for lambda prophage induction endpoint of Microscreen assay in presence of metabolic activation.

Ref. Rossman TG et al., Mutat. Res. 1991 260 349-367

Caused DNA single strand breaks in alkaline elution/rat hepatocyte assay at 3 mM (viability approximately 45%).

Ref. Sina JF et al., Mutat. Res. 1983 113 357-391

Positive in DNA strand break test in mouse lymphoma cells at ≥ 6.55×10^{-3} M.

Ref. Garberg P et al., Mutat. Res. 1988 203 155-176

Positive at low rate in 1 of 2 media in SHE transformation assay.

Ref. Amacher DE and Zelljadt I Carcinogenesis 1983 4 291-295

Negative for SCE and chromosome aberrations in rat liver cell line RL_1 or CHO cells, with or without microsomal activation.

Refs. Dean BJ and Hodson-Walker G Mutat. Res. 1979 64 329-337

Loveday K et al., Environ. Mol. Mutagen. 1990 16 272-303

Negative in chromosome aberration test in bone marrow *in vivo*.

Ref. Lil'p IG Soviet Genet. 1983 18 1467-1472

Negative in mouse lymphoma TK+/- assay, in presence of metabolic activation (not carried out without S9).

Ref. Wangenheim J and Bolcsfoldi G Mutagenesis 1988 3 193-205

Negative in rat hepatocyte UDS assay *in vivo* at up to 400 mg/kg.

Ref. Mirsalis JC and Butterworth BE Carcinogenesis 1980 1 621-625

Bermudez E et al., Environ. Mol. Mutagen. 1982 4 667-679

Binds to calf thymus DNA *in vitro* following activation by microsomes from phenobarbitone-pretreated rats.

Ref. DiRenzo AB et al., Toxicol. Lett. 1982 11 243-252

Apparently binds *in vivo* to hepatic DNA (mouse) and RNA (rat) if animals are pretreated with 3-methylcholanthrene.

Ref. Rocchi P et al., Int. J. Cancer 1973 11 419-425

Overall, there is no convincing evidence for genotoxicity.

Carcinogenicity

Mice Strain A mice were given 0.16, 0.32, 0.64, 1.28 or 2.5 g/kg orally (1-5 days between doses for 30 doses), and the animals examined at 150 days. There were no hepatomas in animals given 30 doses of 2.5 g/kg over 30 days, but a significant number in all groups that received 0.16 g/kg or more over a period of 90 days or more.

Ref. Eschenbrenner AB and Miller E J. Natl. Cancer Inst. 1944 4 385-388

$$\text{PDE} = \frac{160 \text{ x } 50}{12 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x}10} = 0.67 \text{ mg / day}$$

$$\text{Limit} = \frac{0.67 \text{ x } 1000}{10} = 67 \text{ ppm}$$

Strain A mice were given approximately 40, 80, 160 or 320 mg/kg (30 doses at 4-day intervals) or 10, 20, 40 or 80 mg/kg (120 daily doses) orally. The mice were 3 months old when first dosed, and were examined for the presence of hepatomas at 8 months of age. Hepatomas were present in all groups except at 10 mg/kg/day.

Ref. Eschenbrenner AB and Miller E J. Natl. Cancer Inst. 1946 6 325-341

$$\text{PDE} = \frac{10 \text{ x } 50}{12 \text{ x } 10 \text{ x } 10 \text{ x } 10 \text{ x}1} = \ 0.04 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{0.04 \text{ x } 1000}{10} = \ 4 \text{ ppm}$$

B6C3F1 mice received 1250 or 2500 mg/kg orally, 5 days/week for 78 weeks, and were killed 12-14 weeks later. The incidence of hepatocellular carcinomas and adrenal tumours was significantly increased at both doses.

Ref. Weisburger EK Environ. Health Perspect. 1977 21 7-16

$$\text{For continuous exposure} = \frac{1250 \text{ x } 5}{7} = 893 \text{ mg / kg}$$

$$\text{PDE} = \frac{893 \text{ x } 50}{12 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x} 10} = 3.7 \text{ mg / day}$$

$$\text{Limit} = \frac{3.7 \text{ x } 1000}{10} = 370 \text{ ppm}$$

Rats Osborne-Mendel rats received 47 or 94 (males) or 80 or 160 (females) mg/kg orally, 5 days/week for 78 weeks, and were killed 32 weeks later. There was a small increase in incidence of hepatocellular carcinoma, and a greater increase in the incidence of neoplastic nodules, without dose-relationship.

Ref. Weisburger EK Environ. Health Perspect. 1977 21 7-16

$$\text{For continuous exposure} = \frac{47 \text{ x } 5}{7} = 33.6 \text{ mg / kg}$$

$$\text{PDE} = \frac{33.6 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x} 10} = 0.34 \text{ mg / day}$$

$$\text{Limit} = \frac{0.34 \text{ x } 1000}{10} = 34 \text{ ppm}$$

Wistar, Osborne-Mendel, Japanese, Black and Sprague-Dawley rats were given 1.3 mL/kg (2 g/kg) by subcutaneous injection twice weekly. Black and Sprague-Dawley animals died with severe cirrhosis at between 5 and 18 weeks. There was a significant increase in incidence of hepatocellular carcinoma in Wistar, Osborne-Mendel and Japanese rats surviving for 68 weeks or more.

Ref. Reuber MD and Glover EL J. Natl. Cancer Inst. 1970 44 419-427

$$\text{For continuous exposure} = \frac{2000 \text{ x } 2}{7} = 571 \text{ mg / kg}$$

$$\text{PDE} = \frac{571 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x} 10} = 5.7 \text{ mg / day}$$

$$\text{Limit} = \frac{5.7 \text{ x } 1000}{10} = 570 \text{ ppm}$$

Several other earlier and/or grossly inadequately designed oral, inhalation or subcutaneous carcinogenicity studies in mouse, hamster and trout have been carried out. Note that in no study conducted to a currently acceptable design has an entirely convincing no-effect dose for tumorigenesis been determined. The studies reported by Weisburger are of adequate length, and of generally sufficient design, but the lowest doses used were 1250 mg/kg/day in mice, and 47 mg/kg/day in rats. The investigations of Eschenbrenner and Miller are relatively short, and only hepatocellular tumours were scored.

Hamsters Syrian golden hamsters given approximately 200 mg/kg once weekly for 7 weeks, followed by approximately 100 mg/kg for 30 weeks, and survivors killed 25 weeks later. There were liver cell carcinomas in animals dying or being killed from week 43 onwards. Total numbers used in this study were low, and it appears that no concurrent controls were employed. Ref. Della Porta G et al., J. Natl. Cancer Inst. 1961 26 855-863

$$\text{For continuous exposure} = \frac{100 \text{ x } 1}{7} = 14.3 \text{ mg / kg}$$

$$\text{PDE} = \frac{14.3 \text{ x } 50}{10 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x} 10} = 0.07 \text{ mg / day}$$

$$\text{Limit} = \frac{0.07 \text{ x } 1000}{10} = 7 \text{ ppm}$$

Reproductive Toxicity

Sprague-Dawley rats exposed by inhalation to 300 or 1000 ppm, 7h/day on days 6 through 15 of gestation. Foetal body weight and crown-rump length were significantly reduced at both concentrations, and probably associated with reduced maternal food consumption and body weight gain. The incidence of sternebral anomalies was claimed to be increased at 1000 ppm, but in the control group exposed to air concurrently with the 300 ppm group the incidence was as high as in the group exposed to 1000 ppm. LOEL (foetotoxicity) = 300 ppm. Ref. Schwetz BA et al., Toxicol. Appl. Pharmacol. 1974 28 452-464

$$300 \text{ ppm} = \frac{300 \text{ x } 153.84}{24.45} = 1888 \text{ mg / m}^3 = 1.89 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{1.89 \text{ x } 7}{24} = 0.55 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.55 \text{ x } 290}{0.330} = 483 \text{ mg / kg}$$

$$\text{PDE} = \frac{483 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x} 10} = 48.3 \text{ mg / day}$$

$$\text{Limit} = \frac{48.3 \text{ x } 1000}{10} = 4830 \text{ ppm}$$

This appears to be the only satisfactory teratogenicity study to have been conducted. Other studies suggest that very large doses result in foetal death, i.e. that carbon tetrachloride is foetotoxic, but not teratogenic.

Rats given 80 or 200 ppm in the diet (carbon tetrachloride intake up to 10-18 mg/kg/day), commencing two weeks after weaning. Females mated for 5 successive pregnancies (once to control, 4 times to treated males), beginning at 3 months of age. No effects on pregnancy rate or litter parameters. Worst case NOEL = 10 mg/kg/day.

Ref. Alumot E et al., Food Cosmet. Toxicol. 1976 14 105-110

$$\text{PDE} = \frac{10 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x1}} = 10 \text{ mg / day}$$

$$\text{Limit} = \frac{10 \text{ x } 1000}{10} = 1000 \text{ ppm}$$

Large doses of carbon tetrachloride cause testicular (seminiferous tubule and interstitial cell) damage and affect the oestrous cycle in females, but the significance of the changes is impossible to assess, some evidence is contradictory, and the effects of low doses have not been explored.

Toxicity

Oral LD50 in mice 8.26 g/kg.

Ref. Wenzel DG and Gibson RD J. Pharm. Pharmacol. 1951 3 169-176

Oral LD50 in rats 2.81 g/kg.

Ref. Smyth HF et al., Toxicol. Appl. Pharmacol. 1970 17 498-503

Oral LD50 in dogs 2.3 g/kg.

Ref. Klaasen CD and Plaa GL Toxicol. Appl. Pharmacol. 1967 10 119-131

Dermal LD50 in rabbits and guinea pigs > 14 g/kg.

Ref. Roudabush RL et al., Toxicol. Appl. Pharmacol. 1965 7 559-565

Intraperitoneal LD50 in mice 4.675 g/kg.

Ref. Gehring PJ Toxicol. Appl. Pharmacol. 1968 13 287-298

Subcutaneous LD50 in mice 31 g/kg.

Ref. Plaa GL et al., J. Pharmacol. Exp. Ther. 1958 123 224-229

There is a vast literature on the toxicity of carbon tetrachloride in animals, largely dealing with the characteristics and mechanism of liver damage. Low hepatotoxic doses of carbon tetrachloride produce characteristic fatty livers. Higher exposures result in centrilobular necrosis; cirrhosis and hepatic tumours may develop after prolonged administration.

Hepatotoxicity is dependent on activation by cytochrome P450, and agents that induce monooxygenase activity (including ethanol and barbiturates) markedly increase the hepatotoxicity of carbon tetrachloride.

Refs. e.g. Recknagel RO and Glende EA CRC Crit. Rev. Toxicol. 1973 2 263-297

Glende EA et al., Biochem. Pharmacol. 1976 25 2163-2170

Kalf GF et al., Annu. Rev. Pharmacol. Toxicol. 1987 27 399-427

Other target organs include kidney, testes and lung.

Refs. e.g. Chen W-J et al., Lab. Invest. 1977 36 388-394

New PS et al., J. Am. Med. Assoc. 1962 181 903-906

Many papers report the outcome of administration of one or a few doses of carbon tetrachloride. The following comprise a large proportion of those involving administration for 10 days or more that have been reported during the last 50 years.

Mice CD-1 mice treated orally for 90 days at 12, 120, 540 or 1200 mg/kg/day. Dose-related altered serum parameters of liver damage and histopathological changes (including necrosis and fatty degeneration) at 12 mg/kg/day and above. LOEL = 12 mg/kg/day.

Ref. Hayes JR et al., Fund. Appl. Toxicol. 1986 7 454-463

$$\text{PDE} = \frac{12 \text{ x } 50}{12 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x} 10} = 0.10 \text{ mg / day}$$

$$\text{Limit} = \frac{0.10 \text{ x } 1000}{10} = 10 \text{ ppm}$$

CD-1 mice given 1.2, 12 or 120 mg/kg orally, 5 days/week, for 90 days. Dose-related altered serum parameters of liver damage and histopathological changes at 12 mg/kg/day and above. Minimal necrosis in single animal at 1.2 mg/kg/day. Virtual NOEL = 1.2 mg/kg/day.

Ref. Condie LW et al., Fund. Appl. Toxicol. 1986 7 199-206

$$\text{For continuous exposure} = \frac{1.2 \times 5}{7} = 0.857 \text{ mg / kg}$$

$$\text{PDE} = \frac{0.857 \times 50}{12 \times 10 \times 5 \times 1 \times 1} = 0.071 \text{ mg / day}$$

$$\text{Limit} = \frac{0.071 \times 1000}{10} = 7.1 \text{ ppm}$$

Rats Wistar rats exposed by inhalation to 5, 10, 25, 50, 100, 200 or 400 ppm, 7h/day on 127-146 occasions during a period of 173-205 days. Fatty degeneration of the liver at 10 ppm or more; cirrhosis at 50 ppm or more; evidence of increased mortality at 100 ppm or more. Biochemical changes were present above 5 ppm. NOEL = 5 ppm (145 exposures in 205 days). Ref. Adams EM et al., AMA Arch. Ind. Hyg. 1952 6 50-66

$$5 \text{ ppm} = \frac{5 \times 153.84}{24.45} = 31.5 \text{ mg / m}^3 = 0.0315 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.0315 \times 7 \times 145}{24 \times 205} = 0.0065 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.0065 \times 290}{0.425} = 4.44 \text{ mg / kg}$$

$$\text{PDE} = \frac{4.44 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 2.2 \text{ mg / day}$$

$$\text{Limit} = \frac{2.2 \times 1000}{10} = 220 \text{ ppm}$$

Long-Evans or Sprague-Dawley rats exposed continuously for 90 days to atmospheres containing 61 or 6.1 mg/m^3. Hepatic damage at 61 mg/m^3, NOEL 6.1 mg/m^3 = 0.0061mg/L

Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{0.0061 \times 290}{0.425} = 4.16 \text{ mg / kg}$$

$$\text{PDE} = \frac{4.16 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 0.8 \text{ mg / day}$$

$$\text{Limit} = \frac{0.8 \times 1000}{10} = 80 \text{ ppm}$$

Male F344 rats given 5, 10, 20 or 40 mg/kg/day for 10 days. Increased AST and ALT at 20 and 40 mg/kg/day, at least minimal hepatic vacuolar degeneration at all doses, hepatic necrosis at 10 mg/kg/day and more. No consistent changes in parameters of immune function. LOEL = 5 mg/kg/day.

Ref. Smialowicz RJ et al., Fund. Appl. Toxicol. 1991 17 186-196

$$\text{PDE} = \frac{5 \times 50}{5 \times 10 \times 10 \times 1 \times 5} = 0.10 \text{ mg / day}$$

$$\text{Limit} = \frac{0.10 \times 1000}{10} = 10 \text{ ppm}$$

Male F344 rats given 20 or 40 mg/kg orally, 5 days/week for 12 weeks. Dose-related retardation of growth, alterations in serum parameters of liver damage, hepatic necrosis, vacuolar degeneration and cirrhosis at both doses. LOEL = 20 mg/kg/day.

Ref. Allis JW et al., Fund. Appl. Toxicol. 1990 15 558-570

$$\text{For continuous exposure} = \frac{20 \times 5}{7} = 14.3 \text{ mg / kg}$$

$$\text{PDE} = \frac{14.3 \times 50}{5 \times 10 \times 5 \times 1 \times 10} = 0.28 \text{ mg / day}$$

$$\text{Limit} = \frac{0.28 \times 1000}{10} = 28 \text{ ppm}$$

Male Sprague-Dawley rats given 1, 10 or 33 mg/kg orally, 5 days/week for 12 weeks. Retarded growth at 33 mg/kg, and dose-related alterations in serum parameters of liver damage at 10 and 33 mg/kg. Hepatic centrilobular vacuolisation at 10 mg/kg, and extensive degenerative lesions and hyperplastic nodules at 33 mg/kg. NOEL = 1 mg/kg.

Ref. Bruckner JV et al., Fund. Appl. Toxicol. 1986 6 16-34

$$\text{For continuous exposure} = \frac{1 \times 5}{7} = 0.714 \text{ mg / kg}$$

$$\text{PDE} = \frac{0.714 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 0.14 \text{ mg / day}$$

$$\text{Limit} = \frac{0.14 \times 1000}{10} = 14 \text{ ppm}$$

Guinea Pigs of heterogeneous origin exposed by inhalation to 5, 10, 25, 50, 100, 200 or 400 ppm, 7h/day on 93-184 occasions during a period of 126-258 days. Fatty degeneration of the liver at 10 ppm or more; cirrhosis at 25 ppm or more; renal tubular degeneration at 200 ppm and more; increased mortality at 100 ppm or more. Biochemical changes were present above 5 ppm. NOEL = 5 ppm (143 exposures in 203 days).

Ref. Adams EM et al., AMA Arch. Ind. Hyg. 1952 6 50-66

$$5 \text{ ppm} = \frac{5 \text{ x } 153.84}{24.45} = 31.5 \text{ mg / m}^3 = 0.0315 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.0315 \text{ x } 7 \text{ x } 143}{24 \text{ x } 203} = 0.0065 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.0065 \text{ x } 430}{0.500} = 5.6 \text{ mg / kg}$$

$$\text{PDE} = \frac{5.6 \text{ x } 50}{10 \text{ x } 10 \text{ x } 2 \text{ x } 1 \text{ x1}} = 1.4 \text{ mg / day}$$

$$\text{Limit} = \frac{1.4 \text{ x } 1000}{10} = 140 \text{ ppm}$$

Hartley guinea pigs exposed continuously for 90 days to atmospheres containing 61 or 6.1 mg/m^3. Hepatic damage and some deaths at 61 mg/m^3, slight reduction in body weight gain at 6.1 mg/m^3. LOEL 6.1 mg/m^3 = 0.0061mg/L.

Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{0.0061 \text{ x } 430}{0.500} = 5.25 \text{ mg / kg}$$

$$\text{PDE} = \frac{5.25 \text{ x } 50}{10 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x5}} = 0.1 \text{ mg / day}$$

$$\text{Limit} = \frac{0.1 \text{ x } 1000}{10} = 10 \text{ ppm}$$

<u>Rabbits</u> White rabbits exposed by inhalation to 10, 25, 50 or 100 ppm, 7h/day on 139-178 occasions during a period of 197-248 days. Fatty degeneration and cirrhosis of the liver at 25

ppm or more; significant depression of growth at 100 ppm. NOEL = 10 ppm (139 exposures in 197 days). Ref. Adams EM et al., AMA Arch. Ind. Hyg. 1952 6 50-66

$$10 \text{ ppm} = \frac{10 \text{ x } 153.84}{24.45} = 62.9 \text{ mg / m}^3 = 0.0629 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.0629 \text{ x } 7 \text{ x } 139}{24 \text{ x } 197} = 0.0129 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.0129 \text{ x } 1440}{4} = 4.64 \text{ mg / kg}$$

$$\text{PDE} = \frac{4.64 \text{ x } 50}{2.5 \text{ x } 10 \text{ x } 2 \text{ x } 1 \text{ x1}} = 4.6 \text{ mg / day}$$

$$\text{Limit} = \frac{4.6 \text{ x } 1000}{10} = 460 \text{ ppm}$$

New Zealand white rabbits exposed continuously for 90 days to atmospheres containing 61 or 6.1 mg/m^3. Hepatic damage at 61 mg/m^3, reduced body weight gain at 6.1 mg/m^3. LOEL 6.1 mg/m^3 = 0.0061 mg/L Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{0.0061 \text{ x } 1440}{4} = 2.2 \text{ mg / kg}$$

$$\text{PDE} = \frac{2.2 \text{ x } 50}{2.5 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x5}} = 0.18 \text{ mg / day}$$

$$\text{Limit} = \frac{0.18 \text{ x } 1000}{10} = 18 \text{ ppm}$$

Dogs Beagle dogs exposed continuously for 90 days to atmospheres containing 61 or 6.1 mg/m^3. Hepatic damage at 61 mg/m^3, some evidence of reduced body weight gain at 6.1 mg/m^3. LOEL 6.1 mg/m^3 = 0.0061 mg/L

Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{0.0061 \times 9000}{11.5} = 4.77 \text{ mg / kg}$$

$$\text{PDE} = \frac{4.77 \times 50}{2 \times 10 \times 5 \times 1 \times 5} = 0.48 \text{ mg / day}$$

$$\text{Limit} = \frac{0.48 \times 1000}{10} = 48 \text{ ppm}$$

Monkeys Rhesus monkeys exposed by inhalation to 25, 50 or 100 ppm, 7h/day on 148-198 occasions during a period of 212-277 days. Of two monkeys exposed to 100 ppm, slight growth depression in both, some cloudy swelling in the liver of one, and slight fatty degeneration throughout the liver of the other. NOEL = 50 ppm (198 exposures in 277 days).

Ref. Adams EM et al., AMA Arch. Ind. Hyg. 1952 6 50-66

$$50 \text{ ppm} = \frac{50 \times 153.84}{24.45} = 315 \text{ mg / m}^3 = 0.315 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.315 \times 7 \times 198}{24 \times 277} = 0.0657 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.0657 \times 1150}{2.5} = 30.2 \text{ mg / kg}$$

$$\text{PDE} = \frac{30.2 \times 50}{10 \times 10 \times 2 \times 1 \times 1} = 7.6 \text{ mg / day}$$

$$\text{Limit} = \frac{7.6 \times 1000}{10} = 760 \text{ ppm}$$

Human

Carbon tetrachloride is extremely lipophilic; it is readily absorbed in animals and, apparently, in humans after oral ingestion. Fatal human poisonings by carbon tetrachloride have been reported since 1909, and deaths continue to occur occasionally following either inhalation or ingestion. Toxicity is exacerbated by alcoholism or concurrent exposure to alcohol and carbon tetrachloride. Liver and renal damage are the most common effects.

Refs. Veley VH 1909 Lancet 1162-1163

Hardin BL 1954 Ind. Med. Surg. 23 93-105

The genotoxicity of carbon tetrachloride is unconvincing, and liver tumorigenesis in animal species may be related to chronic damage and regenerative cell proliferation. This standpoint generally has been taken in setting occupational exposure limits for carbon tetrachloride. There are only a few anecdotal cases in which exposure has been linked with hepatic tumours in man. Limited epidemiological studies indicate an excess of some cancers in communities exposed to chlorinated hydrocarbons, but the general limitations of the studies and mixed solvent exposure do not allow firm conclusions to be drawn regarding the carcinogenic potential of carbon tetrachloride in man.

Refs. e.g. Tracey JP and Sherlock P N.Y. State J. Med. 1968 8 2202-2204

Simler M et al., Strasbourg Med. 1964 15 910-917

Blair A et al., Am. J. Pub. Health 1979 69 508-511

Capurro PU Clin. Toxicol. 1979 14 285-294

Carbon tetrachloride is classed by IARC in Group 2B (possibly carcinogenic in humans), by NTP in Group 2 (reasonably anticipated to be a carcinogen), by ACGIH as A2 (suspected human carcinogen) and by NIOSH and OSHA as a carcinogen, without further classification.

Environmental Impact

Under the revised Montreal Protocol, production and use of carbon tetrachloride are scheduled to be phased out by the year 2000 by ratifying parties (excluding 10-year derogations for developing nations), because of its contribution to atmospheric ozone depletion (ozone-depleting potential 0.9, similar to that of fully chlorinated CFCs).

Conclusion

Possible human carcinogen. Animal carcinogen (balance of evidence suggests probably by non-genotoxic mechanism). Hepatotoxic at low doses in man and laboratory species. Production scheduled to be phased out in 2000 under Montreal Protocol.

The guideline value for carbon tetrachloride is 0.04 mg/day (4 ppm).

1,2-DICHLOROETHANE

Category: Possible human carcinogen (IARC 2B). Not teratogenic

Toxic Effects:

Repeated exposure induces anorexia, nausea, abdominal pain, irritation of mucous membranes, dysfunction of liver and kidney and neurological disorders. Depression of leukocyte, antibody-forming cell and cellular immunity was found in mice; necrosis of cerebellum and hyperplasia and inflammation of forestomach were observed in male rats after oral administration.

Carcinogenesis:

There is no evidence of carcinogenicity in humans. Forestomach cancer, hemangiosarcoma, breast cancer, uterine cancer and respiratory tract cancer were found in rats or mice after gavage treatment.

Genotoxicity:

The balance of evidence indicates 1,2-dichloroethane is potentially genotoxic.

Assessment:

Excess cancer risk at 10^{-5} is 0.05mg/day for 50 kg human based on hemangiosarcoma using a linearized multistage model without body surface correction.

The guideline value for 1,2-dichloroethane is 0.05 mg per day (5 ppm).

References

Reviews; Environmental Health Criteria 62 (1987)

IARC Monographs 20 (1979)

NCI (1978) TR-55.

1,1-DICHLOROETHENE

Genotoxicity

Some positive in vitro results in Ames test and mouse lymphoma, results being enhanced in presence of liver microsomal samples. Negative results in in vitro SCE and chromosome abberation studies and in CHE cells. Negative results in vivo in micronucleus test, UDS assay and dominant lethal assay.

Refs. Mortelmans K et al., Environ. Mutagen 1986 8 1-119.

Greim H et al., Biochem. Pharmacol. 1975 24 2013-17.

Bronzetti G et al., Mut. Res. 1981 89 179-85.

McGregor D et al., Environ. Mol. Mutagen. 1991 17 (2) 122-9.

Drevon C and Kuroki T. Mut. Res. 1979 67 (2) 173-82.

Sawanda M et al., Mut. Res. 1987 187 (3) 157-63.

Reitz RH et al., Toxicol. Appl. Pharmacol. 1980 52 (3) 357-70.

Anderson D et al., Biochem. Pharmacol. 1977 21 71-8.

Carcinogenicity

Positive results have been reported after inhalation exposure; however, no increase in tumour incidence is noted following oral administration.

Swiss mice exposed to 25 ppm 4 h/day, 5 days/week for 52 weeks and retained until 98 weeks showed an increased incidence of renal adenocarcinomas, mainly in males.

Ref. Maltoni C. Environ. Health Perspect 1977 21 1-5. LOEL = 25 ppm

$$25 \text{ ppm} = \frac{25 \text{ x } 96.94}{24.45} = 99.1 \text{ mg / m}^3 = 0.099 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.099 \text{ x } 4 \text{ x } 5}{24 \text{ x } 7} = 0.012 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.012 \times 43}{0.028} = 18.1 \text{ mg / kg}$$

$$\text{PDE} = \frac{18.1 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 0.08 \text{ mg / day}$$

$$\text{Limit} = \frac{0.08 \times 1000}{10} = 8 \text{ ppm}$$

Sprague-Dawley rats given 100 ppm 4-7 h/day, 5 days/week for 2 years. Others were exposed in utero and then for 2 years following birth and showed an increased incidence of leukaemia.

Ref. Cotti G et al., Ann. NY Acad. Sci. 1988 534 160-68

$$100 \text{ ppm} = \frac{100 \times 96.94}{24.45} = 396 \text{ mg / m}^3 = 0.4 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.4 \times 4 \times 5}{24 \times 7} = 0.047 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.047 \times 290}{0.425} = 32 \text{ mg / kg}$$

$$\text{PDE} = \frac{32 \times 50}{5 \times 10 \times 10 \times 10 \times 1} = 0.32 \text{ mg / day}$$

$$\text{Limit} = \frac{0.32 \times 1000}{10} = 32 \text{ ppm}$$

B6C3F1 mice given 2 and 10 mg/kg by gavage 5 days/week for 2 years showed no increase in tumour incidence (except leukaemia which was discounted because it only occurred in low dose females).

Ref. NTP Programme Tech. Report 228 1982. NEL 10 mg/kg.

$$\text{For continuous dosing} = \frac{10 \times 5}{7} = 7.14 \text{ mg / kg}$$

$$\text{PDE} = \frac{7.14 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 2.98 \text{ mg / day}$$

$$\text{Limit} = \frac{2.98 \times 1000}{10} = 298 \text{ ppm}$$

Sprague-Dawley rats given time-weighted average of 7, 10 and 20 mg/kg (males) and 9, 14 and 30 mg/kg (females) for 2 years in drinking water. No increase in tumour incidence was noted. Ref. Quast JF et al., Fund. Appl. Toxicol. 1983 3 55-62. NOEL = 20 mg/kg

$$\text{PDE} = \frac{20 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 20 \text{ mg / day}$$

$$\text{Limit} = \frac{20 \times 1000}{10} = 2000 \text{ ppm}$$

Reproductive toxicity

Rats given 200 mg/L in drinking water days 6-15 showed no adverse effects and offspring were normal.

Ref. Norris JM in Proceedings of Technical Association of Pulp and Paper Industries Conference, Chicago 1977. NEL = 200 mg / L

Rat drinks 30 mg / day

$$\text{Daily consumption} = \frac{200 \times 30}{1000} = 6 \text{ mg / day}$$

$$\text{Dose} = \frac{6}{0.33} = 18.2 \text{ mg / kg}$$

$$\text{PDE} = \frac{18.2 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 1} = 18.2 \text{ mg / day}$$

$$\text{Limit} = \frac{18.2 \text{ x } 1000}{10} = 1820 \text{ ppm}$$

Rats given 20-160 ppm by inhalation 7 h/day days 6-15. Embryo and foetal toxicity associated with maternal toxicity but no teratogenic effects.

Ref. Norris JM in Proceedings of Technical Association of Pulp and Paper Industries Conference, Chicago 1977.

$$20 \text{ ppm} = \frac{20 \text{ x } 96.94}{24.45} = 79 \text{ mg / m}^3 = 0.08 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.08 \text{ x } 7}{24} = 0.023 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.023 \text{ x } 290}{0.33} = 20.2 \text{ mg / kg}$$

$$\text{PDE} = \frac{20.2 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 10} = 2.02 \text{ mg / day}$$

$$\text{Limit} = \frac{2.02 \text{ x } 1000}{10} = 202 \text{ ppm}$$

Rabbits dosed at 20-160 ppm by inhalation 7 h/day days, 6-18 showed embryo and foetal toxicity associated with maternal toxicity but no teratogenic effects.

Ref. Norris JM in Proceedings of Tech. Assoc. of Pulp and Paper Industries Conference, Chicago 1977.

As above, continual exposure = 0.023 mg/L

$$\text{Daily dose} = \frac{0.023 \times 1440}{4} = 8.28 \text{ mg / kg}$$

$$\text{PDE} = \frac{8.28 \times 50}{2.5 \times 10 \times 1 \times 1 \times 10} = 1.66 \text{ mg / day}$$

$$\text{Limit} = \frac{1.66 \times 1000}{10} = 166 \text{ ppm}$$

Sprague-Dawley rats given 200 mg/L in drinking water in a multigeneration study. No adverse effects seen in 6 sets of litters. Ref. Nitschke KD et al., Fund. Appl. Toxicol. 1983 3 75-9.

As above PDE is 18.2 mg/day (limit 1820 ppm).

Animal toxicity

Sprague-Dawley rats exposed to 10 and 40 ppm by inhalation 6 h/day, 5 days/week for 5 weeks then to 25 and 75 ppm for up to 18 months. Liver changes were noted at 6 months but these reversed after end of treatment. LOEL 25 ppm.

Ref. Quast JF et al., Fund. Appl. Toxicol. 1986 6 (1) 105-44

$$25 \text{ ppm} = \frac{25 \times 96.94}{24.45} = 99.12 \text{ mg / m}^3 = 0.10 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.1 \times 6 \times 5}{24 \times 7} = 0.018 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.018 \times 290}{0.425} = 12.3 \text{ mg / kg}$$

$$\text{PDE} = \frac{12.3 \times 50}{5 \times 10 \times 1 \times 1 \times 10} = 1.23 \text{ mg / day}$$

$$\text{Limit} = \frac{1.23 \times 1000}{10} = 123 \text{ ppm}$$

Sprague-Dawley rats given TWA of 7, 10 and 20 mg/kg (males) and 9, 14 and 30 mg/kg (females) in drinking water for 2 years. Minimal hepatocellular swelling and midzonal fatty changes in females at all levels and in high dose males. These were considered to be adaptive changes. NEL = 20 mg/kg. Ref. Quast JF et al., Fund. Appl. Toxicol. 1983 3 (1) 55-62

$$\text{PDE} = \frac{20 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 20 \text{ mg / day}$$

$$\text{Limit} = \frac{20 \times 1000}{10} = 2000 \text{ ppm}$$

Conclusion

The guideline value for 1,1-dichloroethene is 0.08 mg/day (8 ppm).

1,1,1-TRICHLOROETHANE

Category

Not classifiable as to carcinogenicity to humans (IARC 3).

Genotoxicity

Plate incorporation assays for reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, or in *E. coli* strains, using liquid TCE are consistently negative, as are assays using pre-incubation or a fluctuation protocol. There are indications of mutagenicity in strains TA100 and TA1535 in vapour phase assays in desiccators, although in the most unequivocally positive test the results suggest that activity may be due to an epoxide stabiliser such as butylene oxide. Results of Shimada et al., appear to confirm that activity is due to the stabiliser. Negative for induction of *umu* gene expression in *S. typhimurium* TA1535/pSK1002 when tested at up to 666 ug/mL. Negative in SOS Chromotest (induction of sfiA gene expression in *E. coli*).

Refs. reviewed in Fielder RJ and Williams SD 1,1,1-Trichloroethane (Toxicity Review 9) 1984 Health and Safety Executive, HMSO, London

Haworth S et al., Environ. Mutagenesis 1983 suppl. 1 3-142

Nakamura S et al., Mutat. Res. 1987 192 239-246

Quillardet P et al., Mutat. Res. 1985 147 79-95

Shimada T et al., Cell Biol. Toxicol. 1985 1 159-179

Negative for gene mutation and mitotic recombination in yeasts.

No clear evidence for DNA damage in microorganisms.

Refs. reviewed in Fielder RJ and Williams SD 1,1,1-Trichloroethane (Toxicity Review 9) 1984 Health and Safety Executive, HMSO, London

Not mutagenic at TK locus in TK6 human lymphoblasts at 500 ug/mL.

Ref. Penman BW and Crespi CL Environ. Mol. Mutagen. 1987 10 35-60

No increase in number of SCE in CHO cells at up to 10 ug/mL (with S9) in one study. Negative for SCE without S9 (up to 1000 ug/mL), equivocal for SCE with S9 (tested to 500

ug/mL) in another. In the second, chromosome aberration response positive without S9, negative with S9.

Perry PE and Thomson EJ in Evaluation of Short Term Tests for Carcinogens. Prog. Mutat. Res. 1 (eds. de Serres FJ and Ashby J) 1981 Elsevier pp 560-569

Galloway SM et al., Environ. Mol. Mutagen. 1987 10 (suppl. 10) 1-175

No increase in number of micronucleated polychromatic erythrocytes in mice in 3 studies (various protocols, intraperitoneal doses of up to 2000 mg/kg).

Negative for sex-linked recessive lethal mutation in *Drosophila* at 25 ppm in diet.

No dominant lethal effect in mice when males given up to 5.8 mg/mL in drinking water for 14 weeks.

No unscheduled DNA synthesis in HeLa cells (± S9) or in primary cultures of rat hepatocytes.

Refs. reviewed in Fielder RJ and Williams SD 1,1,1-Trichloroethane (Toxicity Review 9) 1984 Health and Safety Executive, HMSO, London

Positive in one BHK-21 cell transformation assay (± S9), and negative in another. Positive for transformation in Fischer rat embryo F-1706 line. Positive in BALB/c-3T3 cells (but stabilisers may have been present in the test material).

Refs. reviewed in Fielder RJ and Williams SD 1,1,1-Trichloroethane (Toxicity Review 9) 1984 Health and Safety Executive, HMSO, London

Tu AS et al., Cancer Lett. 1985 28 85-92

In summary, the ability of 1,1,1-trichloroethane to produce point mutations in bacteria has been investigated thoroughly, generally with negative results. There is no evidence to suggest that gene or chromosomal damage is produced in mammalian cells. *In vitro* cell transformation assays in BHK cells gave conflicting results, but it is known that reproducibility in this system may give problems. Results in the F-1706 transformation assay were positive without S9, regarded as surprising because trichloroethane would not be expected to be directly acting in this system. Overall evidence of mutagenic potential is limited.

Carcinogenicity

Only two studies, one in mice and one in rats, that conform to current standards, particularly as regards survival or duration of dosing, have been located (Quast et al, 1988). The remainder provide only supporting data.

Mice B6C3F1 mice exposed by inhalation to 150, 500 or 1500 ppm production grade trichloroethane (purity approximately 94%, containing 5% stabilisers), 6h/day, 5 days/week for 2 years. There was no evidence of toxicity or oncogenicity at any dose. NOEL = 1500 ppm. Ref. Quast JF et al., Fund. Appl. Toxicol. 1988 11 611-625

$$1500 \text{ ppm} = \frac{1500 \times 133.42}{24.45} = 8185 \text{ mg / m}^3 = 8.19 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{8.19 \times 6 \times 5}{24 \times 7} = 1.46 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.46 \times 43}{0.028} = 2242 \text{ mg / kg}$$

$$\text{PDE} = \frac{2242 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 934 \text{ mg / day}$$

$$\text{Limit} = \frac{934 \times 1000}{10} = 93{,}400 \text{ ppm}$$

In an NCI programme study, B6C3F1 mice were given a time-weighted average of 2807 or 5615 mg/kg, 5 days/week for 78 weeks (doses increased twice from initial), and killed 13 weeks later. There was no evidence for an increase in any tumour type, but poor survival made this study inadequate for proper assessment.

Ref. NCI. Bioassay of 1,1,1-trichloroethane for possible carcinogenicity, Technical Report Series 3, US DHEW, 1977

Rats F344 rats exposed by inhalation to 150, 500 or 1500 ppm production grade trichloroethane (purity approximately 94%, containing 5% stabilisers), 6h/day, 5 days/week for 2 years. Body weight gain slightly decreased in females at 1500 ppm. Minimal hepatic effects at interim, but not terminal, kills in males and females exposed to 1500 ppm. No evidence of oncogenicity. NOEL for tumours = 1500 ppm. Ref. Quast JF et al., Fund. Appl. Toxicol. 1988 11 611-625

$$1500 \text{ ppm} = \frac{1500 \times 133.42}{24.45} = 8185 \text{ mg / m}^3 = 8.19 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{8.19 \times 6 \times 5}{24 \times 7} = 1.46 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.46 \times 290}{0.425} = 996 \text{ mg / kg}$$

$$\text{PDE} = \frac{996 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 996 \text{ mg / day}$$

$$\text{Limit} = \frac{996 \times 1000}{10} = 99{,}600 \text{ ppm}$$

In an NCI programme study, Osborne-Mendel rats were given 750 or 1500 mg/kg, 5 days/week for 78 weeks, and killed 32 weeks later. There was no evidence for an increase in any tumour type, but poor survival rendered this study inadequate for proper assessment.

Ref. NCI. Bioassay of 1,1,1-trichloroethane for possible carcinogenicity, Technical Report Series 3, US DHEW, 1977

Sprague-Dawley rats exposed by inhalation to 875 or 1750 ppm, 6h/day, 5 days/week for 12 months, and killed 18 months later. There were no adverse findings, except for focal hepatocellular alterations in females at 1750 ppm.

Ref. Rampy LW et al., in Proceedings of the First International Congress of Toxicology (eds. Plaa GL and Duncan WAM) 1978 NY Academic Press p 562

Reproductive Toxicity

Swiss-Webster mice exposed to 875 ppm, 7h/day, on days 6-15 of gestation. There was no evidence of maternal toxicity, foetotoxicity or teratogenicity.

Ref. Schwetz BA et al., Toxicol. Appl. Pharmacol. 1975 32 84-96

$$875 \text{ ppm} = \frac{875 \times 133.42}{24.45} = 4775 \text{ mg / m}^3 = 4.78 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{4.78 \times 7}{24} = 1.39 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.39 \times 43}{0.03} = 1992 \text{ mg / kg}$$

$$\text{PDE} = \frac{1992 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 830 \text{ mg / day}$$

$$\text{Limit} = \frac{830 \times 1000}{10} = 83{,}000 \text{ ppm}$$

Swiss mice given 0.58, 1.75 or 5.83 mg/mL in drinking water in two-generation study modified to include assessment of teratogenicity. There were no effects on fertility, gestation, viability, lactation indices, or pup survival and growth. No teratogenicity was observed. NOEL = 5.83 mg/mL.

Ref. Lane RW et al., Toxicol. Appl. Pharmacol. 1982 63 409-421

Assuming water intake of 6 mL/day and body weight of 30 g

$$\text{Daily dose} = \frac{5.83 \times 6}{0.03} = 1166 \text{ mg / kg}$$

$$\text{PDE} = \frac{1166 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 486 \text{ mg / day}$$

$$\text{Limit} = \frac{486 \times 1000}{10} = 48600 \text{ ppm}$$

Sprague-Dawley rats exposed to 875 ppm, 7h/day, on days 6-15 of gestation. There was no evidence of maternal toxicity, foetotoxicity or teratogenicity.

Ref. Schwetz BA et al., Toxicol. Appl. Pharmacol. 1975 32 84-96

$$875 \text{ ppm} = \frac{875 \times 133.42}{24.45} = 4775 \text{ mg / m}^3 = 4.78 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{4.78 \times 7}{24} = 1.39 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.39 \times 290}{0.330} = 1221 \text{ mg / kg}$$

$$\text{PDE} = \frac{1221 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 1221 \text{ mg / day}$$

$$\text{Limit} = \frac{1221 \times 1000}{10} = 122{,}100 \text{ ppm}$$

Long-Evans rats exposed by inhalation to 2100 ppm, 6h/day on days 1-20 of gestation, with or without premating exposure (6h/day, 5 days/week for 2 weeks) showed no maternal

toxicity, but mean foetal weight was reduced, and there were skeletal and soft tissue variations indicative of retarded development.

Ref. York RG et al., J. Toxicol. Environ. Health 1982 9 251-266

$$2100 \text{ ppm} = \frac{2100 \times 133.42}{24.45} = 11459 \text{ mg / m}^3 = 11.5 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{11.5 \times 6}{24} = 2.88 \text{ mg / L}$$

$$\text{Daily dose} = \frac{2.88 \times 290}{0.330} = 2531 \text{ mg / kg}$$

$$\text{PDE} = \frac{2531 \times 50}{5 \times 10 \times 1 \times 1 \times 10} = 253 \text{ mg / day}$$

$$\text{Limit} = \frac{253 \times 1000}{10} = 25{,}300 \text{ ppm}$$

In a study reported only in abstract, it was claimed that there were cardiac abnormalities (persistent ductus arteriosus and atrial hypoplasia or displacement) in 15/52 offspring of Sprague-Dawley rats given 10 ppm in drinking water from 7 days before, and during, cohabitation, the females then being exposed through gestation and lactation. Ref. Dapson SC et al., Teratology 1984 29 25A

These findings are entirely at odds with other evidence of lack of reproductive toxicity with 1,1,1-trichloroethane, and the following study was conducted to investigate further.

Male and female Sprague-Dawley rats were given 3, 10 or 30 ppm in drinking water for 14 days before cohabitation and during cohabitation. Females continued to be exposed through either gestation days (GD) 1-20, or GD 1-20 + lactation. Males showed no adverse effects. There was no maternal toxicity, no effect on gestational or litter parameters, except for a

slight increase in mortality from implantation to post-natal day 1 at 30 ppm (considered to be due to high loss in one litter), and no increase in cardiac or other malformations. NOEL = 30 ppm. Refs. George JD et al., Fund. Appl. Toxicol. 1989 13 641-651

George JD et al., Developmental toxicity evaluation of 1,1,1-trichloroethane administered to Sprague-Dawley rats. Part I. Postnatal evaluation, Final Study Report, 1987, NTIS Accession No. PB88131321/AS

George JD et al., Developmental toxicity evaluation of 1,1,1-trichloroethane administered to Sprague-Dawley rats. Part II. Teratological evaluation, Final Study Report, 1987, NTIS Accession No. PB88134101

Assuming water intake of 30 mL/day and body weight of 330 g

$$\text{Daily dose} = \frac{0.03 \times 30}{0.330} = 2.7 \text{ mg / kg}$$

$$\text{PDE} = \frac{2.7 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 2.7 \text{ mg / day}$$

$$\text{Limit} = \frac{2.7 \times 1000}{10} = 140 \text{ ppm}$$

The PDE calculated from this study is disregarded since no toxicity was observed.

Toxicity

Oral LD50 in mice 11.24 g/kg (no inhibitor), 9.7 g/kg (+ inhibitor).

Oral LD50 in rats 10.3-12.3 g/kg (no inhibitor), 11.0-14.3 g/kg (+ inhibitor).

Oral LD50 in rabbits 5.66 g/kg (no inhibitor), 10.5 g/kg (+ inhibitor).

Oral LD50 in guinea pigs 9.47 g/kg (no inhibitor), 8.6 g/kg (+ inhibitor).

Ref. Torkelson TR et al., Am. Ind. Hyg. Assoc. J. 1958 19 353-362

Inhalation LC50 in mice (30 min exposure, 24h observation) 22240 ppm.

Ref. Woolverton WL and Balster RL Toxicol. Appl. Pharmacol. 1981 59 1-7

Inhalation LC50 in rats (15 min exposure) 38000 ppm.

Ref. Clark DG and Tinston DJ Human Toxicol. 1982 1 239-247

Intraperitoneal LD50 in rats 5.08 g/kg.

Ref. Klaasen CD and Plaa GL Biochem. Pharmacol 1969 18 2019-2027

Dermal LD50 in rabbits > 15.8 g/kg.

Ref. Torkelson TR et al., Am. Ind. Hyg. Assoc. J. 1958 19 353-362

Mice B6C3F1 mice given 1000, 1780, 3160, 5620 or 10000 mg/kg/day, 5 days/week for 6 weeks, then observed for 2 weeks. No histopathology carried out. Deaths at 10000 mg/kg/day; NOEL = 5620 mg/kg/day.

Ref. NCI. Bioassay of 1,1,1-trichloroethane for possible carcinogenicity, Technical Report Series 3, US DHEW, 1977

$$\text{Daily dose} = \frac{5620 \times 5}{7} = 4014 \text{ mg / kg / day}$$

$$\text{PDE} = \frac{4014 \times 50}{12 \times 10 \times 10 \times 10 \times 1} = 16.7 \text{ mg / day}$$

$$\text{Limit} = \frac{16.7 \times 1000}{10} = 1670 \text{ ppm}$$

Male CF-1 mice exposed by inhalation to 250 or 1000 ppm continuously for 14 weeks. Only liver examined, including EM. Marked liver damage at 1000 ppm, effects at 250 ppm minimal. LOEL = 250 ppm.

Ref. McNutt NS et al., Lab. Invest. 1975 32 642-654

$$250 \text{ ppm} = \frac{250 \times 133.42}{24.45} = 1364 \text{ mg / m}^3 = 1.36 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.36 \times 43}{0.028} = 2088 \text{ mg / kg}$$

$$\text{PDE} = \frac{2088 \times 50}{12 \times 10 \times 5 \times 1 \times 5} = 34.8 \text{ mg / day}$$

$$\text{Limit} = \frac{34.8 \times 1000}{10} = 3480 \text{ ppm}$$

Rats Osborne-Mendel rats given 1000, 1780, 3160, 5620 or 10000 mg/kg/day, 5 days/week for 6 weeks, then observed for 2 weeks. No histopathology carried out. Some deaths at 5620 and 10000 mg/kg/day and reduced weight gain in survivors; NOEL = 3160 mg/kg/day.

Ref. NCI. Bioassay of 1,1,1-trichloroethane for possible carcinogenicity, Technical Report Series 3, US DHEW, 1977

$$\text{Daily dose} = \frac{3160 \times 5}{7} = 2257 \text{ mg / kg}$$

$$\text{PDE} = \frac{2257 \times 50}{5 \times 10 \times 10 \times 10 \times 1} = 22.6 \text{ mg / day}$$

$$\text{Limit} = \frac{22.6 \times 1000}{10} = 2260 \text{ ppm}$$

Male Wistar rats exposed by inhalation to 204 ppm, 8h/day, 5 days/week, for 14 weeks. No detectable effects, including at microscopic examination of a limited number of tissues. NOEL = 204 ppm.

Ref. Eben A and Kimmerle G Arch. Toxicol. 1974 31 233-242

$$204 \text{ ppm} = \frac{204 \times 133.42}{24.45} = 1113 \text{ mg / m}^3 = 1.11 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{1.11 \times 8 \times 5}{24 \times 7} = 0.26 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.26 \times 290}{0.425} = 177 \text{ mg / kg}$$

$$\text{PDE} = \frac{177 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 35.4 \text{ mg / day}$$

$$\text{Limit} = \frac{35.4 \times 1000}{10} = 3540 \text{ ppm}$$

Long-Evans or Sprague-Dawley rats exposed continuously for 90 days to atmospheres containing 754 or 2059 mg/m^3. Non-specific lung changes, but no effects considered to be treatment-related. NOEL 2059 mg/m^3 = 2.06 mg/L

Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{2.06 \times 290}{0.425} = 1405 \text{ mg / kg}$$

$$\text{PDE} = \frac{1405 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 280 \text{ mg / day}$$

$$\text{Limit} = \frac{280 \times 1000}{10} = 28{,}000 \text{ ppm}$$

Rats exposed by inhalation to 5000 ppm, 7h/day, on 31 of 44 days. No effect, except for transiently reduced weight gain in females. LOEL = 5000 ppm.

Ref. Adams EM et al., Arch. Ind. Hyg. Occup. Med. 1950 1 225-236

$$5000 \text{ ppm} = \frac{5000 \times 133.42}{24.45} = 27284 \text{ mg / m}^3 = 27.3 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{27.3 \times 7 \times 31}{24 \times 44} = 5.61 \text{ mg / L}$$

$$\text{Daily dose} = \frac{5.61 \times 290}{0.425} = 3828 \text{ mg / kg}$$

$$\text{PDE} = \frac{3828 \times 50}{5 \times 10 \times 10 \times 1 \times 5} = 76.6 \text{ mg / day}$$

$$\text{Limit} = \frac{76.6 \times 1000}{10} = 7660 \text{ ppm}$$

Rats exposed to 500 ppm by inhalation, 7h/day, 5 days/week for 6 months. No evidence of toxicity, including at microscopic examination of limited tissue list.

Ref. Torkelson TR et al., Am. Ind. Hyg. Assoc. J. 1958 19 353-362

$$500 \text{ ppm} = \frac{500 \times 133.42}{24.45} = 2728 \text{ mg / m}^3 = 2.73 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{2.73 \times 7 \times 5}{24 \times 7} = 0.57 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.57 \times 43}{0.425} = 389 \text{ mg / kg}$$

$$\text{PDE} = \frac{389 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 77.8 \text{ mg / day}$$

$$\text{Limit} = \frac{77.8 \times 1000}{10} = 7780 \text{ ppm}$$

Rabbits New Zealand White rabbits exposed continuously for 90 days to atmospheres containing 754 or 2059 mg/m^3. Reduced weight gain at 2059 mg/m^3. Other changes (non-specific lung and one death at lower concentration) not considered to be treatment-related. NOEL 754 mg/m^3 = 0.754 mg/L.

Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{0.754 \times 1440}{4} = 271 \text{ mg / kg}$$

$$\text{PDE} = \frac{271 \times 50}{2.5 \times 10 \times 5 \times 1 \times 1} = 108.4 \text{ mg / day}$$

$$\text{Limit} = \frac{108.4 \times 1000}{10} = 10{,}840 \text{ ppm}$$

Rabbits exposed by inhalation to 5000 ppm, 7h/day, on 31 of 44 days. No effect, except for slightly reduced weight gain. LOEL = 5000 ppm.

Ref. Adams EM et al., Arch. Ind. Hyg. Occup. Med. 1950 1 225-236

$$5000 \text{ ppm} = \frac{5000 \times 133.42}{24.45} = 27284 \text{ mg / } m^3 = 27.3 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{27.3 \times 7 \times 31}{24 \times 44} = 5.61 \text{ mg / L}$$

$$\text{Daily dose} = \frac{5.61 \times 1440}{4} = 2019 \text{ mg / kg}$$

$$\text{PDE} = \frac{2019 \times 50}{2.5 \times 10 \times 10 \times 1 \times 5} = 80.8 \text{ mg / day}$$

$$\text{Limit} = \frac{80.8 \times 1000}{10} = 8080 \text{ ppm}$$

Guinea pigs Hartley guinea pigs exposed continuously for 90 days to atmospheres containing 754 or 2059 mg/m^3. Non-specific lung changes, but no effects considered to be treatment-related. NOEL 2059 mg/m^3 = 2.06 mg/mL.

Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{2.06 \times 430}{0.500} = 1772 \text{ mg / kg}$$

$$\text{PDE} = \frac{1772 \times 50}{10 \times 10 \times 5 \times 1 \times 1} = 177 \text{ mg / day}$$

$$\text{Limit} = \frac{177 \times 1000}{10} = 17700 \text{ ppm}$$

Guinea pigs exposed by inhalation to 5000 ppm, 7h/day, on 32 of 45 days. Reduced weight gain and hepatic fatty degeneration in both sexes; testicular degeneration in males. LOEL = 5000 ppm. Ref. Adams EM et al., Arch. Ind. Hyg. Occup. Med. 1950 1 225-236

$$5000 \text{ ppm} = \frac{5000 \times 133.42}{24.45} = 27284 \text{ mg / } m^3 = 27.3 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{27.3 \times 7 \times 32}{24 \times 45} = 5.66 \text{ mg / L}$$

$$\text{Daily dose} = \frac{5.66 \times 430}{0.500} = 4867 \text{ mg / kg}$$

$$\text{PDE} = \frac{4867 \times 50}{10 \times 10 \times 10 \times 1 \times 10} = 24.3 \text{ mg / day}$$

$$\text{Limit} = \frac{24.3 \times 1000}{10} = 2430 \text{ ppm}$$

Guinea pigs exposed by inhalation to 3000 ppm, 7h/day, on 20 of 29 days, 1500 ppm on 44/60 days, 650 ppm on 65/92 days or 650 ppm on 40/57 days. Hepatic fatty degeneration at 3000 ppm; transiently reduced weight gain at all concentrations. LOEL = 1500 ppm.

Ref. Adams EM et al., Arch. Ind. Hyg. Occup. Med. 1950 1 225-236

$$1500 \text{ ppm} = \frac{1500 \times 133.42}{24.45} = 8185 \text{ mg / m}^3 = 8.19 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{8.19 \times 7 \times 44}{24 \times 70} = 1.75 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.75 \times 430}{0.500} = 1505 \text{ mg / kg}$$

$$\text{PDE} = \frac{1505 \times 50}{10 \times 10 \times 10 \times 1 \times 5} = 15 \text{ mg / day}$$

$$\text{Limit} = \frac{15 \times 1000}{10} = 1500 \text{ ppm}$$

Guinea pigs exposed to 500 ppm by inhalation, 7h/day, 5 days/week for 6 months. No evidence of toxicity, including at microscopic examination of limited tissue list. Ref. Torkelson TR et al., Am. Ind. Hyg. Assoc. J. 1958 19 353-362

$$500 \text{ ppm} = \frac{500 \times 133.42}{24.45} = 2728 \text{ mg / m}^3 = 2.73 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{2.73 \times 7 \times 5}{24 \times 7} = 0.57 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.57 \times 430}{0.500} = 490 \text{ mg / kg}$$

$$\text{PDE} = \frac{490 \times 50}{10 \times 10 \times 2 \times 1 \times 1} = 122 \text{ mg / day}$$

$$\text{Limit} = \frac{122 \times 1000}{10} = 12200 \text{ ppm}$$

Dogs Beagle dogs exposed continuously for 90 days to atmospheres containing 754 or 2059 mg/m^3. Slightly reduced weight gain at 2059 mg/m^3. Non-specific lung changes, but no effects considered to be treatment-related. NOEL 754 mg/m^3 = 0.754 mg/L.

Ref. Prendergast JA Toxicol. Appl. Pharmacol. 1967 10 270-289

$$\text{Daily dose} = \frac{0.754 \times 9000}{11.5} = 590 \text{ mg / kg}$$

$$\text{PDE} = \frac{590 \times 50}{2 \times 10 \times 5 \times 1 \times 1} = 295 \text{ mg / day}$$

$$\text{Limit} = \frac{295 \times 1000}{10} = 29{,}500 \text{ ppm}$$

Human

1,1,1-Trichloroethane is fairly lipid soluble, and is absorbed after exposure of skin or by inhalation. No studies have been carried out by the oral route, but intoxication after ingestion indicates that absorption occurs. One subject survived accidental ingestion of approximately 600 mg/kg without evidence of renal or hepatic dysfunction, although there was marked gastrointestinal irritancy. Twenty-eight workers with long-term, repetitive, high exposures to

1,1,1-trichloroethane (levels unknown) showed evidence of a toxic encephalopathy, with symptoms similar to those seen after exposure to other solvents. The principal finding at autopsy of victims of occupational poisoning or solvent abuse has generally been lung oedema. Repeated, controlled exposures to up to 500 ppm 1,1,1-trichloroethane produced mild CNS disturbance.

Refs. Stewart RD and Andrews JT JAMA 1966 195 904-906

Stahl CJ et al., J. Forensic Sci. 1969 14 393-397

Hall FB and Hine CH J. Forensic Sci. 1966 11 404-413

Kelafant GA et al., Am. J. Indust. Med. 1994 25 439-446

Stewart RD et al., Arch. Environ. Health 1969 19 467-472

Very few studies have been carried out on workers exposed occupationally to 1,1,1-trichloroethane for long periods. Multiple studies provide no convincing evidence of genotoxicity of 1,1,1-trichloroethane itself. No anecdotal accounts suggesting carcinogenicity in humans have been located, and the solvent gave negative results in 2-year rodent studies.

Environmental Impact

Under the revised Montreal Protocol, production and use of 1,1,1-trichloroethane are scheduled to be phased out by the year 2005 by ratifying parties (excluding 10-year derogations for developing nations), because of its contribution to atmospheric ozone depletion (ozone-depleting potential 0.15, cf. 0.8-1.0 for fully halogenated CFCs, and short residence time, but world production is high).

Conclusion

Animal toxicity generally low; not carcinogenic in well-designed studies. No evidence of reproductive toxicity in adequate studies. Relatively low toxicity in man after acute or repeated exposure.

The PDE for 1,1,1-trichloroethane is 15.0 mg/day (limit 1500 ppm). However, note that production of 1,1,1-trichloroethane is scheduled to be phased out by 2005 under the Montreal Protocol, because of atmospheric ozone depletion.