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ICH guideline Q3C (R6) on impurities – support document 3: toxicological data for class 3 solvents

Step 5

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

TOXICOLOGICAL DATA FOR CLASS 3 SOLVENTS

Q3C SUPPORT DOCUMENT 3

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Q3C SUPPORT DOCUMENT 3
Document History

Document	History
Q3C Support Document 3	This document was originally the Appendix 6 of the Q3C *Step 2* draft Guideline from 1996 which contained the summaries of the toxicity data from which the PDEs for Class 3 solvents were derived. The Appendix 6 was later published as part of *Pharmeuropa, Vol. 9, No. 1, Supplement, April 1997*, and the ICH Q3C Guideline references to this publication. For the convenience of the stakeholders, ICH has published the Appendix 6 as a Support Document on the ICH public website on 3 October 2018.

ACETIC ACID

Genotoxicity

Negative results in Ames tests.

Refs. Zeiger E et al., Environ. Mol. Mutagen. 1992 19

(suppl21) 2-41

Mut. Res 1986 168 69-240.

Carcinogenicity

No relevant data available

Reproductive Toxicity

Doses up to 1.6 g/kg administered by gavage to rabbits from days 6-18. No material toxicity

and no adverse effects on the offspring NOEL 1.6g/kg..

Ref. 1974 FDA Internal report Ref. GRM000080

14:2702

$$\text{PDE} = \frac{1600 \times 50}{2.5 \times 10 \times 1 \times 1 \times 1} = 3200 \text{ mg / day}$$

$$\text{Limit} = \frac{3200 \times 1000}{10} = 320{,}000 \text{ ppm}$$

Animal Toxicity

Oral LD50 in rats is 3.53 g/kg. Ref. Merck Index 10th Edn 1983

Acetic acid is a permitted direct food additive. Ref. 21CFR 184.1005 (1990)

Conclusion

The PDE for acetic acid is 3200 mg/day.

ACETONE

Genotoxicity

Negative in vitro results in Ames test, sister chromatid exchange assay, SHE cell transformation assay and in DNA repair-deficient bacterial tests. Also negative in vivo in micronucleus test.

Refs. De Flora S et al., Mut. Res. 1984 133 (3) 161-78.

Zeiger E et al., Environ. Mol. Mutagen. 1992 19 (Suppl 21) 1-141.

Mut. Res. 1981 87 17.

Mut. Res. 1983 114 283-385.

Mut. Res. 1981 87 211-97.

Mut. Res. 1990 239 29-80.

Carcinogenicity

No increase in tumour incidence when 0.2 ml applied weekly to skin of CF1 mice for 2 years.

Ref. Zakova N et al., Fd. Chem. Toxicol. 1985 23 1081-9

$$0.2 \text{ ml} = 0.2 \times 0.79 = 158 \text{ mg}$$

$$\text{For continuous dosing} = \frac{158 \times 1}{7} = 22.6 \text{ mg}$$

$$\text{Daily dose} = \frac{22.6 \times 1000}{28} \qquad 12 \times 10 \times 1 \times 1 \times 1$$

$$\text{PDE} = \frac{807 \times 50}{2}$$

= 807 mg / kg

= 336 mg / day

$$\text{Limit} = \frac{336 \times 1000}{10} = 33{,}600 \text{ ppm}$$

Reproductive toxicity

No suitable data available.

Animal toxicity

Oral LD50 in rats is 10.7 ml/kg.

Ref. Smyth HF et al., Ind. Hyg. J. 1965 23

95.

Rats given 19,000 ppm by inhalation 3 h/day, 5 days/week for 8 weeks showed no evidence

of toxicity. Ref. Bruckner JV and Peterson RG. Toxicol. Appl. Pharmacol. 1978 45 359.

$$19000 \text{ ppm} = \frac{19{,}000 \times 58}{24.45} = 45{,}072 \text{ mg / m}^3 = 45.1 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{45.1 \times 3 \times 5}{\cancel{24} \times 7} = 4.03 \text{ mg / L}$$

$$\text{Daily dose} = \frac{4.03 \times 290}{0.425} = 2750 \text{ mg / kg}$$

$$\text{PDE} = \frac{2750 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 275 \text{ mg / day}$$

$$\text{Limit} = \frac{275 \times 1000}{10} = 27{,}500 \text{ ppm}$$

F344 rats given 2,500; 5,000; 10,000, 20,000 and 50,000 ppm in drinking water for 13

weeks. Weight gain was depressed and kidney changes were noted at the two highest

concentrations and at 50,000 ppm hypogonadism occurred in the testes. NEL 10,000 ppm

(equivalent to 1050 mg/kg - time weighted average).

Ref. Dietz DD et al., Fund. Appl. Toxicol. 1991 17

347-60.

$$PDE = \frac{1050 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 210 \text{ mg / day}$$

$$\text{Limit} = \frac{210 \times 1000}{10} = 21{,}000 \text{ ppm}$$

Conclusion

The PDE for acetone is 210.0 mg/day.

ANISOLE

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Toxicity

Oral LD50 in rats reported as 3.7 g/kg and 4.29 g/kg.

Refs. Jenner PM et al., Food Cosmet. Toxicol. 1964 2 (3) 327-343

Smyth HF et al., Arch. Ind. Hyg. Occup. Med. 1954 10 61-68

Oral LD50 in mice 2.8 g/kg.

Ref. J. Pharmacol. Exp. Ther. 1946 88

400

Human

Anisole has GRAS status and is permitted for food use as an artificial flavouring substance.

Ref. 21 CFR 172.515

1-BUTANOL

Genotoxicity

Negative results in Ames and SCE assays.

Refs. Jung R et al., Mut. Res. 1992 278 (4) 265-70

Conners T H et al., Toxicol. Lett. 1985 25 (1) 33-40

Mut. Res. 1986 168 69-240

Mut. Res. 1981 87 17-62

Carcinogenicity

No data available.

Reproductive toxicity

Teratogenic when administered into yolk sac of chick embryos.

Ref. McLaughlin J et al., Am. Ind. Hygien. Assoc. J. 1964 25 (3) 282-4.

Animal toxicity

Oral LD50 is 4.36 g/kg.

Ref. Smyth HF et al., Am. Ind. Hygien Occup. Med. J. 1951 4 119.

1-Butanol is a permitted direct food additive.

Ref. 21 CFR 172.515 (1988).

2-BUTANOL

Genotoxicity

Negative in Ames and CHO assays. Ref. Brook TM et al., Mutagen. 1988 3 227-232

Carcinogenicity

No data available

Reproductive Toxicity

Wistar rats given 0.3, 1.0 or 2.0% in drinking water, equivalent to 500. 1500 or 3000mg/kg,

for 8 weeks then mated. The Fia generation was used for a toxicity study (see below). The

foetuses of the Flb generation were examined at the end of pregnancy. (Dosing of generation

continues throughout.) No maternal effects were noted but foetal weight was slightly

reduced at the high dose level only and there was evidence of retarded skeletal development.

NOEL is 1500mg/kg. Ref. 1975 Internal FDA document. ASP

000145

$$PDE = \frac{1500 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 300 \text{ mg / day}$$

$$\text{Limit} = \frac{300 \times 1000}{10} = 30{,}000 \text{ ppm}$$

Animal Toxicity

A parent generation of Wistar rats was given 0.3, 1.0 or 2.0% in drinking water, equivalent to

500, 1500 or 3000 mg/kg, for 8 weeks then mated. Dosing continued throughout pregnancy

and weaning. The F1 generation was treated for 9 weeks then mated. Daily continued

throughout pregnancy at the end of which the F1 generation was killed and examined (routine

laboratory examinations were performed and tissues were examined microscopically). Kidney

changed comprising tubular degeneration and microcysts in the papilla were noted at the high

dose level only. NOEL 1%, equivalent to 1500 mg/kg. Ref. 1975 internal FDA document 000145.

$$PDE = \frac{1500 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 300 \text{ mg / day}$$

$$\text{Limit} = \frac{300 \times 1000}{10} = 30{,}000 \text{ ppm}$$

Oral LD50 in rats is 6.5g/kg. Ref. Merck index 10th Edn (1983)

2- Butanol is a permitted direct food additive. Ref. 21CFR 172.515 (1990)

Conclusion

The PDE for 2-butanol is 300 mg/day.

BUTYL ACETATE

Genotoxicity

Negative in Ames tests. Ref. shimizu H et al., Sangyo lgaku 1985

27 400-419

Carcinogenicity

No data available

Reproductive Toxicity

No data available

Animal Toxicity

CD-1 mice were given 300, 1000 or 3000mg/kg in the diet daily for 90 days. Reduced motor

activity, prostration, and laboured breathing were noted at the high dose level only and serum

cholesterol was reduced in this group . Not microscopic changes were noted at any dose

level. NOEL 1000mg/kg. Ref. 1977 Internal FDA report Ref. FAP 8A3360 2:261

$$PDE = \frac{1000 \times 50}{12 \times 10 \times 5 \times 1 \times 1} = 83.3 \text{ mg / day}$$

$$\text{Limit} = \frac{83.3 \times 1000}{10}$$

$$= 8{,}300 \text{ ppm}$$

Sprague-Dawley rats were given 600, 2000 or 6000 mg/kg daily by gavage for 90 days. All

rats salivated after dosing but this was considered a response to the test of the material rather

than toxicity. Reduced motor activity was seen at the intermediate and high levels with

lachrymation and prostration in a few high dose animals only. High dose level animals

showed reduced weight gain. Stomach lesions were noted in the inter and high dose level

animals. NOEL 600 mg/kg. Ref. 1978 Internal FDA report Ref. FAP 8A3360 5:1197

$$PDE = \frac{600 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 120 \text{ mg / day}$$

$$\text{Limit} = \frac{120 \times 1000}{10} = 12{,}000 \text{ ppm}$$

Oral LD50 in rats is 14.13g/kg. Ref. Merck index 10th Edn 1983

Butyl acetate is a permitted direct food additive. Ref. 21 CFR

172.515 (1990)

Conclusion

The PDE for butyl acetate is 83.3 mg/day.

TERT-BUTYLMETHYL ETHER

Genotoxity

No data available.

Carcinogenicity

No oncogenic effects in F344 rats given 403, 3023 or 7977 ppm 6 h/day, 5 days/week for 2

years. Ref. Chun JS et al., 1992 (summarised in IRIS report Document No. 537 1993).

$$\text{NEL} = 7977 \text{ ppm} = \frac{7977 \times 88.15}{24.45} = 28{,}760 \text{ mg} / \text{m}^3$$

$$= 28.76 \text{ mg} / \text{L}$$

$$\text{For continuous dosisng} = \frac{28.76 \times 6 \times 5}{\cancel{24} \times 7} = 5.14 \text{ mg} / \text{L}$$

Reproductive Toxicity

$$\text{Daily dose} = \frac{5.14 \times 290}{0.425 \text{ kg}}$$

$$\text{PDE} = \frac{3507 \times 50}{5 \times 10 \times 1 \times 1 \times 1}$$

$$\text{Limit} = \frac{3507 \times 1000}{10}$$

= 3507 mg / kg = 3507 mg / day = 350,700 ppm

Sprague-Dawley rats given 250, 1000, or 2,500 ppm by inhalation on days 6-15. No maternal

toxicity and no adverse effects on litters. Ref. Conway CC et al., J. Tox.

Environ.Health

1985 16 797-809

$$\text{NEL} = 2500 \text{ ppm} = \frac{2500 \times 88.15}{24.45} = 9013 \text{ mg / m}^3 = 9.01 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{9.01 \times 6}{24} = 2.25 \text{ mg / L}$$

$$\text{Daily dose} = \frac{2.25 \times 290}{0.33 \text{ kg}} = 1977 \text{ mg / kg}$$

$$\text{PDE} = \frac{1977 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 1977 \text{ mg / day}$$

$$\text{Limit} = \frac{1977 \times 1000}{10} = 197{,}700 \text{ ppm}$$

CD-1 mice given 250, 1000, or 2,500 ppm by inhalation 6h/day, days 6-15. No maternal

effects and no adverse effects on litters. Ref. Conway CC et al., J. Tox. Environ.Health 1985

16 797-809. As above, continuous exposure = 2.25 mg/L.

$$\text{Daily dose} = \frac{2.25 \times 43}{0.03 \text{ kg}} = 3225 \text{ mg / kg}$$

$$\text{PDE} = \frac{3225 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 1344 \text{ mg / day}$$

$$\text{Limit} = \frac{1344 \times 1000}{10} = 134{,}400 \text{ ppm}$$

No adverse effects on litters when male Sprague-Dawley rats exposed by inhalation to 300,

1300 or 3400 ppm 6h/day, 5 day/week for 12 weeks then mated to females dosed for 3 weeks

pre-mating and throughout gestation and from days 5-21 of lactation.

Ref. Biles RW et al., Tox Ind. Health 1987 3 (4)

519-34.

$$3400 \text{ ppm} = \frac{3400 \times 88.15}{24.45} = 12{,}258 \text{ mg / m}^3 = 12.26 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{12.26 \times 6 \times 5}{24 \times 7} = 2.19 \text{ mg / L}$$

$$\text{Daily dose} = \frac{2.19 \times 290}{0.33 \text{ kg}} = 1925 \text{ mg / kg}$$

$$\text{PDE} = \frac{1925 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 1925 \text{ mg / day}$$

$$\text{Limit} = \frac{1925 \times 1000}{10} = 192{,}500 \text{ ppm}$$

Animal Toxicity

F344 rats exposed by inhalation to 403, 3023 or 7977 ppm 6 h/day, 5 days/week for 2 years.

Chronic progressive nephropathy in males associated with α2 µ globulin toxicity. This has

been shown to be of no relevance for humans since they do not produce

that protein.

In females, which do not produce α2 µ globulin, chronic progressive nephropathy was also

seen. NEL 403 ppm.

Ref. Chun JS et al.,1992 (summarised in IRIS report Document No. 537, 1993)

$$\text{NEL} = 403 \text{ ppm} = \frac{403 \times 88.15}{24.45} = 1453 \text{ mg / m}^3 = 1.45 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{1.45 \times 6 \times 5}{\cancel{24} \times 7} = 0.26 \text{ mg / L}$$

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

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

$$\text{Limit} = \frac{177 \times 1000}{10} = 17{,}700 \text{ ppm}$$

Conclusion

The PDE for tert-butylmethyl ether is 177 mg/day.

CUMENE

Genotoxicity

Negative results in Ames test and in Saccharomyces cerevisiae. Positive in in vitro UDS and

in cell transformation assays using mouse embryo

cells.

Refs. Mut. Res. 1986 168 69-240.

Mut. Res. 1984 133 199-244.

EPA Fiche OTS 0509712 (1984)

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Animal Toxicity

No adverse effects noted in rats exposed to 146 mg/m^3 continuously by inhalation for 4

months. Ref. Jenkins LJ et al., Toxicol. Appl. Pharmacol. 1970 16 (3)

818-23.

$$146 \text{ mg}/m^3 = 0.146 \text{ mg} / \text{L}$$

$$\text{Daily dose} = \frac{0.146 \times 290}{0.425} = 19.9 \times 1000$$

Limit

10

$$\text{PDE} = \frac{99.6 \times 50}{5 \times 10 \times 5 \times 1 \times 1}$$

= 99.6 mg / kg

= 19.9 mg / day

= 1990 ppm

Female Wistar rats given 154, 462 and 769 mg/kg by gavage 5 days/week for 6 months. No

histopathological changes but slight increases in kidney weights at two higher doses. NEL

154 mg/kg. Ref. Wolf MA et al., Arch. Ind. Health 1956 14 387-98.

$$\text{For continuous dosing} = \frac{154 \times 5}{7} = 110 \text{ mg / kg}$$

$$\text{PDE} = \frac{110 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 55 \text{ mg / day}$$

$$\text{Limit} = \frac{55 \times 1000}{10} = 5500 \text{ ppm}$$

Conclusion

The 1970 study is disregarded since only a single dose was administered and no effect was

detected. The PDE for cumene is 55.0

mg/day.

DIMETHYL SULFOXIDE

Genotoxicity

Negative in vitro results in Ames and other bacterial tests, CHO cells, and in host mediated
assay.

Conflicting results in mouse lymphoma assay.

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

Zeiger E et al., Environ. Mol. Mutagen. 1992 19 (Suppl 21) 2-141

Fluck ER et al., Chem. Biol. Interact. 1976 15 219-31

Takehisa S and Wolff S. Mut. Res. 1978 58 103-6

Hrelia P et al., Terat. Carcinogen. Mutagen. 1990 10 263-71

Wangenheim J and Bolcsfoldi G. Mutagen. 1988 3 (3) 193-205

Amacher DE et al., Mut. Res. 1980 72 447-74.

Carcinogenicity

Dermal application of 100 mg 3 times weekly to skin opf ICR/Ha mice for 663 days did not
cause skin damage or tumours (only skin examined).

Ref. Van Duuren BL et al., J. Ntl. Cancer Inst. 1967 39

1217-28

$$\text{100 mg to mice weighting 28g} = \frac{100 \times 1000}{28} = 3571 \text{ mg / kg}$$

$$\text{For continuous dosing} = \frac{3571 \times 3}{7} = 1530 \text{ mg / kg}$$

$$\text{PDE} = \frac{1530 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 6375 \text{ mg / day}$$

$$\text{Limit} = \frac{6375 \times 1000}{10} = 637{,}500 \text{ ppm}$$

No tumours in mice dosed with 5 ml/kg orally daily for 50 weeks. (Time of autopsy not

stated). Ref. Kanisawa M and Suzuki S. Gann 1978 69

599-600

$$5 \text{ ml / kg} = 5 \times 1.1 = 5{,}500 \text{ mg / kg}$$

$$\text{PDE} = \frac{5{,}500 \times 50}{12 \times 10 \times 10 \times 1 \times 1} = 229 \text{ mg / day}$$

$$\text{Limit} = \frac{229 \times 1000}{10} = 22{,}900 \text{ ppm}$$

No tumours seen at injection sites after s/c administration of 0.05 ml weekly to ICR/Ha mice

for 76 weeks. Ref. Van Duuren BL et al., J. Nell. Cancer Inst. 1971

46 143-49

$$0.05 \text{ ml} = 0.05 \times 1.1 = 55 \text{ mg}$$

$$55 \text{ mg to mice weighing } 28 \text{ g} = \frac{55 \times 1000}{28} = 1964 \text{ mg / kg}$$

$$\text{For continuous dosing} = \frac{1964 \times 1}{7} = 281 \text{ mg / kg}$$

$$\text{PDE} = \frac{281 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 117 \text{ mg / day}$$

$$\text{Limit} = \frac{117 \times 1000}{10} = 11{,}700 \text{ ppm}$$

Reproductive Toxicity

Oral dose of 5 g/kg to Wistar rats for 4 days pre-mating and throughout pregnancy had no

effects on mother or offspring.

Ref. Caujolle FM et al., C.R. Acad. Sci. Paris 1964 258 (13)

2224-6

$$PDE = \frac{5000 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 5000 \text{ mg / day}$$

$$\text{Limit} = \frac{5000 \times 1000}{10}$$

$$= 500{,}000 \text{ ppm}$$

Swiss mice given 5-12 g/kg orally days 6-12 showed no increase in foetal deaths or reduction

in foetal weight and no abnormalities were observed although maternal toxicity was seen at all

except the lowest level. Ref. Caujolle FM et al., Ann NY Acad. Sci. 1967 141 110-25

$$PDE = \frac{5000 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 2083 \text{ mg / day}$$

$$\text{Limit} = \frac{2083 \times 1000}{10} = 208{,}300 \text{ ppm}$$

Hamsters given 50 to 8250 mg/kg IV on day 8. No evidence of maternal toxicity. Increases

in foetal deaths at 5500 mg/kg and teratogenic effect from 2,500 mg/kg: exencephaly, cleft

lip, and skeletal abnormalities. NEL 1000 mg/kg. Ref. Ferm VH J.Embryol. Exp. Morph.,

1966 16 (1) 49-54

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

$$\text{Limit} = \frac{50 \times 1000}{10} = 5000 \text{ ppm}$$

Animal Toxicity

Dogs dosed orally at 2.5, 5, 10, 20 and 40 g/kg 5 days/week for 23 weeks showed changes in lens refractiveness making the lens clearer rather than translucent. No changes were detected histologically. LOEL = 2.5 g/kg = 2,500 mg/kg.

Ref. Rubin LF and Mattis PA Science 1966 153 83-4

$$\text{For continuous dosing} = \frac{2{,}500 \times 5}{7} = 1786 \text{ mg / kg}$$

$$\text{PDE} = \frac{1786 \times 50}{2 \times 10 \times 2 \times 1 \times 1} = 2233 \text{ mg / day}$$

$$\text{Limit} = \frac{2233 \times 1000}{10} = 223{,}300 \text{ ppm}$$

1, 3 and 9 ml/kg of 90% solution given orally to rhesus monkeys daily for 18 months. Deaths at high dose. NEL 3 ml/kg. Ref. Vogin EE et al., Toxicol. Appl. Pharmacol. 1970 16 606-12.

$$3 \text{ mL/kg} = 3 \times 1.1 \times 1000 \times 90\% = 2970 \text{ mg/kg}$$

$$\text{PDE} = \frac{2970 \times 50}{10 \times 10 \times 5 \times 1 \times 1} = 297 \text{ mg / day}$$

$$\text{Limit} = \frac{297 \times 1000}{10} = 29{,}700 \text{ ppm}$$

2 and 5 g/kg of 50% solution given orally for 45 days to Wistar rats. High dose caused

reduced weight gain and some liver damage. NEL 1 g/kg.

Ref. Caujolle FM et al., Ann NY Acad. Sci. 1967 141

110-25

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

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

Conclusion

The PDE for dimethyl sulfoxide is 50 mg/day.

ETHANOL

Genotoxicity

Negative results in Ames tests and in vitro cytogenetic studies with CHO

and SHE cells. 5 Refs. Lin YC et al., Mut. Res 1989 216 (2) 93-9.

Zeiger E et al., Environ. Mol. Mutagen 1992 19 (Suppl 21) 2-141.

Murt Res 1983 14 283-385.

Carcinogenicity

A 40% solution administered by gavage twice weekly for 78 weeks to male and female BDVI

rats had no oncogenic effects. Volume administered not stated. Ref. Griciute L

et al., Cancer

Letters 1986 31 267-75.

Reproductive Toxicity

Up to 16,000 ppm by inhalation 7 h/day, days 1-20 had no effects on outcome of pregnancy

in Wistar rats.

Negative results when males dosed for 6 weeks at same level then mated to untreated

females. Ref. Nelson BK et al., Neurobehavr. Toxicol. Teratol. 1985 7 779-83.

$$\text{NEL} = 16000 \text{ ppm} = \frac{16000 \times 46.07}{24.45} = 30148 \text{ mg / m}^3 = 30.1 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{30.1 \times 7}{24} = 8.8 \text{ mg / L}$$

$$\text{Daily dose} = \frac{8.8 \times 290}{0.33\ \text{kg}} = 7733\ \text{mg / kg}$$

$$\text{PDE} = \frac{7733 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 7733\ \text{mg / day}$$

$$\text{Limit} = \frac{7733 \times 1000}{10} = 773{,}300 \text{ ppm}$$

Single I/P doses of 2, 4, 6, and 7g/kg given I/P to CD-1 mice on day 10. Increased foetal deaths at high dose and reduced foetal weight at 6 and 7 g/kg. Cleft palate noted at foetotoxic levels. Maternal effects not reported. NEL 4 g/kg.

Ref. Blakley PM and Scott WJ. Toxicol. Appl. Pharmacol. 1984 72 (2) 355-63.

$$\text{PDE} = \frac{4000 \times 50}{12 \times 10 \times 1 \times 10 \times 1} = 166.7 \text{ mg / day}$$

$$\text{Limit} = \frac{166.7 \times 1000}{10} = 16{,}670 \text{ ppm}$$

Animal Toxicity

Oral LD50 in rats 13.7 ml/kg.

Ref. Verschueren K ed in Handbook of Environmental Data of Organic Chemicals 2nd Edn. New York 1983. Ethanol is a permitted direct food additive. Ref. 21 CFR 184 - 1293 (1990)

Rat iv LD50 = 0.96 mL/kg for males, 1.15 mL/kg for females.

Dog iv LD0 >0.52 mL/kg. Ref. Shirai, M., et al., 1996, Jpn Pharmacol Ther 24, 309-322

4-week repeat dose in dogs NEL 0.01 mL kg^{-1} day^{-1}

Ref. Pukutome, A. et al., 1996, Jpn Pharmacol Ther 24,

323-348

Human

The workplace exposure limit for ethanol (TLV-TWA) is 1000 ppm, equal to 1880 mg per
cubic meter. Assuming inhalation of 10 cubic meters during an 8-h workday, total daily
ethanol intake is 18.8 g, or 376 mg/kg. The TLV is designed to avoid eye and upper
respiratory tract irritation, and does not reflect concern about systemic toxicity.

Ref. American Conference of Governmental Industrial Hygienists, Documentation of the

Threshold L:imit Values and Biological Exposure Indices, 1991,

ACGIH Inc.

The maximum recommended social consumption of alcoholic drinks in the UK is 21

units/week for men and 14 units per week for women, where a unit is equivalent to 275 mL of

standard beer or lager (4% alcohol). Based on 2 units per day, a daily alcohol intake of 275 x

2 x 0.04 = 22 mL/day = 17,360 mg/day is considered to be without significant risk to

women. Ref. UK Department of Health Guidelines, latest

revision 1995.

Ethanol is a permitted direct food additive. Ref. 21 CFR 184-1293 (1990)

Conclusion

The PDE for ethanol is 166.7 mg/day.

ETHYL ACETATE

Genotoxicity

Negative results in vitro in Ames tests and in vivo in micronucleus test in Chinese hamsters.

Refs. Zeiger E et al., Environ. Mol. Mutagen 1992 19 (Suppl 21) 2-141

NTP Fiscal Year 1987 Annual Plan. NTP - 87-

001

Basler A. Mut. Res. 1986 174 (1) 11-13.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Animal Toxicity

Oral LD50 in rats 11.3 ml/kg.

Ref. Merck Index 10th Edn.

1983.

Rats given 2000 ppm 4 h/day, 5 days/week for 13 weeks showed no adverse effects on
bodyweight or haematological measurements.

Ref. Quoted in American Conference of Governmental Industrial Hygienists. Documentation
of the TLV and Biological Exposure Indices 5th Edn. 1986.

$$2000 \text{ ppm} = \frac{2000 \times 88.10}{24.45} 7207 \text{ mg} / \text{m}^3 = 7.2 \text{ mg} / \text{L}$$

$$\text{Continuous exposure} = \frac{7.2 \times 4 \times 5}{\cancel{24}\ 7} = 0.86 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.86 \times 290}{0.425 \text{ kg}} = 587 \text{ mg / kg}$$

$$PDE = \frac{587 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 117 \text{ mg / day}$$

$$\text{Limit} = \frac{117 \times 1000}{10} = 11{,}700 \text{ ppm}$$

Ethyl acetate is a permitted direct food additive. Ref. 21 CFR 182.60.

Ethyl acetate is exempt from certification needs for use as a diluent in inks for marking fruit

and vegetables under section 706 (c) of the Federal Food, Drug and

Cosmetic Act.

Ref. 21 CFR 73.1 (1990).

Conclusion

The PDE for ethyl acetate is 117 mg/day.

ETHYL ETHER

Genotoxicity

Negative results in Ames test.

Ref. Waskell L. Mut. Res. 1978 57 141-53

Carcinogenicity

No data available.

Reproductive toxicity

CD-1 mice were maintained anaesthetised from day 13.5 to 15.5 of gestation. No cleft palate
was produced. Actual dosage administered not stated. Ref. Jacobs RM
Teratol. 19 4, 699-
74

Animal toxicity

Oral LD50 in rats is approx 2 mL/kg.

Ref. Kimura ET et al., Toxicol. Appl. Pharmacol. 1971 19 699-74.

ETHYL FORMATE

Genotoxicity

Negative in Ames test (*Salmonella* strains and *Saccharomyces cerevisiae*) with and without

metabolic activation.

Ref. Litton Bionetics Project No. 2468, Mutagenic Evaluation of Compound Ethyl Formate

(FDA 75-49) 1976

Carcinogenicity

A/He mice given ip injections 3 times/week for 8 weeks (total doses of 2.4 or 12.0 g/kg), and

examined for primary lung tumours 24 weeks after the first dose, showed no excess over

controls.

Ref. Stoner GD et al., Cancer Res. 1973 33

3069-3085

'S' strain mice treated dermally with 18 weekly applications of croton oil, and for the first 10

weeks with 0.3 mL/week ethyl formate (total dose 2.76 g), did not have skin cancers when

they were killed and examined one week after the last treatment with croton oil.

Ref. Roe FJC and Salaman MH British J. Cancer (1955) 9

177-203

Reproductive Toxicity

No data available.

Toxicity

Oral LD50 in rats 1850 mg/kg.

Oral LD50 in guinea pigs 1110 mg/kg.

Ref. Jenner PM et al., Food Cosmet. Toxicol. 1964 2 (3) 327-343

Oral LD50 in rabbits 2075 mg/kg. Ref. Munch JL Ind. Med. Surg. 1972 41 (4) 31

Osborne-Mendel rats given 1000, 2500 or 10000 ppm in the diet for 17 weeks showed no
macroscopic effects, or microscopic findings in major organs. NEL 10000 ppm.

Ref. Hagan EC et al., Food Cosmet. Toxicol. 1967 5 141-157

Assume rat consumes 30 g/day.

$$\text{Daily dose} = \frac{30 \times 10}{0.425} = 705.9 \text{ mg / kg}$$

$$\text{PDE} = \frac{705.9 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 141.2 \text{ mg / day}$$

$$\text{Limit} = \frac{141.2 \times 1000}{10} = 14{,}120 \text{ ppm}$$

Human

Ethyl formate has GRAS status, and is a permitted food additive. Ref. 21 CFR 172.515

Conclusion

The PDE for ethyl formate is 141.2

mg/day.

FORMIC ACID

Genotoxicity

Negative in Ames test.

Ref. Zeiger E et al., Environ. Mol. Mutagen 1992 19 (Suppl 21) 2-141

Carcinogenicity

No data available

Reproductive Toxicity

No data available

Animal Toxicity

Rats given 8 to 360 mg/kg in drinking water for up to 27 weeks showed only reduced weight
gain at highest dose. Virtual NEL 360 mg/kg.

Ref. Malorny G. Z. Ernaehrungswiss 1969 9

332-9

$$PDE = \frac{360 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 180 \text{ mg / day}$$

$$\text{Limit} = \frac{180 \times 1000}{10} = 18{,}000 \text{ ppm}$$

F344/N rats and B6C3F1 mice were given 8, 16, 32, 64, or 128 ppm by inhalation 6 h/day, 5
days per week for 13 weeks. Two mice died at the highest dose level and body weight gain in
mice was reduced at the 64 and 128 ppm levels. Lesions were generally limited to the highest

dose in both species and comprised squamous metaplasia and degeneration of the respiratory
and olfactory epithelia. The changes are consistent with the administration of an irritant
chemical by the inhalation route. There was no evidence of systemic toxicity.

Ref . NTP Tech Report Tox 19, 1992. NOAEL for irritancy 32 ppm in both

species.

$$32 \text{ ppm} = \frac{32 \times 46.02}{24.45} = 60.2 \text{ mg / m}^3$$

$$= 0.06 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{0.06 \times 6 \times 5}{\times 7 \quad 24} = 0.011 \text{ mg / L}$$

$$\text{Rat daily dose} = \frac{0.011 \times 290}{0.425 \text{ kg}} = 7.51 \text{ mg / kg}$$

$$\text{PDE} = \frac{7.51 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 1.5 \text{ mg / day}$$

$$\text{Limit} = \frac{1.5 \times 1000}{10}$$

$$= 150 \text{ ppm}$$

$$\text{Mouse daily dose} = \frac{0.011 \times 43}{0.028 \text{ kg}} = 16.9 \text{ mg / kg}$$

$$\text{PDE} = \frac{16.9 \times 50}{12 \times 10 \times 5 \times 1 \times 1} = 1.4 \text{ mg / day}$$

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

Formic acid is a permitted direct food additive. Ref. 21 CFR 172.515 (1990)

Conclusion

The inhalation study is disregarded since no systemic toxicity was noted. The PDE for formic

acid is 180.0 mg/day.

HEPTANE

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Toxicity

Wistar rats given 3000 ppm 12 h/day 7 days/week for 16 weeks. Slight effect on weight gain

but no effects on motor nerve conduction velocity, mixed nerve conduction velocity or distal

latency. NEL 3000 ppm. Ref. Takeuchi Y et al., Clin. Tox. 1981 18 (12) 1395-1402

$$3000 \text{ ppm} = \frac{3000 \times 100.2}{24.45} = 12294 \text{ mg / m}^3$$

$$= 12.3 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{12.3 \times 12}{24}$$

$$= 6.15 \text{ mg / L}$$

$$\text{Daily dose} = \frac{6.15 \times 290}{0.425} = 4{,}196 \text{ mg / kg}$$

$$\text{PDE} = \frac{4196 \times 50}{5 \times 10 \times 5 \times 1 \times 1}$$

$$= 840 \text{ mg / day}$$

Conclusion

$$\text{Limit (ppm)} = \frac{840 \times 1000}{10} = 84{,}000 \text{ ppm}$$

The PDE for heptane is 840 mg/day.

ISOBUTYL ACETATE

Genotoxicity

Data not available.

Carcinogenicity

Data not available.

Reproductive Toxicity

Data not available.

Animal Toxicity

Oral LD50 in rats is 15.4 ml/kg.

Ref. Smyth HF et al., Am. Ind. Hyg. Assoc. J. 1962

23 95.

Given GRAS status by FEMA 1965.

Isobutyl acetate is a permitted direct food additive.

Ref. 21 CFR 172. 515 (1990)

ISOPROPYL ACETATE

Genotoxicity

Negative in Ames test.

Ref. Zeiger E et al., Environ. Mol. Mutagen 1992 19 (Suppl 21) 2-141.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Animal Toxicity

Oral LD50 in rats 6.75 g/kg.

Ref. Merck Index 10th Edn. 1983.

Isopropyl acetate is a permitted direct food additive

Ref. 21 CFR 172.515 (1990)

METHYL ACETATE

Genotoxicity

Negative in Ames tests.

Ref. Zeiger E. et al., Environ. Mol. Mutagen 1992 19 (Suppl 21) 2-141.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Animal Toxicity

Oral LD50 in rats 3.7 g/kg.

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

Methyl acetate is a permitted direct food additive.

Ref. 21 CFR 172.515 (1990).

3-METHYL-1-BUTANOL

Genotoxicity

No data available.

Carcinogenicity

No suitable data available.

Reproductive Toxicity

No teratogenic effects were seen when 8 mg was injected into the yolk sac of chick embryos.
Higher doses caused the death of the embryos.

Ref. McLaughlin J et al., Am. Ind. Hyg. Assoc. J. 1964 25 282-4.

Animal Toxicity

No adverse effects when 150, 500 or 1000 mg/kg given orally to Ash/LSE rats daily for 17
weeks.

Ref. Carpanini FMB et al., Fd. Cosmet. Toxicol. 1973 11

713-24.

$$NEL = 1000 \text{ mg / kg}$$

$$PDE = \frac{1000 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 200 \text{ mg / day}$$

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

$$= 20{,}000 \text{ ppm}$$

3-methyl-1-butanol is a permitted direct food additive. Ref. 21 CFR 172.515 (1990)

Conclusion

The PDE for 3-methyl-1-butanol is 200 mg/day.

METHYLETHYL KETONE

Genotoxicity

Negative results in wide range of in vitro tests and in MNT using mice and hamsters

Refs. O'Donoghue JL et al., Mut. Res. 1988 206

149-61

EPA Doc No. 878210125 Fiche No. 206206 (1982)

Basler A. Mut. Res. 1986 174 11-13

Carcinogenicity

No oral or inhalation carcinogenicity data available.

Reproductive Toxicity

Rats Exposure to 412, 1002 or 3005 ppm by inhalation 7 h/day, days 6-15 caused decreased

maternal weight gain and mild developmental retardation at the high dose only. NEL 1002

ppm. Ref. Deacon MM et al., Toxicol. Appl. Pharmacol. 1981 59 (3) 620-22

$$1002 \text{ ppm} = \frac{1002 \times 72.1}{24.45} = 2955 \text{ mg / m}^3 = 2.96 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{2.96 \times 7}{24} = 0.86 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.86 \times 290}{0.33}$$

$$\text{PDE} = \frac{756 \times 50}{5 \times 10 \times 1 \times 1 \times 1}$$

= 756 mg / kg

= 756 mg / day

$$\text{Limit} = \frac{756 \times 1000}{10} = 75{,}600 \text{ ppm}$$

Mice

Swiss mice given 398, 1010 or 3,020 ppm by inhalation 7 h/day, days 6-15. Slightly
decreased foetal weight at high dose only but no materanl effects. NEL 1010 ppm.

Ref. Schwetz BA et al., Fund. Appl. Toxicol. 1991 16

742-48

$$1010 \text{ ppm} = \frac{1010 \times 72.1}{24.45} = 2978 \text{ mg / m}^3 = 2.98 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{2.98 \times 7}{24} = 0.869 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.869 \times 43}{0.03 \text{ kg}} = 1246 \text{ mg / kg}$$

$$\text{PDE} = \frac{1246 \times 50}{12 \times 10 \times 1 \times 5 \times 1} = 104 \text{ mg / day}$$

$$\text{Limit ppm} = \frac{104 \times 1000}{10} = 10{,}400 \text{ ppm}$$

Toxicity

F344 rats exposed to 1250, 2,500 or 5,000 ppm by inhalation 6 h/day, 5 days/week for 90
days. Decreased weight gain and increased liver weights at high dose only. No

neuropathological or histopathological changes. NEL 2,500 ppm.

Ref. Cavender FL et al., Fund. Appl. Toxicol. 1983 3

264-70

$$2{,}500 \text{ ppm} = \frac{2{,}500 \times 72.1}{24.45} = 7372 \text{ mg / m}^3 = 7.37 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{7.37 \times 6 \times 5}{\cancel{24} \times 7} = 1.316 \text{ mg / L}$$

$$\text{Average wt 425 g} = \frac{1.316 \times 290}{0.425} = 898 \text{ mg / kg}$$

$$\text{PDE} = \frac{898 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 180 \text{ mg / day}$$

$$\text{Limit} = \frac{180 \times 1000}{10} = 18{,}000 \text{ ppm}$$

Cats

150 mg/kg s/c bid 5 days/week for 8.5 months did not produce detectable nervous system

damage. Ref. Spenser PS and Schaumberg HH. Toxicol. Appl. Pharmacol. 1976 37 301-11

Dose/day = 300 mg/kg

$$\text{For continuous exposure} = \frac{300 \times 5}{7} = 214 \text{ mg / kg}$$

$$\text{PDE} = \frac{214 \times 50}{10 \times 10 \times 2 \times 1 \times 1} = 54 \text{ mg / day}$$

$$\text{Limit (ppm)} = \frac{54 \times 1000}{10} = 5{,}400 \text{ ppm}$$

No significant behavioural changes in rats in 90 day study dosed by gavage 5 days/week at

2.2 m mole/kg. NOAEL 2.2 m mole/kg.

Ref. Ralston WH et al., Toxicol. Appl. Pharmacol. 1985 81 319-27.

2.2 mmole / kg = 160 mg / kg

$$\text{For continuous dosing} = \frac{160 \times 5}{7} = 114 \text{ mg / kg}$$

$$\text{PDE} = \frac{114 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 22.8 \text{ mg / day}$$

$$\text{Limit} = \frac{22.8 \times 1000}{10} = 2280 \text{ ppm}$$

Human Results

There are no relevant data

available.

Conclusion

The 1976 study in cats and the 1985 study in rats are disregarded since they are single dose
studies and no toxicity was detected. The PDE for methylethyl ketone is 104.0 mg/day.

METHYLISOBUTYL KETONE

Genotoxicity

Negative is in vitro and in vivo studies.

Ref. O'Donoghue JL et al., Mut. Res. 1988 206 149-61

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Toxicity

F344 rats exposed to 50, 250 or 1000 ppm by inhalation 6 h/day, 5 days/week for 14 weeks.

Slight increase in liver weight at high dose but no histopathological change. Slight increase in

incidence and extent of hyaline droplets in proximal kidney tubule cells at 250 and 1000 ppm.

This is a rat-specific finding related to the occurrence of α–2μ globulin in that species. Virtual

NEL =1000 ppm. Ref. Phillips RD et al., Fund. Appl. Toxicol.1987 9 380-88

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

$$\text{For continuous exposure} = \frac{4.1 \times 6 \times 5}{\cancel{24} \times 7} = 0.73 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.73 \times 290}{0.425} \qquad \text{Limit} = \frac{5 \times 10 \times 5 \times 1 \times 1}{10}$$

$$\text{PDE} = \frac{498 \times 50}{\cancel{45}} \qquad 99.6 \times 1000$$

= 498 mg / kg

= 99.6 mg / day

= 9,960 ppm

150 mg/kg S/C bid 5 days/week for 8.5 months did not produce nervous system damage to

cats. Ref. Spenser PS and Schaumburg HH. Toxicol. Appl. Pharmacol. 1976 37 301-11

$$\text{For continuous exposure} = \frac{300 \times 5}{7} = 214 \text{ mg / kg}$$

$$\text{PDE} = \frac{214 \times 50}{10 \times 10 \times 2 \times 1 \times 1} = 53.5 \text{ mg / day}$$

$$\text{Limit} = \frac{53.5 \times 1000}{10} = 5{,}350 \text{ ppm}$$

Conclusion

The 1976 study in cats is disregarded since it is a single dose study and no toxicity was

detected. The The PDE for methylisobutyl ketone is 100

mg/day.

2-METHYL-1-PROPANOL

Genotoxicity

Negative results in Ames test.

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

Carcinogenicity

No suitable data available.

Reproductive Toxicity

No data available.

Animal Toxicity

Acute oral LD50 in rats 2.46 g/kg. Ref. Merck Index 10th

Edn. 1983

1-Molar solution given as sole drinking fluid to rats for 4 months did not produce any adverse
reactions on liver.

Ref. Hilbbom ME et al., Res. Commun. Chem. Path. Pharmacol. 1974 9

(1) 177-80.

1 M = 74 g/L = 74 mg/mL

Rat consumes 30 mL/day

$$\text{Daily dose} = \frac{74 \times 30}{\quad}$$

0.425

$$PDE = \frac{5224 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 5224 \text{ mg / kg}$$

$$= 1044.8 \text{ mg / day}$$

$$\text{Limit} = \frac{1044.8 \times 1000}{10} = 104{,}480 \text{ ppm}$$

2-methyl-1-propanol is a permitted direct food additive Ref. 21 CFR 172.515 (1990)

Conclusion

The PDE for 2-methyl-1-propanol is 1044.8 mg/day.

PENTANE

Genotoxicity

Negative in Ames test.

Ref. Kirwin CJ et al., J. Soc. Cosmet. Chem. 1980 31 367-70.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Animal Toxicity

Rats exposed to 3000 ppm by inhalation 12 h/day for 16 weeks did not develop peripheral
nerve damage. Ref. Takeuchi Y et al., Br. J. Ind. Med. 1980 37 (3) 241-7.

$$\text{NEL 3000 ppm} = \frac{3000 \times 72.15}{24.45} = 8853 \text{ mg / m}^3$$

$$= 8.85 \text{ mg / L}$$

$$\text{Continuous exposure} = \frac{8.85 \times 12}{24}$$

$$= 4.43 \text{ mg / L}$$

$$\text{Daily dose} = \frac{4.43 \times 290}{0.425 \text{ kg}}$$

Conclusion

$$\text{PDE} = \frac{3023 \times 50}{5 \times 10 \times 5 \times 1 \times 1}$$

$$\text{Limit} = \frac{604.6}{10} \times 1000 = 30230 \text{ mg/kg}$$

$$= 604.6 \text{ mg / day}$$

$$= 60{,}460 \text{ ppm}$$

The PDE for pentane is 604.6 mg/kg.

1-PENTANOL

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive toxicity

14,000 mg/m^3 by inhalation 7 h/day, days 1-19 had no adverse effects on the foetuses of
Sprague-Dawley rats. Ref. Nelson BK et al., J. Amer. Coll. Tox. 1989 8

(2) 405-10.

$$14{,}000 \text{ mg} / \text{m}^3 = 14 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{14 \times 7}{24} = 4.08 \text{ mg} / \text{L}$$

$$\text{Daily dose} = \frac{4.08 \times 290}{0.33}$$

Animal toxicity

$$\text{PDE} = \frac{3585 \times 50}{5 \times 10 \times 1 \times 1 \times 1}$$

$$\text{Limit} = \frac{3585 \times 1000}{10}$$

= 3585 mg / kg = 3585 mg / day = 358,500 ppm

50, 150 and 1000 mg/kg administered by gavage daily to ASH/CSE rats for 13 weeks

produced no adverse effects. NEL 1000 mg/kg.

Ref. Butterworth KR et al., Fd. Cosmet. Toxicol. 1978 16 (3)

203-8

$$PDE = \frac{1000 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 200 \text{ mg / day}$$

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

1-Pentanol is a permitted direct food additive. Ref. 21 CFR 172.515 (1990).

Conclusion

The PDE for 1-pentanol is 200 mg/day.

1-PROPANOL

Genotoxicity

Negative in vitro results in Ames test. Mouse lymphoma assay, SCE.

Refs. Short Term Programs NCI

1984

Mut Res. 1981 87 17-62.

Carcinogenicity

No suitable data available.

Reproductive Toxicity

No data available.

Animal Toxicity

Oral LD50 in rats 1.9 g/kg.

Ref. Smyth HF et al., Arch. Ind. Hyg. Occup. Med.

1954 10 1

1-Propanol is a permitted direct food additive

Ref. 21 CFR 172.515 (1990)

2-PROPANOL

Genotoxicity

Negative in vitro results in Ames tests and in transformation assay in SHE cells.

Refs. Shimizu H et al., Ipn. J. Ind Health 1985 27 400-419

Zeiger E et al., Environ. Mol. Mutagen 1992 19 (suppl21)

2-141 7 Mut Res 1983 114 283-385

Carcinogenicity

Mice exposed to 3000ppm. 7hr/day 5 days/week for 8 months by inhalation. No tumourigenic activity when examined at 12 months of age.

Ref. Neil CS et al., Arch. Ind. Hygien. Assoc. J 1952 5

535-547.

Reproductive Toxicity

A 1.5% solution in drinking ware was administered to rats for 2 generations. Other than a

slight early growth retardation in the first generation, no adverse effects were seen**.** NOEL

1.5%. Ref. Lehman A J et al., Pharmacul;. Exp. Therap. 1945 85 61

1.5% = 1.5mL/100mL = 1.5 x 0.78505 = 1.18 g/100 mL. Rat consumes 30 mL/day

$$\text{Daily dose} = \frac{1180 \times 30}{100 \times 0.425} = 833 \text{ mg / kg}$$

$$\text{PDE} = \frac{833 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 833 \text{ mg / day}$$

$$\text{Limit} = \frac{833 \times 1000}{10} = 83{,}300 \text{ ppm}$$

400, 800 or 1200 mg/kg were administered by gavage to 5D rats daily from day 6-15. Deaths

were noted in the dams at the intermediate and high levels. Foetal weights were reduced at

the intermediate and high levels but no tertogenic on embryocellular effects were noted.

NOEL 400mg/kg. Ref. 1990 FDA Internal report Ref. SBJ000051 3 681-973

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

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

120, 240 or 480 mg/kg were administered by gavage to NZW rabbits on days 6-18. Deaths

and reduced maternal weight gain were noted in dams at the high dose level only. No adverse

effects were noted in any of the foetuses. NOEL 240 mg/kg.

Ref. 1990 FDA Internalreport Ref. SBJ000051

3:447-680

$$PDE = \frac{240 \times 50}{2.5 \times 10 \times 1 \times 1 \times 1} = 480 \text{ mg / day}$$

$$\text{Limit} = \frac{480 \times 1000}{10} = 48{,}000 \text{ ppm}$$

Animal Toxicity

Male rats were given 0.5 or 2.5% and females 1% or 5% in drinking water for 6 months.

Deaths, not thought to be associated with treatment, were noted in animals from the 0.5%

and 2.5% groups. Decreased weight gain was noted in the female animals but there were no

gross or microscopic changes at any dose level. Ref. Lehman AJ and Chase HF J. Lat. 24

Med. 1944 29 561. NOEL = 0.5% = 0.5 mL/100 mL = 0.5 x 0.78505 = 0.39 g/100 mL

$$\text{Daily dose} = \frac{390 \times 30}{100 \times 0.425} = 275 \text{ mg / kg}$$

$$PDE = \frac{275 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 138 \text{ mg / day}$$

$$\text{Limit} = \frac{138 \times 1000}{10} = 13{,}800 \text{ ppm}$$

Rhesus monkeys were given 2 or 20 mg/kg by gavage for 9 months. No adverse effects were

noted. NOEL is 20 mg/kg. Ref. 1968 FDA Internal Report Ref. SBJ000051 2:339-405.

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

$$\text{Limit} = \frac{1 \times 1000}{10} = 100 \text{ ppm}$$

2- Propanol is a permitted direct food additive. Ref. 21 CFR 172.515 (1990)

Conclusion

The 1968 study by the FDA in monkeys is disregarded since no toxicity was detected. The

PDE for 2-propanol is 138 mg/day.

PROPYL ACETATE

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive Toxicity

No data available.

Animal Toxicity

Oral LD50 in rats 9.4 g/kg. Ref. Merck Index 10th Edn 1983

Propyl acetate is a permitted direct food additive. 21 CFR 172.515 (1990)

TETRAHYDROFURAN

Genotoxicity

Negative in Ames test and SCE assay.

Ref. Florin I. Et al., Toxicol. 1980 15 219-32.

Mortelmans K et al., Environ. Mut. 1986 8 (Suppl 7) 1-119

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

Carcinogenicity

No data available.

Reproductive Toxicity

600, 800, or 5,000 ppm given by inhalation to SC rats 6 h/day, days 6-19 of gestation.

Reduced maternal weight gain and foetal weight at high dose level only but no abnormalities.

NOEL 1800 ppm. Ref Mast TJ et al., Fund. Appl. Toxicol 1992 18 255-265

$$\text{NEL} = 1800 \text{ ppm} = \frac{1800 \times 72.10}{24.45} = 5308 \text{ mg / m}^3 = 5.31 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{5.31 \times 6}{24} = 1.33 \text{ mg / L}$$

$$\text{Daily dose} = \frac{1.33 \times 290}{0.33}$$

$$\text{PDE} = \frac{1166 \times 50}{53}$$

$$5 \times 10 \times 1 \times 1 \times 1$$

$$\text{Limit} = \frac{1166 \times 1000}{10}$$

= 1166 mg / kg

= 1166 mg / day

= 116,600 ppm

CD-1 mice were given 600, 1800, or 5000 ppm by inhalation 6 h/day on days 6-17. Deaths at

high dose and sedation at intermediate and high levels. Reduced weight gain at 5000 ppm.

Increased incidence of intrauterine deaths at intermediate and high levels. No teratogenic

effects. NOEL 600 ppm. Ref Mast TJ et al., Fund. Appl. Toxicol 1992 18 255-265

$$\text{NEL} = 600 \text{ ppm} = \frac{600 \times 72.10}{24.45} = 1769 \text{ mg / m}^3 = 1.77 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{1.77 \times 6}{24} = 0.44 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.44 \times 43}{0.03} = 633.5 \text{ mg / kg}$$

$$\text{PDE} = \frac{633.5 \times 50}{12 \times 10 \times 1 \times 1 \times 1} = 264 \text{ mg / day}$$

$$\text{Limit} = \frac{264 \times 1000}{10} = 31{,}800 \text{ ppm}$$

Toxicity

Reported that 17,000 ppm by inhalation 6 h/day, 5 days/week for 6 weeks produced no

evidence of liver or kidney damage in rabbits.

Ref. Oettel H - Personal communication to ACIG TLV committee

$$17{,}000 \text{ ppm} = \frac{17{,}000 \times 72.10}{24.45} = 50131 \text{ mg / m}^3 = 50 \text{ mg / L}$$

$$\text{For continuous exposure} = \frac{50 \times 6 \times 5}{\cancel{24} \times 7} = 8.9 \text{ mg / L}$$

$$\text{Daily dose} = \frac{8.9 \times 1440}{4} = 3204 \text{ mg / kg}$$

$$\text{PDE} = \frac{3204 \times 50}{2.5 \times 10 \times 10 \times 1 \times 1} = 641 \text{ mg / day}$$

$$\text{Limit} = \frac{641 \times 1000}{10} = 64{,}100 \text{ ppm}$$

F344 rats given 66, 200, 600, 1800 or 5000 ppm by inhalation 6 h/day, 5 days/week for 13

weeks. High dose level animals were ataxic and had slightly increased liver weights.

Acanthosis and inflammation of the fore stomach were noted at the high dose only. NOEL

1800 ppm. Ref. Chhabra RS et al., Fund. Appl. Toxicol. 1990 14 338-345

$$\text{NEL} = 1800 \text{ ppm} = \frac{1800 \times 72.10}{24.45} = 5308 \text{ mg / m}^3 = 5.31 \text{ mg / L}$$

$$\text{For continuous dosing} = \frac{5.31 \times 6 \times 5}{\cancel{24} \times 7} = 0.95 \text{ mg / L}$$

$$\text{Daily dose} = \frac{0.95 \times 290}{0.425} = 646.9 \text{ mg / kg}$$

$$\text{PDE} = \frac{646.9 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 129 \text{ mg / day}$$

$$\text{Limit} = \frac{129 \times 1000}{10} = 12{,}900 \text{ ppm}$$

B6C3F1 mice exposed to 66, 200, 600, 1800, or 5000 ppm by inhalation 6 h/day, 5

days/week for 13 weeks. Reduced weight gain, narcosis, and deaths at high dose level.

Decreased thymic and spleen weights and increased liver weights at high dose. Mild

centrilobular hepatocytomegaly in high dose level animals of both sexes and atrophy of uterus

and degeneration of inner cortex of adrenal cortex in females. NOEL 1800 ppm.

Ref. Chhabra RS et al., Fund. Appl. Toxicol. 1990 14 338-345

As above, 1800 ppm = 0.95 mg/L continuous exposure

$$\text{Daily dose} = \frac{0.95 \times 43}{0..028} = 1456 \text{ mg / kg}$$

$$\text{PDE} = \frac{1456 \times 50}{12 \times 10 \times 5 \times 1 \times 1} = 121 \text{ mg / day}$$

$$\text{Limit} = \frac{121 \times 1000}{10} = 12{,}100 \text{ ppm}$$

Human Results

No data available.

Conclusion

The PDE for tetrahydrofuran is 121 mg/day.