APPENDIX 5. TOXICOLOGICAL DATA FOR CLASS 2 SOLVENTS

ACETONITRILE

Genotoxicity

Negative in most studies.

Ref. Schlegelmilch R et al., J. Appl. Toxicol. 1988 8 (3) 201-9

EPA Doc No. 40-8446070 Fiche No. OTS 0507279 (1984)

NTP Tech Report 447; NIH Pub. No. 96 - 3363 (1996)

Carcinogenicity

F344 rats were given 100, 200 or 400 ppm by inhalation 6 h/day, 5 days/week for 2 years. Slight increase in incidence of hepatocellular adenoma or carcinoma (combined) in the high dose males which was slightly higher than the historic control range. NOEL 200 ppm.

Ref. NTP Tech Report 447, NIH Pub. No. 96 - 3363 (1996)

$$200 \text{ ppm} = \frac{200 \times 41.05}{24.45} = 335.8 \text{ mg / m}^3 = 0.336 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.336 \times 6 \times 5}{24 \times 7} = 0.06 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.06 \times 290}{0.425} = 40.9 \text{ mg / kg}$$

$$\text{PDE} = \frac{40.9 \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 4.1 \text{ mg / day}$$

$$\text{Limit} = \frac{4.1 \times 1000}{10} = 410 \text{ ppm}$$

B6C3F1 mice were given 50, 100 or 200 ppm by inhalation, 6 h/day, 5 days/week for 2 years. No treatment related oncongenic changes were noted.

NOEL 200 ppm. Ref. NTP Tech Report 447, NIH Pub. No. 96 - 3363 (1996)

As above 200 ppm = 0.336 mg/L

$$\text{For continuous exposure} = \frac{0.336 \times 6 \times 5}{24 \times 7} = 0.06 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.06 \times 43}{0.028} = 92.1 \text{ mg / kg}$$

$$\text{PDE} = \frac{92.1 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 38 \text{ mg / day}$$

$$\text{Limit} = \frac{38 \times 1000}{10} = 3800 \text{ ppm}$$

Reproductive Toxicity

125, 190 and 275 mg/kg given by gavage to Sprague-Dawley rats, days 6-19. Some mortality, reduced maternal weight gain and increased foetal loss at high dose only. No teratogenic effects but reduced ossification associated with the maternal toxicity. NEL 190 mg/kg. Ref. Johannsen FR et al., Fund. Appl. Toxicol. 1986 7 33-40

$$\text{PDE} = \frac{190 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 190 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{190 \times 1000}{10} = 19{,}000 \text{ ppm}$$

100, 400 or 1200 ppm by inhalation 6 h/day to rats on days 6-19. One death at 400 and 2 at 1200 ppm but no other maternal signs of toxicity. No adverse effects on foetuses. NOEL 1200 ppm for teratogenicity. Ref. NTP Tech Report 447, NIH Pub. No. 94 - 3363 (1994)

$$1200 \text{ ppm} = \frac{1200 \times 41.05}{24.45} = 2015 \text{ mg / m}^3 = 2.015 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{2.015 \times 6}{24} = 0.504 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.504 \times 290}{0.33} = 443 \text{ mg / kg}$$

$$\text{PDE} = \frac{443 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 443 \text{ mg / day}$$

$$\text{Limit} = \frac{443 \times 1000}{10} = 44{,}300 \text{ ppm}$$

2, 15, 30 mg/kg by gavage to NZW rabbits days 6-18. Deaths and abortions in dams at high dose and reduced weight gain at 15 and 30 mg/kg. Reduction in numbers of live foetuses at high dose level but survivors unaffected. Virtual NEL 15 mg/kg.

Ref. EPA Doc No. 40-8446070 Fiche No. OTS 0507279 (1984)

$$\text{PDE} = \frac{15 \times 50}{2.5 \times 10 \times 1 \times 1 \times 1} = 30 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{30 \times 1000}{10} = 3{,}000 \text{ ppm}$$

Toxicity

Rats exposed to 25, 50, 100, 200 and 400 ppm by inhalation 6.5 h/day, 5 days/week for 13 weeks caused cytoplasmic vacuolisation of hepatocytes at 400 ppm only. NEL 200 ppm.

Ref. Hazleton Labs Reports for NTP 1983 (referenced in Am.Conf. of Governmental Ind. Hyg. Doc of TLU and Biological Exposure Indices 1986)

$$200 \text{ ppm} = \frac{200 \text{ x } 41.05}{24.45} = 336 \text{ mg / m}^3 = 0.34 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.34 \text{ x } 6.5 \text{ x } 5}{24 \text{ x } 7} = 0.066 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.066 \text{ x } 290}{0.425} = 45 \text{ mg / kg}$$

$$\text{PDE} = \frac{45 \text{ x } 50}{5 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x } 1} = 9.0 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{9.0 \text{ x } 1000}{10} = 900 \text{ ppm}$$

Mice exposed to 50, 100, 200, 400 ppm by inhalation 6.5 h/day, 5 days/week for 13 weeks. No effects at 50 ppm. 100 ppm caused only slightly increased liver weight in females and at higher levels changes in liver seen and RBC and WBC reduced. Virtual NEL 100 ppm

Ref. Hazleton Labs Report for NTP 1983 (referenced in ACIG Document as above)

$$100 \text{ ppm} = \frac{100 \text{ x } 41.05}{24.45} = 168 \text{ mg / m}^3 = 0.168 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.168 \text{ x } 6.5 \text{ x } 5}{24 \text{ x } 7} = 0.033 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.033 \text{ x } 43}{0.028} = 50.7 \text{ mg / kg}$$

$$\text{PDE} = \frac{50.7 \text{ x } 50}{12 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x } 1} = 4.22 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{4.22 \times 1000}{10} = 422 \text{ ppm}$$

Human

No chronic data available. Acute death at high unknown exposure probably due to thiocyanate.

Ref. Amdur ML J. Occup. Med. 1959 1 627

Metabolism

Acetonitrile slowly metabolised to cyanide but blood cyanide and urinary thiocyanate measurements not good indicators of low level exposure.

Conclusion

The PDE for acetonitrile is 4.1 mg/day.

CHLOROBENZENE

Genotoxicity

Negative results in a range of studies comprising Ames test, against Aspergillus nidulans chinese hamster ovary cell chromosome aberration assay, in vitro rat liver UDS assay and a sex linked recessive lethal assay in Drosophila

Refs. NTP Tech. Report Series No. 261 NIH Pub.No. 86-2517 (1985)

Prasad I and Pramer D. Genetics 1968 60 212-213

EPA Doc. No. 40-8320545. Fiche No. OTS 0511274 (1982)

EPA Doc. No. FYI-0284-0291. Fiche No. OTS 0000291-0 (1984)

Carcinogenicity

Rats Fischer 344 rats given 60 or 120 mg/kg by gavage 5 days/week for 2 years. Weight gain unaffected by treatment but reduced survival in high dose males. Increased incidence of hyperplastic nodules in livers of high dose male rats only. After 2 years, not considered carcinogenic response.

Ref. NTP Tech Report Series No. 261. NIH Pub.No. 86-2517 (1985)

NEL 60 mg/kg

$$\text{Continuous exposure} = \frac{60 \times 5}{7} = 43 \text{ mg / kg}$$

$$\text{PDE} = \frac{43 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 43.0 \text{ mg / day}$$

$$\text{Limit} = \frac{43.0 \times 1000}{10} = 4300 \text{ ppm}$$

Mice Female B6C3F1 mice given 60 or 120 mg/kg and male mice given 30 or 60 mg/kg by gavage 5 days/week for 2 years. No effects on survival or tumour incidence were noted.

Ref. NTP Tech Report Series No. 261 NIH Pub.No. 86-2517 (1985)

NEL is 60 mg/kg as above.

$$\text{Continuous exposure} = \frac{60 \times 5}{7} = 43 \text{ mg / kg}$$

$$\text{PDE} = \frac{43 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 17.9 \text{ mg / day}$$

$$\text{Limit} = \frac{17.9 \times 1000}{10} = 1790 \text{ ppm}$$

Reproductive Toxicity

Rats Fischer 344 rats given 75, 210 or 590 ppm by inhalation 6 h/day during days 6-15 of gestation. There was decreased maternal weight gain and food consumption at the high dose level but no embryotoxic or teratogenic effects. Ossification was slightly delayed at the maternally toxic level.

Ref. John JA et al., Toxicol. Appl. Pharmacol. 1984 76 365-7

NEL 590 ppm

$$\frac{590 \times 112.56}{24.45} = 2716 \text{ mg / m}^3 = 2.72 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{2.72 \times 6}{24} = 0.68 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.68 \times 290}{0.33} = 598 \text{ mg / kg}$$

$$\text{PDE} = \frac{598 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 598 \text{ mg / day}$$

$$\text{Limit} = \frac{599 \times 1000}{10} = 59{,}800 \text{ ppm}$$

Sprague-Dawley rats received 50, 150 or 450 ppm by inhalation 6 h/day through a 10 week premating period and then throughout 2 successive generations. No effects on fertility or reproductive performance were noted. Ref. Nair RS et al., Fund. Appl. Toxicol. 1987 9 678-86

NEL is 450 ppm

$$\frac{450 \times 112.56}{24.45} = 2072 \text{ mg / m}^3 = 2.07 \text{ mg / L}$$

$$\text{Continuous dosing} = \frac{2.07 \times 6}{24} = 0.52 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.52 \times 290}{0.33} = 457 \text{ mg / kg}$$

$$\text{PDE} = \frac{457 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 457 \text{ mg / day}$$

$$\text{Limit} = \frac{457 \times 1000}{10} = 45{,}700 \text{ ppm}$$

Rabbits NZW rabbits were given 75, 210 or 590 ppm by inhalation 6 h/day, days 6-18. Slight maternal toxicity at intermediate and high levels. No effects on litter size or mean foetal weight. Slight increase in malformations in all treatment groups but with no dose-related trends in frequency or nature of the defects. The study was repeated using levels of 10, 30, 75 or 590 ppm. Higher incidence of resorptions at the highest level but no embryotoxic or teratogenic effects. The increased level of resorptions was within the historical range and was not considered to be a drug induced effect.

Ref. John JA et al., Toxicol. Appl. Pharmacol. 1984 76 365-73. NEL 590 ppm

As above for continuous exposure = 0.68 mg / L

$$\text{Daily dose} = \frac{0.68 \times 1440}{4} = 245 \text{ mg / kg}$$

$$\text{PDE} = \frac{245 \times 50}{2.5 \times 10 \times 1 \times 1 \times 1} = 490 \text{ mg / day}$$

$$\text{Limit} = \frac{490 \times 1000}{10} = 49{,}000 \text{ ppm}$$

Animal Toxiocity

Dogs Given 27.25, 54.5 or 272.5 mg/kg by gavage 5 days/week for 3 months. Deaths occurred at the high dose level with damage to liver, kidneys, GI tract and haemopoeitic system. No changes were observed at lower levels. NEL 54.5 mg/kg

Ref. Knapp WK et al., Toxicol. Appl. Pharmacol. 1971 19 393

$$\text{Continuous dosing} = \frac{54.5 \times 5}{7} = 38.9 \text{ mg / kg}$$

$$\text{PDE} = \frac{38.9 \times 50}{2 \times 10 \times 5 \times 1 \times 1} = 19.5 \text{ mg / day}$$

$$\text{Limit} = \frac{19.5 \times 1000}{10} = 1950 \text{ ppm}$$

Rats Given 12.5, 50 or 250 mg/kg in diet daily for 3 months. Reduced weight gain in males at high dose level. Liver and kidney weights increased at intermediate and high levels but no pathology.

Ref. Knapp WK et al., Toxicol. Appl. Pharmacol. 1971 19 393. NEL 50 mg/kg

$$\text{PDE} = \frac{50 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 10.0 \text{ mg / day}$$

$$\text{Limit} = \frac{5.0 \times 1000}{10} = 1{,}000 \text{ ppm}$$

Fischer 344 rats given 60, 125, 250, 500 or 750 mg/kg by gavage 5 days/week for 13 weeks. The 500 and 750 mg/kg levels were lethal. Weight gain in males was depressed in those animals receiving 250 mg/kg or more and for females that received 500 mg/kg or more. Relative liver weights were increased at doses of 250 mg/kg and above in both sexes and in the 125 mg/kg females. Relative kidney weights were increased at 500 mg/kg and above. Absolute kidney weights were only increased in the high dose female group and absolute liver weights were increased in all except the low dose group.

Centrilobular hepatocellular necrosis was noted at 250 mg/kg and above with increasing severity. Renal tubular degeneration was seen in male and female rats at 750 mg/kg and in male rats at 500 mg/kg. Lymphoid depletion of the thymus occurred in both sexes at the high dose and myeloid depletion of the marrow was seen at the 500 and 750 mg/kg levels in both sexes.

Ref. NTP Tech Report Series No. 261 NIH Pub.No. 86-2517 (1985). NOEL 125 mg/kg

$$\text{Continuous dosing} = \frac{125 \times 5}{7} = 89 \text{ mg / kg}$$

$$\text{PDE} = \frac{89 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 17.8 \text{ mg / day}$$

$$\text{Limit} = \frac{17.8 \times 1000}{10} = 1780 \text{ ppm}$$

Mice B6C3F1 mice given 60, 125, 250, 500 or 750 mg/kg by gavage 5 days/week for 13 weeks. All animals receiving the two highest dosages died by week 9 and deaths were also noted at 125 and 250 mg/kg. Absolute and relative liver weights were increased in surviving males at 125 and 250 mg/kg and in surviving females at 250 and 500 mg/kg. Hepatic necrosis was seen in one male at 60 mg/kg, one at 125 mg/kg and more generally at higher levels. Necrosis of the renal tubular epithelium was observed in male mice at 250 mg/kg and above but only at 250 mg/kg in females. Myeloid depletion of the bone marrow and lymphoid depletion or necrosis of the thymus occurred in both sexes at 250 mg/kg and above. NOEL 60 mg/kg (apart from one instance of hepatic necrosis)

Ref. NTP Tech Report Series No. 261 NIH Pub. No. 86-2517 (1985)

$$\text{Continuous dosing} = \frac{60 \times 5}{7} = 43 \text{ mg / kg}$$

$$\text{PDE} = \frac{43 \times 50}{12 \times 10 \times 5 \times 1 \times 1} = 3.58 \text{ mg / day}$$

$$\text{Limit} = \frac{3.58 \times 1000}{10} = 358 \text{ ppm}$$

Conclusion

The PDE for chlorobenzene is 3.6 mg/day.

CHLOROFORM

Genotoxicity

Chloroform has been widely examined in in vitro studies, the bulk of which give negative results. Some more equivocal results have been obtained in in vivo studies but many of the studies are of questionable quality and the weight of in vivo evidence is convincingly negative.

Refs. Ashby J in Prog. In Mut Res. 1981 1 111-171

Reitz RH et al., Environ. Health Perspect. 1982 46 163-68

IARC Monograph 1987 Suppl. 6

Carcinogenicity

As per Pharm. Forum 1990 P543-549

Mouse Roe FC et al., J. Environ. Path Toxicol. 1979 2 799-819

Liver and renal tumours in male mice at 60 mg/kg 6 days/week

NOEL 17 mg/kg corrected to 14.6 mg/kg for 7 days/week treatment

$$\text{PDE} = \frac{14.6 \times 50}{12 \times 10 \times 1 \times 10 \times 1} = 0.61 \text{ mg / day}$$

$$\text{Limit ppm} = \frac{0.61 \times 1000}{10} = 61 \text{ ppm}$$

Rat Jorgenson TA et al., Fund.Appl. Toxicol. 1985 5 760-69

Kidney tumours at 400 mg/L in drinking water for 2 years

(TWA 38 mg/kg) NEL 200 mg/L (19 mg/kg)

$$\text{PDE} = \frac{19 \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 1.9 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{1.9 \times 1000}{10} = 190 \text{ ppm}$$

Reproductive Toxicity

Ref. Thompson D et al., Toxicol. Appl. Pharmacol. 1974 29 348-57

Rats given 20, 50, or 126 mg/kg by gavage, days 6-15. Maternal and foetal toxicity at high dose but no teratogenic effects. NOEL 50 mg/kg.

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

$$\text{Limit (ppm)} = \frac{50 \times 1000}{10} = 5{,}000 \text{ ppm}$$

Rabbits given 20, 35, or 50 mg/kg by gavage, days 6-18. Hepatotoxicity and death in some high dose level animals. Reduced foetal weight at high dose only but no teratogenic effects. NOEL 35 mg/kg.

$$\text{PDE} = \frac{35 \times 50}{2.5 \times 10 \times 1 \times 1 \times 1} = 70 \text{ mg / day}$$

$$\text{Limit} = \frac{70 \times 1000}{10} = 7000 \text{ ppm}$$

Toxicity

25 ppm given by inhalation 7 h/day, 5 days/week for 6 months to rats was NEL. Higher doses caused liver and kidney damage.

Ref. Torkelson T et al., Am.Ind.Hyg.J. 1976 37 697-705

$$25 \text{ ppm} = \frac{25 \times 119.38}{24.45} = 122 \text{ mg / m}^3 = 0.12 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.12 \times 7 \times 5}{24 \times 7} = 0.025 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.025 \times 290}{0.425 \text{ kg}} = 17.1 \text{ mg / kg}$$

$$\text{PDE} = \frac{17.1 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 8.6 \text{ mg / day}$$

$$\text{Limit} = \frac{8.6 \times 1000}{10} = 860 \text{ ppm}$$

15 and 30 mg/kg given by gavage, 6 days/week for 7.5 years to beagle dogs. Fatty cysts in kidneys and nodular liver changes with increased enzyme activities at both levels. LOAEL 15 mg/kg. Ref. Heywood R et al., J. Environ. Path. Tox. 1979 2 835-51

$$\text{For continuous dosing} = \frac{15 \times 6}{7} = 12.9 \text{ mg / kg}$$

$$\text{PDE} = \frac{12.9 \times 50}{2 \times 10 \times 1 \times 1 \times 10} = 3.2 \text{ mg / day}$$

$$\text{Limit} = \frac{3.2 \times 1000}{10} = 320 \text{ ppm}$$

Human

No epidemiological data available.

Conclusion

The PDE for chloroform is 0.6 mg/day.

CYCLOHEXANE

Genotoxicity

Negative in in vitro studies.

Refs. McCann JE et al., Proc. Ntl. Acad. Sci. USA. 1975 72 5135-39

Perocco P et a.. Toxicol Lett. 1983 16 69-75

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Toxicity

Exposure of rabbits to 434 and 786 ppm by inhalation 6 h/day, 5 days/week for 10 weeks had no adverse effects. 786 ppm caused slight changes in liver and kidneys. NEL 434 ppm.

Ref. Treon JE et al., J. Ind. Hyg. 1943 25 199

$$434 \text{ ppm} = \frac{434 \text{ x } 84.16}{24.45} = 1494 \text{ mg / m}^3 = 1.5 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{1.5 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.27 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.27 \text{ x } 1440}{4} = 97.2 \text{ mg / kg}$$

$$\text{PDE} = \frac{97.2 \text{ x } 50}{2.5 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x } 1} = 38.8 \text{ mg / day}$$

$$\text{Limit} = \frac{38.8 \text{ x } 1000}{10} = 3880 \text{ ppm}$$

Human

No relevant Data.

Conclusion

The PDE for cyclohexane is 38.8 mg/day.

1,2-DICHLOROETHENE

Genotoxicity

Negative in Ames test and in Saccharomyces cerevisiae. Only the cis isomer showed some activity in the host-mediated assay.

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

Bronzetti G et al., Teratogen. Carcinogen. Mutagen. 1984 4 (4) 365-75.

Carcinogenicity

No data available.

Reproductive toxicity

No data available.

Animal toxicity

Rats exposed to 500 to 1000 ppm by inhalation 7 h/day, 5 days/week for 6 months showed no adverse effects. NOEL 1000 ppm.

Ref. Reported in American Conference of Governmental Industrial Hygienists. Documentation of TLV and Biological Exposure Indices 6th Edn. 1991 P430.

$$1000 \text{ ppm} = \frac{1000 \times 96.95}{24.45} = 3965 \text{ mg / m}^3 = 3.97 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{3.97 \times 7 \times 5}{24 \times 7} = 0.83 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.83 \times 290}{0.425} = 566 \text{ mg / kg}$$

$$\text{PDE} = \frac{566 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 284 \text{ mg / day}$$

$$\text{Limit} = \frac{284 \times 1000}{10} = 28{,}400 \text{ ppm}$$

CD-1 mice were dosed in the drinking water for 90 days at levels giving time-weighted average of 17, 175 and 387 mg/kg (males), and 23, 224 and 452 mg/kg (females). Minimal changes were observed. Thymus weights were reduced in females only at high dose level. No histopathological examination undertaken. NEL 224 mg/kg.

Ref. Barnes DW et al., Drug. Chem. Toxicol. 1985 8 (5) 373-392.

$$\text{PDE} = \frac{224 \times 50}{12 \times 10 \times 5 \times 1 \times 1} = 18.7 \text{ mg / day}$$

$$\text{Limit} = \frac{18.7 \times 1000}{10} = 1870 \text{ ppm}$$

Conclusion

The PDE for 1,2-dichloroethene is 18.7 mg/day.

DICHLOROMETHANE

Genotoxicity

Methylene chloride gives some positive results in vitro but not in vivo.

Refs. Sivak A Food Solvent Workshop No. 1. Washington 1984

Jongen WMF et al., Mut. Res. 1981 81 203-13

Carcinogenicity

Rats F344 rats given inhaled doses of 1000, 2000, 4000 ppm 6 h/day, 5 days/week for 2 years had increased incidence of benign mammary tumours at all levels but no increase in malignant tumours. Ref. NTP Tech Report No. 306 NIH Pub No. 86 - 2562 (1986)

$$1000 \text{ ppm} = \frac{1000 \times 84.94}{24.45} = 3479 \text{ mg / m}^3 = 3.5 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{3.5 \times 6 \times 5}{24 \times 7} = 0.625 \text{ mg / L}$$

$$\text{Assuming average rat wt} = 0.425 \text{ kg}$$

$$\text{Daily dose} = \frac{0.625 \times 290}{0.425 \text{ kg}} = 426 \text{ mg / kg}$$

$$\text{PDE} = \frac{426 \times 50}{5 \times 10 \times 1 \times 5 \times 10} = 8.5 \text{ mg / day}$$

$$\text{Limit} = \frac{8.5 \times 1000}{10} = 850 \text{ ppm}$$

Mice B6C3F1 mice exposed 6 h/day, 5 day/week to 2,000 or 4,000 ppm by inhalation for 2 years. Lung and hepatocellular carcinomas at both levels

Ref. NTP Tech Report No. 306 NIH Pub. No. 86 - 2562 (1986)

$$2{,}000 \text{ ppm} = 7 \text{ mg / L}$$

$$\text{For continuous exposure} = 1.25 \text{ mg / L}$$

Assuming average mouse wt 28g

$$\text{Daily dose} = \frac{1.25 \times 43}{0.028} = 1920 \text{ mg / kg}$$

$$\text{PDE} = \frac{1920 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 8.0 \text{ mg / day}$$

$$\text{Limit} = \frac{8.0 \times 1000}{10} = 800 \text{ ppm}$$

Reproductive Toxicity

Rats given 4,500 ppm by inhalation 6 h/day 7 days/week for 2 weeks before mating and until day 17 of pregnancy. No teratogenic effects.

Ref. Hardin BD and Manson JM Toxicol. Appl. Pharmacol. 1980 52 22-28

4,500 ppm = 15633 mg/m^3 = 15.6mg/L

$$\text{For continuous exposure} = \frac{15.6 \times 6}{24} = 3.9 \text{ mg / L}$$

Assuming average wt of 330 g

$$\text{Daily dose} = \frac{3.9 \times 290}{0.33} = 3427 \text{ mg / kg}$$

$$\text{PDE} = \frac{3427 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 3427 \text{ mg / day}$$

$$\text{Limit} = \frac{3427 \times 1000}{10} = 342{,}700 \text{ ppm}$$

Toxicity

Rats 6, 50, 125 or 250 mg/kg given to Fischer 344 rats in drinking water daily for 2 years. Reduced weight gain, fatty liver changes and areas of foci. No increase in neoplastic changes in liver or any other tissue. NOEL 6 mg/kg

Ref. Serota DG et al., Toxicol. Appl. Pharmacol. 1986 24 (9) 951-58

$$\text{PDE} = \frac{6 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 6.0 \text{ mg / day}$$

$$\text{Limit} = \frac{6.0 \times 1000}{10} = 600 \text{ ppm}$$

Human Results

No changes in mortality or tumour incidence following inhalation exposures up to 350 ppm for several years or TWA of 26 ppm for 22 years.

Refs. Friedlander BR et al., J. Occup. Med. 1978 20 (10) 657-66

Hearne FT et al., J. Occup. Med. 1987 29 (3) 217-28

Metabolism

Methylene chloride is metabolised to carbon monoxide and carbon dioxide by mixed function oxidase systems. When these systems become saturated a disproportionate amount is metabolised via the glutathione-s-transferase system producing reactive intermediate. Mice have much greater glutathione activity than rats or humans therefore more metabolism by this pathway.

An I/P dose of 412 mg/kg to rats results in >90% being excreted unchanged in expired air whereas in mice at 100 mg/kg only 40% is expired unchanged.

Ref. Yesair DW et al., Fdn. Proc. Fdn. Am. Soc. Exp.Biol. 1977 36 988

Conclusion

No carcinogenic risk.

The PDE for dichloromethane is 6.0 mg/day.

1,2-DIMETHOXYETHANE

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive Toxicity

Mice given 250, 350 or 490 mg/kg daily on days 7-10 of gestation. No effects on maternal weight gain. Increased foetal deaths at all dose levels. Teratogenic effects - neural tube closure defects, cleft palate and skeletal defects.

Ref. Uemura K. Acta Obstet. Gynaec. Japan 1980 32 (1) 113-121. LOEL 250 mg/kg

$$\text{PDE} = \frac{250 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 1.04 \text{ mg / day}$$

$$\text{Limit} = \frac{1.04 \times 1000}{10} = 104 \text{ ppm}$$

Animal Toxicity

Female rats exposed to 1000, 2000, 4000 or 8000 ppm by inhalation 4 h/day 5 days/week for 2 weeks. Reduced growth rate in each group and mortalities at 4,000 and 8,000 ppm. Gross autopsy revealed massive haemorrhage to lungs and GI tract. (Surviving animals were not autopsied.)

Ref. Goldberg ME et al., Am. Ind. Hygien. Assoc. J. 1964 25 369-375. LOEL = 1000 ppm

$$1000 \text{ ppm} = \frac{1000 \times 90.12}{24.45} = 3686 \text{ mg / m}^3 = 3.69 \text{ mg / L}$$

$$\text{Continuous dosing} = \frac{3.69 \times 4 \times 5}{24 \times 7} = 0.44 \text{ mg / L}$$

1 $$\text{Daily dose} = \frac{0.44 \times 290}{0.425} = 300 \text{ mg / kg}$$

$$\text{PDE} = \frac{300 \times 50}{5 \times 10 \times 10 \times 1 \times 5} = 6.00 \text{ mg / day}$$

$$\text{Limit} = \frac{6.00 \times 1000}{10} = 600 \text{ ppm}$$

2

3 **Conclusion**

4 The PDE for 1,2-dimethoxyethane is 1.0 mg/day.

N,N-DIMETHYLACETAMIDE

Genotoxicity

Negative results reported in Ames test, in vitro UDS in rat hepatocytes, dominant lethal test in rats and in rat micronucleus test.

Ref. McGregor DB NIOSH report. Government Report Announcements No. 27 PB83 - 14973 - 2 1980. Zeiger E et al., Environ. Mol. Mutagen. 1988 11 (Suppl 12) 1-158.

Carcinogenicity

Rats 25, 100, or 350 ppm administered by inhalation to Sprague-Dawley rats 6 h/day, 5 days/week for 2 years had no effect on survival and no oncogenic effects were observed. NEL 350 ppm.

Ref. Malley, L. A., et al., Fund. Appl. Toxicol., 1995, 28, 80-93.

$$350 \text{ ppm} = \frac{350 \times 87.12}{24.45} = 1247 \text{ mg / m}^3 = 1.25 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{1.25 \times 6 \times 5}{24 \times 7} = 0.223 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.223 \times 290}{0.425} = 152 \text{ mg / kg}$$

$$\text{PDE} = \frac{152 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 152 \text{ mg / day}$$

$$\text{Limit} = \frac{152 \times 1000}{10} = 15{,}200 \text{ ppm}$$

Mice 25, 100, or 350 ppm administered by inhalation to CD-1 mice 6 h/day, 5 days/week for 18 months had no effect on survival and no oncogenic effects were observed.

Ref. Malley, L. A., et al., Fund. Appl. Toxicol., 1995, 28, 80-93.

As above for continuous dosing at 350 ppm = 0.223 mg / L

$$\text{Daily dose} = \frac{0.223 \times 43}{0.028} = 343 \text{ mg / kg}$$

$$\text{PDE} = \frac{343 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 142.9 \text{ mg / day}$$

$$\text{Limit} = \frac{142.9 \times 1000}{10} = 14{,}290 \text{ ppm}$$

Reproductive Toxicity

Rats dosed up to 300 ppm by inhalation 6h/day, 5 days/week for 10 weeks pre-mating and during mating, pregnancy and lactation. Treatment had no adverse effects on mating or on the outcome of pregnancy.

Ref. Ferenz RL and Kennedy G.L. Fund. Appl. Toxicol. 1986 7 132-7

$$\text{NEL} = 300 \text{ ppm} = \frac{300 \times 87.12}{24.45} = 1069 \text{ mg / m}^3 = 1.07 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{1.07 \times 6 \times 5}{24 \times 7} = 0.19 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.19 \times 290}{0.33} = 167 \text{ mg / kg}$$

$$\text{PDE} = \frac{167 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 167 \text{ mg / day}$$

$$\text{Limit} = \frac{167 \times 1000}{10} = 16{,}700 \text{ ppm}$$

Complete resorption in rabbits dosed orally at 500microL/kg during days 6 to 18 of gestation and increased resorptions and decreased foetal weight at 300 microL/kg. Maternal weight gain reduced at both levels. No effects at the non-maternally toxic dose of 100 microL/kg.

Ref. Merkle J. and Zeller H. Arzneimittel Forsch 1980 30 (9) 1557-62.

$$\text{NEL } 100\,\text{mL / kg} = 100 \times 0.9429 = 94\ \text{mg / kg}$$

$$\text{PDE} = \frac{94 \times 50}{2.5 \times 10 \times 1 \times 1 \times 1} = 188\ \text{mg / day}$$

$$\text{Limit} = \frac{188 \times 1000}{10} = 18{,}800\ \text{ppm}$$

Sprague-Dawley rats given 65, 160 and 400 mg/kg by gavage days 6-19. Reduced maternal body weight at high dose with increased foetal loss, decreased foetal weight; heart and c/v defects.

NEL 160 mg/kg. Ref. Johannsen FR et al., Fund. Appl. Toxicol. 1987 9 550-56.

$$\text{PDE} = \frac{160 \times 50}{5 \times 10 \times 1 \times 5 \times 1} = 32\ \text{mg / day}$$

$$\text{Limit} = \frac{32 \times 1000}{10} = 3200\ \text{ppm}$$

Animal Toxicity

25, 100, or 350 ppm administered by inhalation 6 h/day, 5 days/week for 2 years to Sprague-Dawley rats. Increased liver weights, hepatic focal cystic degeneration, hepatic peliosis and haemosiderin accumulation in Kupffer cells. NEL 25 ppm. Ref. Malley LA et al., Fund. Appl. Toxicol. 1995 28 80-93.

$$25\ \text{ppm} = \frac{25 \times 87.12}{24.45} = 89\ \text{mg/m}^3 = 0.089\ \text{mg/L}$$

$$\text{For continuous dosing} = \frac{0.089 \times 6 \times 5}{24 \times 7} = 0.016\ \text{mg/L}$$

1 $$\text{Daily dose} = \frac{0.016 \times 290}{0.425} = 10.9\ \text{mg/kg}$$

$$\text{PDE} = \frac{10.9 \times 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 1} = 10.9\ \text{mg/day}$$

$$\text{Limit} = \frac{10.9 \times 1000}{10} = 1{,}090\ \text{ppm}$$

2 **Conclusion**

3 The PDE for N,N-dimethylacetamide is 10.9 mg/day.

N,N-DIMETHYLFORMAMIDE

Genotoxicity

Negative in most studies reported.

Refs. Brams A et al., Tox. Lett 1987 38 123-33

Mayer VW and Goin GJ Mut. Res. 1987 187 21-30

Williams GM Cancer Res. 1977 37 1845-51

Topham JC Mut. Res. 1980 74 379-87

Mitchell AD et al., Environ. Mol. Mutagen. 1988 12 (Suppl 13) 37-101

Carcinogenicity

Daily oral doses of 75 - 150 mg/kg to rats for 250-500 days did not produce tumours. NEL 150 mg/kg. Ref. Druckrey H et al., Z. Krebforsch 1967 69 103-201

$$\text{PDE} = \frac{150 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 30 \text{ mg / day}$$

$$\text{Limit} = \frac{30 \times 1000}{10} = 3{,}000 \text{ ppm}$$

Reproductive Toxicity

Russian rabbits given 46.4, 68.1 or 200 microL/kg. Some abortions at high dose. No increase in uterine deaths but decreased foetal weight at 200 microL/kg. Hydrocephalus at 68.1 and 200 microL/kg, also umbilical hernia at high dose. No maternal effects at 68.1 microL/kg. NEL 46.4 microL/kg.

Ref. Merkle J and Zeller H. Arzneimittel Forsch. 1980 30 (9) 1557-62

$$46 / 4 \text{ ml / kg} = 46.4 \times 0.9445 = 43.8 \text{ mg / kg}$$

$$\text{PDE} = \frac{43.8 \times 50}{2.5 \times 10 \times 1 \times 10 \times 1} = 8.76 \text{ mg / kg}$$

$$\text{Limit} = \frac{8.76 \times 1000}{10} = 876 \text{ ppm}$$

However no adverse effects were reported when 200 mg/kg, 1/17 of lethal dose, was applied dermally to NZW rabbits days 8 -16.

Ref. Stula EF and Krauss WC. Toxicol. Appl. Pharmacol. 1977 41 (1) 35-56

$$\text{PDE} = \frac{200 \times 50}{2.5 \times 10 \times 1 \times 1 \times 1} = 400 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{400 \times 1000}{10} = 40{,}000 \text{ ppm}$$

Rats given 600, 1200 or 2,400 mg/kg, 1/4 of lethal dose, dermally at varying times. Increased foetal loss and decreased foetal weight associated with maternal toxicity at high dose only. NEL 1200 mg/kg.

Ref. Stula EF and Drauss WC. Toxicol.Appl. Pharmacol. 1977 41 (1) 35-56

$$\text{PDE} = \frac{1200 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 1200 \text{ mg / day}$$

$$\text{Limit} = \frac{1200 \times 1000}{10} = 120{,}000 \text{ ppm}$$

Toxicity

Slightly increased liver weight, regarded as adaptive change, when 1000 ppm diet fed to rats in 90 day study. No microscopic changes. Higher doses caused minimal hepatocellular enlargement and increased mitotic figures. Virtual NOAEL 1000 ppm diet.

Ref. Kennedy GL and Sherman H. Drug Chem. Toxicol. 1986 9 147-70.

Rat eats 30 g/day

$$\text{Daily dose} = \frac{30 \times 1000}{1000 \times 0.425} = 70.6 \text{ mg / kg}$$

$$\text{PDE} = \frac{70.6 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 14.1 \text{ mg / day}$$

$$\text{Limit} = \frac{14.1 \times 1000}{10} = 1{,}410 \text{ ppm}$$

Single I/P doses of 0.6, 0.9 and 1.2 ml/kg given to Wistar rats. Inflammatory changes at 0.6 ml/kg with necrosis at higher doses. LOEL 0.6 ml/kg.

Ref. Mathew T et al., Lab. Invest. 1980 42 (2) 257-62

$$0.6 \text{ ml / kg} = 0.6 \times 0.9445 = 567 \text{ mg / kg}$$

$$\text{PDE} = \frac{567 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 56.7 \text{ mg / day}$$

$$\text{Limit} = \frac{56.7 \times 1000}{10} = 5{,}670 \text{ ppm}$$

Human

Possible risk of testicular germ cell cancer in humans. (Exposure not specified and other causes not excluded)

Ref. IARC Monograph 47 186

Levin SM et al., Lancet 1987 II 1153

Conclusion

The PDE for N,N-dimethylformamide is 8.8 mg/day.

1,4-DIOXANE

Genotoxicity

Consistently negative results in in vitro studies.

Refs. McGregor DB et al., Environ. Mol. Mutagen. 1991 17 196-218

Zimmermann FK et al., Mut. Res. 1985 149 339-51

Stott WT et al., Toxicol. Appl. Pharmacol. 1981 60 (2) 287-300

Limited in vivo data also negative

Ref. Stott WT et al., Toxicol. Appl. Pharmacol. 1981 60 (2) 287-300

1,4 - Dioxane is not genotoxic.

Carcinogenicity

Mice Hepatocellular tumours in B6C3F1 mice given 0.5% or 1% v/v in drinking water for 90 weeks. Ref. NCI Tech Repeat No. 80. NIH Pub No. 78-1330 (1978)

Assuming mice drink 5 ml/day

$$\text{Daily dose} = \frac{500 \times 5 \times 1.00329}{100 \times 0.028} = 922 \text{ mg / kg}$$

$$\text{PDE} = \frac{922 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 3.84 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{3.84 \times 1000}{10} = 384 \text{ ppm}$$

Rats 0.01, 0.1 or 1.0% v/v in drinking water for 23 months. Severe liver and renal toxicity at 1.0% with hepatocellular and nasal carcinoma (equivalent to 1015 mg/kg males; 1599 mg/kg females). Renal and liver degenerative changes at 0.1% (equivalent to 94 and 148 mg/kg to

males and females) but no neoplastic changes. No changes at 0.01% (equivalent to 9.6 and 19 mg/kg to male and female rats).

Ref. Kociba RJ et al., Toxicol. Appl. Pharmacol. 1974 30 275-86

$$\text{PDE} = \frac{94 \text{ mg / kg x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 1} = 9.4 \text{ mg / day}$$

$$\text{Limit ppm} = \frac{9.4 \text{ x } 1000}{10} = 940 \text{ ppm}$$

Reproductive Toxicity

No teratogenicity in rats at 0.25, 0.5, and 1 mL/kg when administered by gavage during days 6-15 of pregnancy. Slightly reduced foetal weights associated with maternal toxicity at high dose level. NEL = 1 mL/kg = 1.03 g/kg. Ref. Giavini E et al., Toxicol. Lett. 1985 26 (1) 85-8

$$\text{PDE} = \frac{1030 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 1} = 1030 \text{ mg / day}$$

$$\text{Limit} = \frac{1030 \text{ x } 1000}{10} = 103{,}000 \text{ ppm}$$

Toxicity

Rats Ref. Kociba RJ et al., Toxicol. Appl. Pharmacol. 1974 30 275-86

As above NEL 9.6 mg/kg (males) and 19 mg/kg (females)

$$\text{PDE} = \frac{9.6 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 1} = 9.6 \text{ mg / day}$$

$$\text{Limit} = \frac{9.6 \text{ x } 1000}{10} = 960 \text{ ppm}$$

Human Results

Fatalities have been reported following varying exposures to very high levels by inhalation.

Refs. Barber H Guys Hosp. Rep. 1934 84 267-80

A follow-up study indicated no increase in cancer-induced deaths above the expected in workers exposed to low levels (approx 2 ppm) for several years.

Ref. Buffler PA et al., J. Occup. Med. 1978 20 (4) 255-59.

Metabolism

In rats oral doses up to 10 mg/kg or inhaled doses of 50 ppm for 6 hours are eliminated within about one hour. At higher doses metabolism to β hydroxyethoxy-acetic acid is saturated and dioxane is excreted in the breath. Toxicity only occurs at these levels. In man 50 ppm for 6 hours is eliminated in urine within one hour and no toxicity is seen.

Conclusion

The PDE for 1,4-dioxane is 3.8 mg/day.

2-ETHOXYETHANOL

Genotoxicity

Negative in Ames test.

Ref. Shimazu H et al., Jpn. J. Ind. Health 1985 27 400-19

Carcinogenicity

No data available.

Reproductive Toxicity

1 to 4.2 g/kg by gavage to CD-1 mice days 8-14. Reduced weight gain and increased resorptions and abnormalities from 1.8 g/kg, syndactyly, exencephaly, open eyes, cleft palate. Reduced foetal weight at 1g/kg. LOEL 1g/kg.

Ref. Wier PJ et al., Terat.Carc. Mutagen. 1987 7 55-64

$$\text{PDE} = \frac{1000 \times 50}{12 \times 10 \times 1 \times 5 \times 10} = 8.3 \text{ mg / day}$$

$$\text{Limit} = \frac{8.3 \times 1000}{10} = 830 \text{ ppm}$$

200 or 765 ppm by inhalation to rats 6 h/day, days 1-19. Maternal toxicity and total litter loss at high dose. Reduced foetal weight, increased skeletal and C/V defect at low dose.

Ref. Hardin BD et al., Scand. J. Work Environ. Health 1981 7 (suppl 4) 66-75

$$200 \text{ ppm} = \frac{200 \times 90.12}{24.45} = 737 \text{ mg / m}^3 = 0.74 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.74 \times 6}{24} = 0.185 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.185 \times 290}{0.33\ \text{kg}} = 163\ \text{mg / kg}$$

$$\text{PDE} = \frac{163 \times 50}{5 \times 10 \times 1 \times 10 \times 10} = 1.63\ \text{mg / day}$$

$$\text{Limit} = \frac{1.63 \times 1000}{10} = 163\ \text{ppm}$$

NZW rabbits given 160 or 615 ppm by inhalation 6 h/day, days 1-18. Maternal deaths and weight loss at high dose with complete litter loss. Increased foetal deaths and renal, C/V and ventral body wall anomalies at low dose with slight maternal toxicity.

Ref. Hardin BD et al., Scand. J. Work. Environ. Health 1981 7 (Suppl 4) 66-75

$$160\ \text{ppm} = \frac{160 \times 90.12}{24.45} = 590\ \text{mg / m}^3 = 0.59\ \text{mg / L}$$

$$\text{For continuous exposure} = \frac{0.59 \times 6}{24} = 0.148\ \text{mg / L}$$

$$\text{Daily dose} = \frac{0.148 \times 1440}{4} = 53.3\ \text{mg / kg}$$

$$\text{PDE} = \frac{53.3 \times 50}{2.5 \times 10 \times 1 \times 5 \times 10} = 2.13\ \text{mg / day}$$

$$\text{Limit} = \frac{2.13 \times 1000}{10} = 213\ \text{ppm}$$

Toxicity

Rats fed 1.45% in diet for 2 years showed testicular oedema and atrophy.

Ref. Morris HJ et al., J. Pharmacol. Exp. Therap. 1942 74 266-73

Assume rat consumes 30 g/day

1.45% of 30,000 mg = 435 mg

Average weight = 0.425 kg

$$\text{Daily consumption} = \frac{435}{0.425} = 1024 \text{ mg / kg}$$

$$\text{PDE} = \frac{1024 \times 50}{5 \times 10 \times 1 \times 1 \times 10} = 102.4 \text{ mg / day}$$

$$\text{Limit} = \frac{102.4 \times 1000}{10} = 10{,}240 \text{ ppm}$$

Oral doses of 500 and 1000 mg/kg to Sprague-Dawley rats for 11 days caused damage to primary spermatocytes and spermatogonia. NEL 250 mg/kg.

Ref. Foster PMD et al., Toxicol.Appl.Pharmacol. 1983 69 385-99

$$\text{PDE} = \frac{250 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 25 \text{ mg / day}$$

$$\text{Limit} = \frac{25 \times 1000}{10} = 2{,}500 \text{ ppm}$$

Oral dose of 150 mg/kg by gavage to Long-Evans rats 5 days/week for 6 weeks caused changes in sperm counts and morphology. Benchmark dose (BMD) at 10% incidence was calculated with 95% confidence limits to be 31 mg/kg per day.

Ref. Hurtt, ME and Zenick H Fund. Appl. Toxicol., 1986, 7, 348-53.

$$PDE = \frac{31 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 6.2 \text{ mg / day}$$

$$\text{Limit} = \frac{3.1 \times 1000}{10} = 310 \text{ ppm}$$

Human Results

Reduced sperm counts in workers exposed to varying unknown concentrations of 2-ethoxyethanol and other solvents.

Refs. Ratcliffe JM et al., Br. J. Occup.Med. 1989 46 399

Welch LS et al., Am. J. Ind. Med. 1988 14 509-36

Metabolism

Metabolic product, 2-ethoxyacetic acid, but not 2-ethoxyethanol, caused degeneration of pachytene and dividing spermatocytes when added to primary mixed cultures of germ cells and Sertoli cells.

Ref. Grey TJB et al., Toxicol. Appl. Pharmacol. 1985 79 490-501

Conclusion

The PDE for 2-ethoxyethanol is 1.6 mg/day.

ETHYLENEGLYCOL

Genotoxicity

Negative results in microbial mutagenicity assays, mouse lymphoma assay and in vivo in a dominant lethal assay.

Refs. Clark CR et al., Toxicol. Appl. Pharmacol. 1979 51 529-35

McGregor DB et al., Environ. Mol. Mutagen. 1991 17 (3) 196-219

DePass LR et al., Fund. Appl. Toxicol. 1986 7 566-72.

Carcinogenicity

Negative results have been obtained in all the studies reported.

Rats Fischer 344 rats were given 40, 200 or 1000 mg/kg daily in the diet for 2 years.

All the high dose male rats died within 475 days. No oncogenic effects were observed.

Ref. DePass LR et al., Fund. Appl. Toxicol. 1986 7 547-65.

NOEL 200 mg/kg

$$\text{PDE} = \frac{200 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 200 \text{ mg / day}$$

$$\text{Limit} = \frac{200 \times 1000}{10} = 20{,}000 \text{ ppm}$$

Fischer 344 rats given 30, 100, 300 or 1000 mg/kg by S/L injection twice weekly for 1 year then retained until 18 months. No increase in tumour incidence was observed.

Ref. Mason MM et al., Clin Toxicol 1971 4 (2) 185-204

$$\text{Continuous dosing} = \frac{1000 \times 2}{7} = 286 \text{ mg / kg}$$

$$\text{PDE} = \frac{286 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 28.6 \text{ mg / day}$$

$$\text{Limit} = \frac{28.6 \times 1000}{10} = 2860 \text{ ppm}$$

Mice

CD-1 mice given 40, 200 or 1000 mg/kg/day in diet for 2 years. No evidence of oncogenicity was seen.

Ref. DePass LR et al., Fund. Appl. Toxicol. 1986 7 547-65. NOEL is 1000 mg/kg

$$\text{PDE} = \frac{1000 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 416.7 \text{ mg / day}$$

$$\text{Limit} = \frac{416.7 \times 1000}{10} = 41{,}670 \text{ ppm}$$

Reproductive Toxicity

Rats Fischer 344 rats given 40, 200 or 1000 mg/kg in diet daily from days 6-15 of gestation. No maternal or embryotoxicity was noted and there was no increase in malformations.

Ref. Maronpot RR et al., Drug Chem. Tox. 1983 6 (6) 579-94. NEL 1000 mg/kg

$$\text{PDE} = \frac{1000 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 1000 \text{ mg / day}$$

$$\text{Limit} = \frac{1000 \times 1000}{10} = 100{,}000 \text{ ppm}$$

Sprague-Dawley rats were given 1250, 2500 or 5,000 mg/kg by gavage daily from day 6-15 of gestation. There was a dose-related reduction in maternal weight gain at all levels; the number of live foetuses and mean foetal weights were reduced at the intermediate and high levels, and malformations were noted at all levels including cleft palate, neural tube closure defects and axial skeletal dysplasia.

Ref. Price CJ et al., Toxicol. Appl. Pharmacol. 1985 81 113-127. LOEL is 1250 mg/kg.

$$\text{PDE} = \frac{1250 \times 50}{5 \times 10 \times 1 \times 5 \times 10} = 25 \text{ mg / day}$$

$$\text{Limit} = \frac{25 \times 1000}{10} = 2500 \text{ ppm}$$

Mice CD-1 mice were given 750, 1500 or 3000 mg/kg by gavage daily from day 6-15 of gestation. Maternal weight gain was reduced at the intermediate and high dose levels and the number of live foetuses was reduced at the high dose level. Mean foetal weights were reduced and malformations were noted at all dose levels including craniofacial, neural tube closure defects and axial skeletal dysplasia.

Ref. Price CJ et al., Toxicol. Appl. Pharmacol. 1985 81 113-127. LOEL is 750 mg/kg

$$\text{PDE} = \frac{750 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 3.12 \text{ mg / day}$$

$$\text{Limit} = \frac{3.12 \times 1000}{10} = 312 \text{ ppm}$$

Animal Toxicity

Rats were given 0.05, 0.1, 0.25 and 1% in diet for 16 weeks. Oxalate crystals and damage were seen in the kidneys of the male animals given 0.25 and 1% and similar but lesser effects were seen in the high dose females. NOEL was 0.1% (equivalent to approx 80 mg/kg).

Ref. Gaunt IF et al., BIBRA Bull 1975 14 109-11

$$PDE = \frac{80 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 16 \text{ mg / day}$$

$$Limit = \frac{16 \times 1000}{10} = 1600 \text{ ppm}$$

Sprague-Dawley rats fed 0.1, 0.2, 0.5, 1 or 4% in diet for 2 years. Increased mortality in males at 1 and 4%. Calcification of kidney tubules and oxalate - containing calculi in males at 0.5, 1 and 4%. In females tubular calcification noted at 1 and 4% and oxalate calculi only at 4%. Ref. Blood FR Fd. Cosmet. Toxicol. 1965 3 229-34. NEL 0.2%

Assume rat consumes 30 g/day

0.2% of 20,000 = 60 mg

Av Wt 0.425 kg

$$Daily\ consumption = \frac{60}{0.425} = 141 \text{ mg / kg}$$

$$PDE = \frac{141 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 141 \text{ mg / day}$$

$$Limit = \frac{141 \times 1000}{10} = 14{,}100 \text{ ppm}$$

Fischer 344 rats fed 40, 200 or 1000 mg/kg in diet daily for 2 years. The high dose level was lethal to the male rats. Urinary calcium oxalate and uric acid crystals and increased kidney weights were noted in the high dose female animals and fatty changes were seen in the livers of the intermediate and high dose females.

Renal tubular hyperplasia and dilation was noted in high dose males killed after 6 months.

Ref. DePass LR et al., Fund. Appl. Toxicol. 1986 7 547-65. NOEL is 40 mg/kg

$$\text{PDE} = \frac{40 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 40 \text{ mg / day}$$

$$\text{Limit} = \frac{40 \times 1000}{10} = 4000 \text{ ppm}$$

Human Results

Single oral lethal dose estimated at 1.4 ml/kg

Ref. Lang EP et al., J. Ind. Hygien. Toxicol. 1939 21 173

Volunteers maintained in atmosphere of 3 or 67 mg/m^3 22 h/day for 30 days. Little evidence of absorption and no serious signs of toxicity.

Ref. Wills JH et al., Clin. Toxicol. 1974 7 (5) 463-76. NEL 67 mg/m^3 = 0.067 mg/L

$$\text{Continuous exposure} = \frac{0.067 \times 22}{24} = 0.061 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.061 \times 28{,}800}{50} = 35 \text{ mg / kg}$$

Conclusion

The PDE for ethyleneglycol is 3.1 mg/day.

FORMAMIDE

Genotoxicity

Negative in Ames test.

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

Carcinogenicity

No data available

Reproductive toxicity

1 ml I/P to rats days 11-16 increased resorptions, decreased foetal weight and caused cleft palate and digital defects.

Ref. Thiersch JB in Tuchmann-Duplessis H Ed.

Malformations Congenitals des Mammiferes, Paris, 1971

20, 70 and 200µl/kg dosed orally to Russian rabbits days 6-18.

200 µl/kg was lethal to litters and 70 µl/kg caused decreased foetal weight, increased resorption and cleft lip/palate and anasarca. NEL was 20 µl/kg.

Ref. Merckle J and Keller H. Arzneimittel Forsch. 1980 30 (a) 1557-62.

$$\text{NEL} = 20\ \text{ml/kg} = 20 \times 1.1334 = 22.7\ \text{mg/kg}$$

$$\text{PDE} = \frac{22.7 \times 50}{2.5 \times 10 \times 1 \times 10 \times 1} = 4.54\ \text{mg/day}$$

$$\text{Limit} = \frac{4.54 \times 1000}{10} = 454\ \text{ppm}$$

Animal toxicity

Oral LD_{50} in rats is 6 g/kg

Ref. Thiersch JB J Reprod. Fert 1962 4 219

100, 500 or 1500 ppm given 6 h/day, 5 day/week for 2 weeks to rats.

Decreased weight gain and necrosis of renal tubulular epithelium at high dose. Decreases in platelets and/or lymphocytes at 500 and 1500 ppm. NEL 100 ppm

Ref. Warheit DB et al., Fund. Appl. Toxicol. 1989 13 702-13

$$\text{NEL} = 100 \text{ ppm} = \frac{100 \times 45.04}{24.45} = 184 \text{ mg} / \text{ m}^3 = 0.184 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.184 \times 6 \times 5}{24 \times 7} = 0.033 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.033 \times 290}{0.425 \text{ kg}} = 22.4 \text{ mg / kg}$$

$$\text{PDE} = \frac{22.4 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 2.2 \text{ mg / day}$$

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

Conclusion

The PDE for formamide is 2.2 mg/day.

HEXANE

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive Toxicity

F344 rats given 1000 ppm by inhalation 6 h/day, day 8-16. No adverse effects on dams or litters. NOEL 1000 ppm. Ref. Bus JS et al., Toxicol. Appl. Pharmacol. 1979 51 295-302

$$1000 \text{ ppm} = \frac{1000 \times 86.17}{24.45} = 3524 \text{ mg / m}^3 = 3.5 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{3.5 \times 6}{24} = 0.875 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.875 \times 290}{0.33 \text{ kg}} = 769 \text{ mg / kg}$$

$$\text{PDE} = \frac{769 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 769 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{769 \times 1000}{10} = 76{,}900 \text{ ppm}$$

Toxicity

100 ppm 12 h/day for 24 weeks to Wistar rats by inhalation did not effect motor nerve conduction velocity, mixed nerve conduction velocity or distal latency. Higher doses cause severe effects with giant axonal swelling and fibre degeneration in both CNS and PNS.

Refs. Takeuchi Y et al., Br. J. Ind. Med. 1983 40 199-203

Schmidt R et al., Respiration 1984 46 362-69.

$$100 \text{ ppm} = \frac{100 \times 86.17}{24.45} = 352 \text{ mg / m}^3 = 0.35 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{0.35 \times 12}{24} = 0.175 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.175 \times 290}{0.425} = 119 \text{ mg / kg}$$

$$\text{PDE} = \frac{119 \times 50}{5 \times 10 \times 10 \times 1 \times 2} = 5.95 \text{ mg / day}$$

$$\text{Limit} = \frac{5.95 \times 1000}{10} = 595 \text{ ppm}$$

200 and 570 mg/kg administered to rats by gavage 5 days/week for 13 weeks.

Severe hindlimb weakness or paralysis with tibial nerve lesions and atrophy of testicular germinal epithelium at 570 mg/kg. Liver and kidney weights increased at 200 mg/kg.

NOEL 200 mg/kg. Ref. Til HP, et al., Final report, Zeist. The Netherlands, TNO-CIVO Institutes (Project No. B/88-0541, Report No. V/89.089) 1989 166 pp.

$$\text{For continuous dosing} = \frac{200 \times 5}{7} = 143 \text{ mg / kg}$$

$$\text{PDE} = \frac{143 \times 50}{5 \times 10 \times 10 \times 5 \times 1} = 2.86 \text{ mg / day}$$

$$\text{Limit} = \frac{2.86 \times 1000}{10} = 286 \text{ ppm}$$

Human Results

Several reports of polyneuropathy in workers exposed to n-hexane by inhalation. Dose range is 500 - 2,500 ppm.

Refs. Iida M et al., Electromyogr. 1969 9 247-61

Sobue I et al., Int. J. Neurol. 1978 11 317-30

Rizzuto N et al., Eur. Neurol. 1980 19 308-15

Metabolism

In guinea pigs n-hexane metabolised to 2,5-hexanedione and 5-hydroxy-2-hexanone. Both are also metabolites of methyl butyl ketone which is also neurotoxic.

Refs. DiVincenzo GD et al., Toxicol. Appl. Pharmacol. 1976 36 511

Schaumburg HH and Spenser PS. Brain 1976 99 183

Conclusion

The PDE for hexane is 2.9 mg/day.

METHANOL

Genotoxicity

Negative results in vitro in Ames test and SCE assays.

Refs. Shimizu H et al., Jpn. J. Ind. Health 1985 27 400 - 19.

Latt SA et al., Mut. Res. 1981 87 (1) 17-62.

Campbell JA Mut. Res. 1991 260 257-64

Carcinogenicity

No data available.

Reproductive Toxicity

Rats given 5000, 10,000, and 20,000 ppm by inhalation 7 h/day throughout gestation. Slight maternal toxicity and increases in defects in skeletal, cardiac and urinary systems at high dose and reduced foetal weights at intermediate level with small increase in abnormalities.

NEL 5,000 ppm. Ref. Nelson BK et al., Fund. Appl. Toxicol. 1985 5 727-36.

$$\text{NEL} = 5{,}000 \text{ ppm} = \frac{5{,}000 \times 32.04}{24.45} = 6552 \text{ mg / m}^3 = 6.55 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{6.55 \times 7}{24} = 1.91 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.91 \times 290}{0.33 \text{ kg}} = 1678 \text{ mg / kg}$$

$$\text{PDE} = \frac{1678 \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 167.8 \text{ mg / day}$$

$$\text{Limit} = \frac{167.8 \times 1000}{10} = 16{,}780 \text{ ppm}$$

Animal Toxicity

Oral LD50 in rats 3.56 g/kg.

Ref. Reported in Patty's Industrial Hygiene and Toxicology, 3rd Edn. New York 1982.

6 g/kg given by gavage to rhesus monkeys for 3 days causes lethal acidosis but if this is treated with sodium bicarbonate survivors show characteristic retinal oedema as seen in humans. Ref. Potts A.M. Am J. Ophthalmol. 1955 39 86-92.

$$\text{PDE} = \frac{6000 \times 50}{10 \times 10 \times 10 \times 1 \times 10} = 30 \text{ mg / day}$$

$$\text{Limit} = \frac{30 \times 1000}{10} = 3{,}000 \text{ ppm}$$

Metabolism

Characteristic methanol toxicity is seen in monkeys and humans but not in rats and mice. There is a strong correlation with low hepatic tetrahydrofolate levels and decreased hepatic 10 - formyltetrahydrofolate dehydrogenase activity in susceptible species.

Ref. Johlin FC et al., Mol. Pharmacol. 1987 31 (5) 557-61.

Conclusion

The PDE for methanol is 30 mg/day.

2-METHOXYETHANOL

Genotoxicity

Negative in in vitro studies. Negative in vivo SCE in rat bone marrow. Positive in dominant lethal in rats and mice. Effect on spermatids and spermatogonia (not genotoxic - effect on fertility). Refs. McGreger BD et al., Toxicol.Appl. Pharmacol. 1983 70 303-16

Chapin RE et al., Fund.Appl.Toxicol. 1985 5 182-9

Rao KS et al., Fund.Appl.Toxicol. 1983 33 80-85

Carcinogenicity

Data not available.

Reproductive Toxicity

New Zealand white rabbits exposed to 3, 10, or 50 ppm by inhalation 6h/day on days 6-18. Decreased weight gain at high dose during exposure period with partial recovery later. Decreased foetal weight at high dose with high incidence of abnormalities to skeletal and c/v systems. NEL 10 ppm. Ref. Hanley TR et al., Toxicol. Appl. Pharmacol. 1984 75 409-22

$$10 \text{ ppm} = \frac{10 \times 76.09}{24.45} = 31.1 \text{ mg / m}^3 = 0.031 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{0.031 \times 6}{24} = 0.008 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.008 \times 1440}{4} = 2.88 \text{ mg / kg}$$

$$\text{PDE} = \frac{2.88 \times 50}{2.5 \times 10 \times 1 \times 1 \times 5} = 1.15 \text{ mg / day}$$

$$\text{Limit} = \frac{1.15 \times 1000}{10} = 115 \text{ ppm}$$

Toxicity

Oral doses of 50, 100, 250 and 500 mg/kg orally for 11 days to Sprague-Dawley rats caused testicular damage affecting spermatocytes and spermatogonia. NEL 50 mg/kg.

Ref. Foster PMD et al., Toxicol.Appl.Pharmacol. 1983 69 385-99

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

$$\text{Limit} = \frac{5 \times 1000}{10} = 250 \text{ ppm}$$

Sprague-Dawley rats given 30, 100 or 300 ppm by inhalation 6 h/day, 5 days/week for 13 weeks. Bodyweight, thymus and testicular weight reduced at high dose with degeneration of germinal epithelium. NEL 100 ppm. Ref. Miller RP et al., Fund. Appl.Toxicol 1983 3 49-54

$$100 \text{ ppm} = \frac{100 \times 76.09}{24.45} = 311 \text{ mg / m}^3 = 0.311 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.311 \times 6 \times 5}{24 \times 7} = 0.056 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.056 \times 290}{0.425} = 38.2 \text{ mg / kg}$$

$$\text{PDE} = \frac{38.2 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 7.64 \text{ mg / day}$$

$$\text{Limit} = \frac{7.64 \times 1000}{10} = 764 \text{ ppm}$$

NZW rabbits given 30, 100, 300 ppm by inhalation 6 h/day, 5 days/week for 13 weeks. Deaths in rabbits. Decreased testicular size at all levels, degeneration of germinal epithelium at all levels (minimal change at 30 ppm). LOEL 30 ppm.

Ref. Miller RP et al., Fund.Appl.Pharmacol. 1983 3 49-54

$$30 \text{ ppm} = \frac{30 \times 76.09}{24.45} = 93.36 \text{ mg / m}^3 = 0.093 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.093 \times 6 \times 5}{24 \times 7} = 0.017 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.017 \times 1440}{4} = 6.1 \text{ mg / kg}$$

$$\text{PDE} = \frac{6.1 \times 50}{2.5 \times 10 \times 5 \times 1 \times 5} = 0.49 \text{ mg / day}$$

$$\text{Limit} = \frac{0.49 \times 1000}{10} = 49 \text{ ppm}$$

Human Results

Groups of shipyard workers exposed to 2-methoxyethanol and other materials at varying concentrations had anaemia and reduced sperm counts.

Ref. Welch LS et al., Am. J. Ind. Med. 1988 14 509-36

Conclusion

The PDE for 2-methoxyethanol is 0.5 mg/day.

METHYLBUTYL KETONE

Genotoxicity

No data available

Carcinogenicity

No data available

Reproductive toxicity

F344 rats were exposed to 500, 1000 and 2000 ppm by inhalation 6 h/day throughout gestation. Maternal weight gain reduced at 1000 and 2000 ppm with reduced litter size and pup weights at high dose. No abnormalities but pups were hyperactive at 1000 and 2000 ppm. Postnatal results at 500 ppm not available. NOEL 1000 ppm for foetal toxicity. Post natal results uninterpretable.

Ref. Peters MA et al., Ecotox and Environ. Safety 1981 5 291-306.

$$1000 \text{ ppm} = \frac{1000 \times 100.16}{24.45} = 4097 \text{ mg / m}^3 = 4.1 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{4.1 \times 6}{24} = 1.03 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.03 \times 290}{0.33} = 905 \text{ mg / kg}$$

$$\text{PDE} = \frac{905 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 905 \text{ mg / day}$$

$$\text{Limit} = \frac{905 \times 1000}{10} = 90{,}500 \text{ ppm}$$

Animal toxicity

Several papers report peripheral neuropathy after oral administration or by inhalation. Axonal swelling, beading and degeneration with demyelination are usually noted.

Wistar rats given 50 ppm by inhalation 8 h/day, 5 days/week for 13 weeks showed evidence of demyelination but nothing was seen at 40 ppm.

Ref. Duckett S et al., Experientia 1979 35 (10) 1365-7.

$$40 \text{ ppm} = \frac{40 \times 100.16}{24.45} = 164 \text{ mg / m}^3 = 0.164 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.164 \times 8 \times 5}{24 \times 7} = 0.039 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.039 \times 290}{0.425} = 26.6 \text{ mg / kg}$$

$$\text{PDE} = \frac{26.6 \times 50}{5 \times 10 \times 10 \times 1 \times 5} = 0.53 \text{ mg / day}$$

$$\text{Limit} = \frac{0.53 \times 1000}{10} = 53 \text{ ppm}$$

Male rats were given 0.25, 0.5 and 1% in drinking water for 13 months. Reduced weight gain at all levels. Clinical signs of neuropathy at intermediate and high levels but morphological changes seen at all dosages. LOEL = 0.25%

Ref. Krasavage WJ et al., Toxicol. Appl. Pharmacol. 1979 48 A205

$$0.25\% = 250 \text{ mg / 100 ml}$$

$$\text{Rat drinks } 30 \text{ ml / day}$$

$$\text{i.e. consumes } \frac{250 \times 30}{100} = 75 \text{ mg / day}$$

$$\text{Daily dose} = \frac{75 \times 1000}{425} = 176 \text{ mg / kg}$$

$$\text{PDE} = \frac{176 \times 50}{5 \times 10 \times 1 \times 10 \times 10} = 1.76 \text{ mg / day}$$

$$\text{Limit} = \frac{1.76 \times 1000}{10} = 176 \text{ ppm}$$

Human Results

Several reports of peripheral polyneuropathy. Similar pathology seen to animal studies.

Refs. Davenport JG et al., Neurol. 1976 26 912-23

Billmaier D et al., J. Occup. Med. 1974 16 (10) 665-71

Wickersham CW and Fredericks EJ Conn. Med. 1976 40 311-12

Allen N et al., Arch. Neurol. 1975 32 209-18

Mallov JS. J. Am. Med. Assoc. 1976 235 1455-57.

Conclusion

The PDE for methylbutyl ketone is 0.5 mg/day.

METHYLCYCLOHEXANE

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Toxicity

Oral LD50 in mice 2.25 g/kg. Oral LDLo in rabbits 4 g/kg.

Ref. Nikunen E Environmental Properties of Chemicals 1990 VAPK Publishing, Helsinki

Inhalation LC50 (2h) in mice 41,500 mg/m^3.

Ref. Izmerov NF et al., Toxicometric Parameters of Industrial Toxic Chemicals under Single Exposure 1982 CIP, Moscow

The tissues of rabbits exposed to 0.948 or 4.57 mg/L (241 or 1162 ppm), 6h/day, 5 days/week for 10 weeks showed no evidence of toxicity when examined microscopically 2 months after exposure ceased. NEL 4.57 mg/L.

Ref. Treon JF J. Indust. Hyg. Toxicol. 1943 25 (6) 323-347

$$\text{Continuous exposure} = \frac{4.57 \times 6 \times 5}{24 \times 7} = 0.82 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.82 \times 1440}{4} = 295 \text{ mg / kg}$$

$$\text{PDE} = \frac{295 \times 50}{2.5 \times 10 \times 10 \times 5 \times 1} = 11.8 \text{ mg / day}$$

$$\text{Limit} = \frac{11.8 \times 1000}{10} = 1180$$

Human

No relevant data.

Conclusion

The PDE for methylcyclohexane is 11.8 mg/day.

N-METHYLPYRROLIDONE

Genotoxicity

Negative in Ames test, caused aneuploidy in Saccharomyces cerevisiae.

Refs. Wells DA et al., J. Appl. Toxicol. 1988 8 (2) 135-9

Mayer VW et al., Environ. Mol. Mutagen 1988 11 (1) 31-40

Carcinogenicity

0.04 and 0.4 mg/L given by inhalation 6 h/day, 5 days/week to Sprague-Dawley rats for 2 years.

No toxic or carcinogenic effects. Ref. Lee KP et al., Fund. Appl. Toxicol. 1987 9 222-35.

NEL = 0.4 mg/L

$$\text{For continuous dosing} = \frac{0.4 \times 6 \times 5}{24 \times 7} = 0071 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.071 \times 290}{0.425} = 48.4 \text{ mg / kg}$$

$$\text{PDE} = \frac{48.4 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 48.4 \text{ mg / day}$$

$$\text{Limit} = \frac{48.4 \times 1000}{10} = 4840 \text{ ppm}$$

Reproductive Toxicity

Single I/P dose of 166 mg/kg to mice on day 7 caused increased resorptions. The same dose on day 9 caused malformations. Ref. Schmidt R. Biol. Rundsch. 1976 14 (1) 38.

0.1 and 0.36 mg/L 6 h/day days 6-15 had no adverse effects on pregnancy in Sprague-Dawley rats.

Ref. Lee KP et al., Fund. Appl. Toxicol. 1987 9 222-35. NEL 0.36 mg/L

$$\text{For continuous dosing} = \frac{0.36 \times 6}{24} = 0.09 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.09 \times 290}{0.33 \text{ kg}} = 79 \text{ mg / kg}$$

$$\text{PDE} = \frac{79 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 79 \text{ mg / day}$$

$$\text{Limit} = \frac{79 \times 1000}{10} = 7900 \text{ ppm}$$

Animal Toxicity

As in 'carcinogenicity' above, no adverse effects seen after 0.4 mg/L administered 6 h/day, 5 days/week for 2 years to Sprague-Dawley rats.

Ref. Lee KP et al., Fund. Appl. Toxicol. 1987 9 222-35.

Conclusion

The PDE for N-methylpyrrolidone is 48.4 mg/day.

NITROMETHANE

Genotoxicity

Negative in up to 5 strains of *Salmonella typhimurium* in several Ames tests, at concentrations of up to 10000 ug/plate, and in the presence or absence of metabolic activating systems from rat and hamster liver. Negative in a sex-linked recessive lethal assay in *Drosophila*. Negative in micronucleus tests in mouse bone marrow at intraperitoneal doses of up to 1830 mg/kg *in vivo*.

Refs. Mortelmans K et al., Environmental Mutagenesis 1986 8 (suppl. 7) 1-119

Gocke E et al., Mutation Research 1981 90 (2) 91-109

Chiu CW et al., Mutation Research 1978 58 11-22

Lofroth G et al., Environmental Mutagenesis 1981 3 (3) 336

Dellarco VL and Prival MJ Env. Mol. Mutagenesis 1989 13 (2) 116-127

Carcinogenicity

F344 rats given 94, 188, or 375 ppm by inhalation 6h/day, 5 days/week for 2 years. Mammary gland fibroadenoma, or fibroadenoma/adenoma combined with fibroadenoma, adenoma, or carcinoma (combined) in females, in intermediate and high groups increased. Also incidences of mammary gland carcinoma and of adenoma or carcinoma (combined) in the high dose group was increased. Ref NTP Tech Report 461 NIH Pub No. 95-3377 (1995)

$$94 \text{ ppm} = \frac{94 \times 61.04}{24.45} = 234.6 \text{ mg / m}^3 = 0.235 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.235 \times 6 \times 5}{24 \times 7} = 0.042 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.042 \times 290}{0.425} = 28.7 \text{ mg / kg}$$

$$\text{PDE} = \frac{28.7 \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 2.87 \text{ mg / day}$$

$$\text{Limit} = \frac{2.87 \times 1000}{10} = 287 \text{ ppm}$$

B6C3F1 mice given 188, 375, or 750 ppm by inhalation 6h/day, 5 days/week for 2 years. Harderian gland adenoma and adenoma or carcinoma (combined) increased at intermediate and high levels. Incidence of Harderian gland carcinoma also increased at intermediate and high levels. Incidence of alveolar/broncheolar carcinoma in males at high level and females at intermediate level also increased. Female low and high level mice had increased hepatocellular adenoma and adenoma or carcinoma combined. Eosinophilic liver foci increased at intermediate and high levels. Degeneration and metaplasia of olefactory epithelium increased in all groups. Ref NTP Tech Report 461 NIH Pub No. 95-3377 (1995)

$$188 \text{ ppm} = \frac{188 \times 61.04}{24.45} = 469 \text{ mg / m}^3 = 0.469 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{0.469 \times 6 \times 5}{24 \times 7} = 0.08 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.08 \times 43}{0.028} = 123 \text{ mg / kg}$$

$$\text{PDE} = \frac{123 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 0.51 \text{ mg / day}$$

$$\text{Limit} = \frac{0.51 \times 1000}{10} = 51 \text{ ppm}$$

Reproductive Toxicity

No data on teratogenicity available. Female rats were given 0.5 mL of 1.5 M nitromethane in NaCl every third day from one week before mating, and at least throughout gestation (unclear whether dosing continued through lactation). No effects on fertility, litter parameters or pup behaviour were found. There was a suggestion of impaired maze-learning when pups were tested at 2.5 months old.

Ref. Whitman RD et al., J. Abnorm. Psychol. 1977 86 662-664

$$\text{Virtual NEL} = \frac{0.5 \times 1.5 \times 61.04}{0.330} = 138.8 \text{ mg / kg}$$

$$\text{Continuous exposure} = \frac{138.8}{3} = 46.3 \text{ mg / kg}$$

$$\text{PDE} = \frac{46.3 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 46.3 \text{ mg / day}$$

$$\text{Limit} = \frac{46.3 \times 1000}{10} = 4630 \text{ ppm}$$

Toxicity

Oral LD50 in mice 1440 mg/kg.

Ref. Weatherby JH Arch. Ind. Hyg. Occup. Med. 1955 11 102-106

Oral LD50 in rats 1210 mg/kg.

Ref. Martin JL and Baker PJ in Kirk-Othmer Encyclopedia of Chemical Technology (ed. Standen A), 2nd ed. 1967 13 864-888, Wiley, New York

Oral LDLo in dogs 125 mg/kg. Pathologic lesions generally confined to liver, and appeared to be dose-related.

Oral LDLo in rabbits 750 mg/kg.

Intravenous LDLo in dogs and rabbits 750-800 mg/kg.

Ref. Weatherby JH Arch. Ind. Hyg. Occup. Med. 1955 11 102-106

Rats given 0.25 or 0.1% in drinking water for 15 weeks; daily doses estimated as 150 and 80 mg/kg/day. 3/10 and 4/10 rats died at 0.25 and 0.1%, respectively. Reduced weight gain in survivors and evidence of liver damage. LOEL = 80 mg/kg

Ref. Weatherby JH Arch. Ind. Hyg. Occup. Med. 1955 11 102-106

$$\text{PDE} = \frac{80 \times 50}{5 \times 10 \times 5 \times 1 \times 10} = 1.6 \text{ mg / day}$$

$$\text{Limit} = \frac{1.6 \times 1000}{10} = 160 \text{ ppm}$$

B6C3F1 mice exposed by inhalation to 0, 94, 188, 375, 750, 1500 ppm for 6 h/day, 5 days/week for 13 weeks. Dose-related changes in olfactory and respiratory epithelium in both sexes at ≥ 375 ppm, and in females at 188 ppm. Hyaline droplets in females at 94 and 188 ppm. LOEL 94 ppm.

Ref. Battelle Pacific Northwest Laboratories, 13-Week Subchronic Inhalation Toxicity Study Report on Nitromethane in Mice, NTP Contract No. N01-ES-75189, 12122, 1989, Battelle, Richland, WA

$$94 \text{ ppm} = \frac{94 \times 61.04}{24.45} = 234.7 \text{ mg / m}^3 = 0.235 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{0.235 \times 6 \times 5}{24 \times 7} = 0.042 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.042 \times 43}{0.028} = 64.5 \text{ mg / kg}$$

$$\text{PDE} = \frac{64.5 \times 50}{12 \times 10 \times 5 \times 1 \times 5} = 1.08 \text{ mg / day}$$

$$\text{Limit} = \frac{1.08 \times 1000}{10} = 108 \text{ ppm}$$

Fischer 344 rats exposed by inhalation to 0, 94, 188, 375, 750, 1500 ppm for 6 h/day, 5 days/week for 13 weeks. Reductions in body weight gain,erythrocyte values, grip strength, and cellularity of bone marrow were found, with degeneration of olfactory epithelium and respiratory epithelial hyaline droplet formation. Sciatic nerve and spinal cord degeneration was evident at ≥ 375 ppm. NEL 94 ppm.

Ref. Battelle Pacific Northwest Laboratories, 13-Week Subchronic Inhalation Toxicity Study Report on Nitromethane in Rats, NTP Contract No. N01-ES-75189, 12122, 1989, Battelle, Richland, WA

$$94 \text{ ppm} = \frac{94 \times 61.04}{24.45} = 234.7 \text{ mg / m}^3 = 0.235 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{0.235 \times 6 \times 5}{24 \times 7} = 0.042 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.042 \times 290}{0.425} = 28.7 \text{ mg / kg}$$

$$\text{PDE} = \frac{28.7 \times 50}{5 \times 10 \times 5 \times 10 \times 1} = 0.57 \text{ mg / day}$$

$$\text{Limit} = \frac{0.57 \times 1000}{10} = 57 \text{ ppm}$$

Sprague-Dawley rats exposed by inhalation to 0, 98 or 745 ppm, 7 h/day, 5 days/week for 6 months. Ten rats from treated and control groups killed after 2 days, 10 days, 1, 3 and 6 months. Effects on haematocrit and Hb, decreased weight gain at 745 ppm; small increases in thyroid weight at 98 and 745 ppm. LOEL 98 ppm.

Ref. Lewis TR et al., J. Environ. Pathol. Toxicol. 1979 2 233-249

$$98 \text{ ppm} = \frac{98 \times 61.04}{24.45} = 244.7 \text{ mg / m}^3 = 0.245 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{0.245 \times 7 \times 5}{24 \times 7} = 0.05 \text{ mg / L}$$

1 $$\text{Daily dose} = \frac{0.05 \times 290}{0.425} = 34.1 \text{ mg / kg}$$

$$\text{PDE} = \frac{34.1 \times 50}{5 \times 10 \times 2 \times 1 \times 5} = 3.41 \text{ mg / day}$$

$$\text{Limit} = \frac{3.41 \times 1000}{10} = 341 \text{ ppm}$$

2

3 New Zealand White rabbits exposed by inhalation to 0, 98 or 745 ppm, 7h/day, 5 days/week
4 for 6 months. Five rabbits from treated and control groups killed after 2 days, 10 days, 1, 3
5 and 6 months. Haemoglobin concentration decreased marginally only at 1 month. Slight
6 increase in thyroid weight at 745 ppm and decreased serum T4 at 98 and 745 ppm. LOEL 98
7 ppm. Ref. Lewis TR et al., J. Environ. Pathol. Toxicol. 1979 2 233-249

8

$$\text{As above, continuous exposure} = 0.05 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.05 \times 1440}{4} = 18 \text{ mg / kg}$$

9

$$\text{PDE} = \frac{18 \times 50}{2.5 \times 10 \times 2 \times 1 \times 5} = 3.6 \text{ mg / day}$$

$$\text{Limit} = \frac{3.6 \times 1000}{10} = 360 \text{ ppm}$$

10

11 **Human**

12 Probable human oral lethal dose has been estimated to be 0.5-5 g/kg. Occupational exposure
13 to very high levels has been reported, with gross conversion of haemoglobin to
14 methaemoglobin and sulphaemoglobin. Nitromethane is a weak narcotic. It inactivates

histidase, and has been used experimentally to produce an animal model for the study of the human genetic disorder characterised by histidinaemia.

Conclusion

The PDE for nitromethane is 0.5 mg/day.

PYRIDINE

Genotoxicity

Negative in all tests reported.

Refs. Aesbacher HV et al., Fd. Chem. Tox. 1989 27 (4) 227-32

Ishidate M and Odoshima S. Mut. Res. 1977 48 337-54

Abe S and Sasaki M. J. Ntl. Cancer Inst. 1977 58 (6) 1635-41

Florin I et al., Toxicol. 1980 15 219-32.

Carcinogenicity

No effect on tumour incidence when twice weekly s/c injections given to F344 rats for one year - animals retained after treatment. Animals were examined after a delay. NEL 100 mg/kg. Ref. Mason MM et al., Clin. Tox. 1971 4 (2) 185-204

$$\text{For continuous dosing} = \frac{100 \times 2}{7} = 28.6 \text{ mg / kg}$$

$$\text{PDE} = \frac{28.6 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 2.86 \text{ mg / day}$$

$$\text{Limit} = \frac{2.86 \times 1000}{10} = 286 \text{ ppm}$$

Reproductive Toxicity

No data available.

Toxicity

Slightly increased liver weights at 10 mg/kg in 90 day gavage study in Sprague-Dawley rats. Bile duct proliferation and vacuolated hepatocytes at 50 mg/kg. Virtual NOEL 10 mg/kg.

Ref. Anderson RC 1987 EPA Doc No. 530/SW-88/016A

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

$$\text{Limit} = \frac{2 \times 1000}{10} = 200 \text{ ppm}$$

Human Results

Transient symptoms (nausea, headache etc) but with no liver or kidney damage after exposure to 125 ppm 4 h/day for 2 weeks.

Symptoms of CNS injury reported from chronic exposure from 6-12 ppm.

Ref. Teisinger J. J. Ind.Hyg. Tox. 1948 30 58.

Pyridine is a permitted direct food additive

Ref. 21 CFR 172.515 (1988).

Conclusion

The PDE for pyridine is 2.0 mg/day.

SULFOLANE

Genotoxicity

Sulfolane gave negative results in Ames test assays. Chinese hamster ovary cell sister chromatid exchange assay and gene conversion assay with Saccharomyces cerevisae and in a rat micronucleus test.

Refs. Shimizu H et al., Sangyo Igaku 1985 27 (6) 400-419

EPA Doc. No. FYI-OTS-0484-0304. Fiche No. OTS0000304-0 (1982)

Glaxo Wellcome R&D - Unpublished data

A positive result was obtained in a mouse lymphoma forward mutation assay

Ref. EPA Doc. No. FYI-OTS-0484-0304. Fiche No. OTS0000304-0 (1982)

Carcinogenicity

No data available

Reproductive Toxicity

Subcutaneous doses of 25, 100 or 400 mg/kg were given to Sprague-Dawley rats daily from day 6-15 of gestation. Loss of condition and reduced maternal weight gain was noted at the intermediate and high dose levels. Foetal weight was marginally reduced at the high dose level but there were no embryolethal or teratogenic effects.

Ref. Glaxo Wellcome unpublished data. NOEL for teratogenicity 400 mg/kg

$$\text{PDE} = \frac{400 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 400 \text{ mg / day}$$

$$\text{Limit} = \frac{400 \times 1000}{10} = 40{,}000 \text{ ppm}$$

Animal Toxicity

1g/kg cream containing 40% w/w sulfolane was applied to the shaven skin of albino rats daily for 31 days. No adverse effects were noted.

Ref. Glaxo Wellcome unpublished data.

NOEL 1g/kg of 40% w/w sulfolane cream = 400 mg/kg sulfolane

$$\text{PDE} = \frac{400 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 40 \text{ mg / day}$$

$$\text{Limit} = \frac{40 \times 1000}{10} = 4000 \text{ ppm}$$

Sprague-Dawley rats were exposed by inhalation to 495 mg/m^3 8h/day, 5 days/week for 27 days of exposure. All animals survived and no effects on weight gain were noted. All animals had chronic lung and chronic liver inflammation. A slight decrease in WBC count was also noted. Ref. Andersen ME et al., Toxicol. Appl. Pharmacol. 1977 40 463-472

LOEL is 495 mg/m^3 = 0.495 mg/L

$$\text{Continuous exposure} = \frac{0.495 \times 8 \times 5}{24 \times 7} = 0.118 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.118 \times 290}{0.425} = 80.5 \text{ mg / kg}$$

$$\text{PDE} = \frac{80.5 \times 50}{5 \times 10 \times 10 \times 1 \times 5} = 1.61 \text{ mg / day}$$

$$\text{Limit} = \frac{1.61 \times 1000}{10} = 161 \text{ ppm}$$

Male Sprague-Dawley rats were exposed by inhalation to 2.8, 4 or 20 mg/m^3 23 h/day for 3 months. Females were also exposed at the high level. No adverse effects were seen.

Ref. Andersen ME et al., Toxicol. Appl. Pharmacol. 1977 40 463-72

NOEL 20mg/m^3 = 0.02 mg/L

$$\text{Continuous exposure} = \frac{0.02 \times 23}{24} = 0.019 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.019 \times 290}{0.425} = 13 \text{ mg / kg}$$

$$\text{PDE} = \frac{13 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 2.6 \text{ mg / day}$$

$$\text{Limit} = \frac{2.6 \times 1000}{10} = 260 \text{ ppm}$$

Guinea pigs were exposed by inhalation to 200 mg/m^3 23 h per day for one month. All animals survived with no effects on weight gain. Chronic pleuritis and fatty vacuolation of the liver was noted. These changes were considered adaptive.

Ref. Andersen ME et al., Toxicol. Appl. Pharmacol. 1977 40 463-72

NOEL 200 mg/m^3 = 0.2 mg/L

$$\text{Continuous exposure} = \frac{0.2 \times 23}{24} = 0.19 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.19 \times 430}{0.5} = 165 \text{ mg / kg}$$

$$\text{PDE} = \frac{165 \times 50}{10 \times 10 \times 10 \times 1 \times 1} = 8.25 \text{ mg / day}$$

$$\text{Limit} = \frac{8.25 \times 1000}{10} = 825 \text{ ppm}$$

Guinea pigs were exposed by inhalation to 20 or 159 mg/m^3 23 h/day for 3 months. No adverse effects were noted. Ref. Andersen ME et al., Toxicol. Appl. Pharmacol. 1977 40 463-72. NOEL 159 mg/m^3 = 0.16 mg/L

$$\text{Continuous exposure} = \frac{0.16 \times 23}{24} = 0.15 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.15 \times 430}{0.5} = 129 \text{ mg / kg}$$

$$\text{PDE} = \frac{129 \times 50}{10 \times 10 \times 5 \times 1 \times 1} = 12.9 \text{ mg / day}$$

$$\text{Limit} = \frac{12.9 \times 1000}{10} = 1290 \text{ ppm}$$

ADME

Rapid and complete absorption from the GI tract in rats. Easy passage through blood-brain and placental barriers. Mainly eliminated by kidneys.

Ref. Zhan Zhenhua et al., J W CUMS 1988 19 (1) 61-4

Whole body autoradiography studies indicate widespread distribution following a single s/c injection of 50 mg/kg to Sprague-Dawley rats. Radio label was still measurable in the lens of the eye 4 weeks after exposure.

Ref. Glaxo Wellcome unpublished data.

Conclusion

The PDE for sulfolane is 1.6 mg/day.

TETRALIN

Genotoxicity

Not mutagenic with or without metabolic activation in bacterial (Ames) test, at up to 3 umol/plate (limited by toxicity).

Ref. Florin I et al., Toxicology 1980 18 219-232

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Toxicity

Oral LD50 in rats 2.86 g/kg.

Dermal LD50 in rabbits 17.3 mL/kg.

Ref. Smyth HF et al., Arch. Indust. Hyg. Occup. Med. 1951 4 119

Inhalation LCLo in guinea pigs 275 ppm for seventeen 8h exposures.

Ref. Sandmeyer EE Alicyclic Hydrocarbons. In: Clayton GD and Clayton FE (eds), Patty's Industrial Hygiene and Toxicology, 3rd Rev. Ed., Vol. 2B, p. 3241, Wiley, New York.

One report (experimental design poorly defined) indicated that two guinea pigs exposed to a presumably saturated atmosphere, evidently for 30 min/day for 6 days, developed cataracts.

Ref. Badinand A et al., Arch. Mal. Prof. 1947 8 124-130

Rabbits given 0.2-1.0 mL tetralin/day orally for 30-40 days also developed cataracts.

Ref. Gerarde HW in Toxicology and Biochemistry of Aromatic Hydrocarbons 1960, 234-235, Elsevier, NY

Weanling rats fed diet containing 2% tetralin for at least 2 months did not develop cataracts, but cataractogenesis was observed in rats given 0.25% or more dietary β-tetralol within a few weeks.

Ref. Fitzhugh OG and Buschke WH Arch. Ophthalmol. 1949 41 572-582

The species differences may be related to the amount of β-tetralol formed; this appears to be a more significant metabolite in rabbits than in rats. Very limited evidence suggests that β-tetralol is not a major metabolite in man. Refs. Elliott TH and Hanam J Biochem. J. 1968 108 551-559; Drayer DE and Reidenberg MM Drug Metab. Dispos. 1973 1 577-579

For rabbits: LOEL = 0.2 mL/day = 194 mg/day = 194/4 = 48.5 mg/kg

$$\text{PDE} = \frac{48.5 \times 50}{2.5 \times 10 \times 10 \times 1 \times 10} = 0.97 \text{ mg / day}$$

$$\text{Limit} = \frac{0.97 \times 1000}{10} = 97 \text{ ppm}$$

Male Fischer 344 rats given 0.5 mL/kg (485 mg/kg) orally every other day for 14 days (maximum tolerated regimen). Only kidneys examined histologically; damage characteristic of hydrocarbon nephropathy. This is a rat-specific finding related to the presence of α-2μ globulin in that species, and is not of relevance to risk assessment for man. Ref. Serve MP et al., J. Toxicol. Environ. Health 1989 26 267-275. Virtual NEL = 243 mg/kg per day.

$$\text{PDE} = \frac{243 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 24.3 \text{ mg / day}$$

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

Human

Nausea, vomiting and evidence of mild, reversible renal and hepatic involvement in a woman who ingested approximately 250 mL of Cuprex containing 31.5% tetralin. Human lethal dose estimated to be 0.5-5 g/kg.

Ref. Drayer DE and Reidenberg MM Drug Metab. Dispos. 1973 1 577-579

Cases of occupational toxicity have also been recognised. Production of green-coloured urine is characteristic.

Conclusion

The PDE for tetralin is 1.0 mg/day.

TOLUENE

Genotoxicity

Negative results in in vitro studies. Small increase (2-3 fold) in micronuclei after 2 I/P injections up to 0.5 ml/kg. Negative in sperm morphology assay up to 1.5 ml/kg I/P.

Refs. NTP Tech Report No. 371. NIH Pub. No. 90-2563 (1990)

Bos RP et al., Mut. Res. 1981 88 273-9

Gerner-Smidt P and Friedrich U. Mut. Res. 1978 58 313-16

Topham JC Mut. Res. 1980 74 379-87

Mohtashamipur E et al., Arch. Toxicol. 1985 58 106-9.

Carcinogenicity

Rat No evidence of carcinogenicity in F344 rats given 1200 ppm by inhalation 6.5 h/day, 5 days/week for 2 years. Ref. NTP Tech Report No. 371 NIH Pub. No. 90-2563 (1990)

$$1200 \text{ ppm} = \frac{1200 \times 92.13}{24.45} = 4521 \text{ mg} / \text{m}^3 = 4.52 \text{ mg} / \text{L}$$

$$\text{For continuous dosing} = \frac{4.52 \times 6.5 \times 5}{24 \times 7} = 0.874 \text{ mg} / \text{L}$$

$$\text{Daily dose} = \frac{0.874 \times 290}{0.425} = 596 \text{ mg} / \text{kg}$$

$$\text{PDE} = \frac{596 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 596 \text{ mg} / \text{day}$$

$$\text{Limit} = \frac{596 \times 1000}{10} = 59{,}600 \text{ ppm}$$

Mice 120, 600 or 1200 ppm by inhalation 6.5 h/day, 5 days/week for 2 years did not increase tumour incidence in B6C3F1 mice. Ref. NTP Tech. Report No. 371. NIH Pub. No. 90-2563 (1990). As above continuous dose is 0.874 mg/L

$$\text{Daily dose} = \frac{0.874 \times 43}{0.028} = 1342 \text{ mg / kg}$$

$$\text{PDE} = \frac{1342 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 559 \text{ mg / day}$$

$$\text{Limit} = \frac{559 \times 1000}{10} = 55{,}900 \text{ ppm}$$

Reproductive Toxicity

CFY rats given 266 ppm by inhalation 8 h/day, days 1-21. No teratogenic effects, slight decrease in foetal weight and some retardation in development. Ref: Hudak A and Ungvary G. Toxicol. 1978 11 55-63

$$226 \text{ ppm} = \frac{226 \times 92.13}{24.45} = 1002 \text{ mg / m}^3 = 1 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{1 \times 8}{24} = 0.33 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.33 \times 290}{0.33 \text{ kg}} = 290 \text{ mg / kg}$$

$$\text{PDE} = \frac{290 \times 50}{5 \times 10 \times 1 \times 5 \times 1} = 58 \text{ mg / day}$$

$$\text{Limit} = \frac{58 \times 1000}{10} = 5{,}800 \text{ ppm}$$

CFLP mice given 133 ppm by inhalation 24 h/day, days 6-13. Slight decrease in foetal weight and development but no teratogenic effects.

Ref. Hudak A and Ungvary G. Toxicol. 1978 11 55-63

$$133 \text{ ppm} = \frac{133 \times 92.13}{24.45} = 501 \text{ mg / m}^3 = 0.5 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.5 \times 43}{0.03 \text{ kg}} = 717 \text{ mg / kg}$$

$$\text{PDE} = \frac{717 \times 50}{12 \times 10 \times 1 \times 5 \times 1} = 59.8 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{59.8 \times 1000}{10} = 5980 \text{ ppm}$$

Toxicity

CFY rats given 1000 mg/m^3 by inhalation 6 h/day, 5 days/week for 6 months. No histological changes but increased liver weight and SER proliferation. These were regarded as adaptive changes. NOAEL 1000 mg/m^3.

Ref. Ungvary G et al., J. Hyg. Epidemial. Microbiol. Immunol. 1980 24 (3) 242-52

$$1000 \text{ mg / m}^3 = 1 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{1 \times 6 \times 5}{24 \times 7} = 0.179 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.179 \times 290}{0.425} = 122 \text{ mg / kg}$$

$$\text{PDE} = \frac{122 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 61 \text{ mg / day}$$

$$\text{Limit} = \frac{61 \times 1000}{10} = 6100 \text{ ppm}$$

Rats and mice given 312, 625, 1,250, 2,500 or 5,000 mg/kg by gavage, dosed 5 days/week for 13 weeks. All animals receiving 5,000 mg/kg died during the first week and deaths were also noted at the 2,500 mg/kg level. Brain lesions were noted in rats at 1,250 mg/kg and liver and kidney weights were increased at lower dosage. These changes were regarded as adaptive. NOEL 625 mg/kg. Ref. NTP Document TR371 1990

$$\text{For continuous dosing} = \frac{625 \times 5}{7} = 446 \text{ mg / kg}$$

$$\text{PDE} = \frac{446 \times 50}{5 \times 10 \times 10 \times 5 \times 1} = 8.9 \text{ mg / day}$$

$$\text{Limit} = \frac{8.9 \times 1000}{10} = 890 \text{ ppm}$$

Human Results

Workers exposed to 100-1100 ppm had liver enlargement and moderate decrease in RBC but no leucopenia. Ref. Greenburg L et al., J.Am.Med. Asso;c. 1942 118 573

Two children born of mothers with long history of toluene inhalation had microcephaly, CNS dysfunction hyperactivity and delayed development.

Ref. Hersh JH. J. Med. Genet. 1989 26 (5) 333-7

Conclusion

The PDE for toluene is 8.9 mg/day.

1,1,2-TRICHLOROETHENE

Genotoxicity

Generally negative results when pure, unstabilised trichloroethylene is used. Trichloroethylene is often stabilised with 1,2-epoxybutane or epichlorohydrin, both of which are known mutagens and are probably responsible for the positive results seen in some studies. Refs. McGregor DB et al., Environ. Mol. Mutagen. 1989 13 197-202

Shimada T et al., Cell Biol. Toxicol. 1985 1 (3) 159-79

Ashby J. In Progress in Mut. Res. 1981 1 111-71.

Trichloroethylene should not be considered genotoxic.

Carcinogenicity

Rats Osborne-Mendel rats given 500 or 1000 mg/kg/day 5 days/week by gavage for 18 months did not develop tumours. NEL 1000 mg/kg.

Ref. NCI Tech Report No. 2 NIH Pub. No. 76-802 (1976)

$$\text{For continuous exposure} = \frac{1000 \times 5}{7} = 714 \text{ mg / kg}$$

$$\text{PDE} = \frac{714 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 714 \text{ mg / day}$$

$$\text{Limit} = \frac{714 \times 1000}{10} = 71{,}400 \text{ ppm}$$

Exposure to 100, 300, 600 ppm by inhalation 7 h/day, 5 days/week for 2 years produced dose-related increase in Leydig cell tumours in Sprague-Dawley rats and renal tumours at the high dose level only. LOEL = 100 ppm Ref. Maltoni C et al., Ann. N.Y. Acad. Sci. 1988 534 316-42

$$100 \text{ ppm} = \frac{100 \times 131.4}{24.45} = 537 \text{ mg} / \text{m}^3 = 0.537 \text{ mg} / \text{L}$$

$$\text{For continuous exposure} = \frac{0.537 \times 7 \times 5}{24 \times 7} = 0.112 \text{ mg} / \text{L}$$

$$\text{Daily dose} = \frac{0.112 \times 290}{0.425} = 76 \text{ mg} / \text{kg}$$

$$\text{PDE} = \frac{76 \times 50}{5 \times 10 \times 1 \times 10 \times 10} = 0.76 \text{ mg} / \text{day}$$

$$\text{Limit} = \frac{0.76 \times 1000}{10} = 76 \text{ ppm}$$

Mice B6C3F1 mice given 1200 or 2400 mg/kg (males), 900 or 1800 mg/kg (females) by gavage 5 days/week for 18 months developed hepatocellular carcinomas.

Ref. NCI Tech Report No. 2 NIH Pub. No. 76-802 (1976). LOEL 900 mg/kg

$$\text{For continuous exposure} = \frac{900 \times 5}{7} = 643 \text{ mg} / \text{kg}$$

$$\text{PDE} = \frac{643 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 2.68 \text{ mg} / \text{day}$$

$$\text{Limit} = \frac{2.68 \times 1000}{10} = 268 \text{ ppm}$$

Reproductive Toxicity

Rats given 1800 ppm by inhalation 6h/day, 7 days/week before and during gestation showed no effects on maternal weight gain or litter size and weight.

Ref. Dorfmueller MA et al., Toxicol. 19 79 14 153-66

$$1800 \text{ ppm} = \frac{1800 \times 131.4}{24.45} = 9674 \text{ mg / m}^3 = 9.7 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{9.7 \times 6}{24} = 2.43 \text{ mg / L}$$

$$\text{Daily dose} = \frac{2.43 \times 290}{0.33} \; 2135 \text{ mg / kg}$$

$$\text{PDE} = \frac{2135 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 2135 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{2135 \times 1000}{10} = 213{,}500 \text{ ppm}$$

Toxicity

Doses of 17.9 mg/kg/day and above in drinking water to mice for 6 months suppressed cell mediated immune responses to sheep red blood cells and inhibited bone marrow stem cell colonization. LOEL 17.9 mg/kg.

Ref. Sanders V et al., Toxicol. Appl. Pharmacol. 1982 62 358-68.

$$\text{PDE} = \frac{17.9 \times 50}{12 \times 10 \times 1 \times 1 \times 2} = 3.73 \text{ mg / day}$$

$$\text{Limit} = \frac{3.73 \times 1000}{10} = 373 \text{ ppm}$$

In mice doses above 18.4 mg/kg in drinking water caused hepatic changes in 6 month study. NOAEL 18.4 mg/kg.

Ref. Tucker A et al., Toxicol. Appl. Pharmacol. 1982 62 351-57

$$\text{PDE} = \frac{18.4 \times 50}{12 \times 10 \times 1 \times 1 \times 2} = 3.83 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{3.83 \times 1000}{10} = 383 \text{ ppm}$$

Human Results

Large cohort study failed to show association between exposure and mortality due to cancer

Ref. Shindell S and Slack U J. Occup. Med. 1985 27 (8) 577-79

Metabolism

Qualitatively similar metabolism in mice, rats and humans. One of its metabolites, trichloroacetic acid, can stimulate peroxisome proliferation in mouse livers.

Conclusion

The PDE for 1,1,2-trichloroethene is 0.8 mg/day.

XYLENE

(Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethylbenzene).

Genotoxicity

Consistently negative in in vitro studies and in micronucleus test in mice with 2 x 0.5 ml/kg I/P.

Refs. Bos R P et al., Mut. Res. 1981 88 273-79

NTP Tech Report No. 327 NIH Pub. No. 87-2583 (1986)

Gerner-Smidt P and Friedrich U. Mut. Res. 1978 58 313-16

Mohtashamipur E et al., Arch. Toxicol. 1985 58 106-9

Carcinogenicity

250 or 500 mg/kg by gavage in corn oil to F344 rats 5 days/week for 2 years gave no evidence of carcinogenicity. Ref. NTP Tech. Report No. 327 NIH Pub. No. 87-2583(1986)

$$\text{For daily dosing} = \frac{500 \times 5}{7} = 357 \text{ mg / kg}$$

$$\text{PDE} = \frac{357 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 357 \text{ mg / day}$$

$$\text{Limit} = \frac{357 \times 1000}{10} = 35{,}700 \text{ ppm}$$

Mice In same reference - no carcinogenic effects at 1000 mg/kg 5 days/week for 2 years in B6C3F1 mice.

As above PDE = 360 mg/day

Limit = 36,000 ppm

Reproductive Toxicity

CD-1 mice given 0.6 - 4.8 mL/kg by gavage in cottonseed oil days 6-15.

4.8 mL/kg was lethal, maternal toxicity at 3.6 mL/kg, increased resorptions at 3 mL/kg, foetal weight decreased from 2.4 mL/kg, cleft palate, open eyes and exencephaly from 1.2 mL/kg. (SG = 0.86) NEL 0.6 mL/kg x 0.86 = 520 mg/kg

Ref. Marks TA et al., J. Tox. Environ. Health 1982 9 97-105.

$$\text{PDE} = \frac{520 \times 50}{12 \times 10 \times 1 \times 10 \times 1} = 21.7 \text{ mg / day}$$

$$\text{Limit} = \frac{21.7 \times 1000}{10} = 2170 \text{ ppm}$$

Toxicity

In F344 rats reduced weight gain at 1000 mg/kg by gavage in corn oil for 13 weeks. NEL 500 mg/kg. Ref. NTP Tech Report No. 327 NIH Publ No. 87-2583 (1986)

$$\text{PDE} = \frac{500 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 100 \text{ mg / day}$$

$$\text{Limit} = \frac{100 \times 1000}{10} = 10{,}000 \text{ ppm}$$

Conclusion

The PDE for xylene is 21.7 mg/day.