ICH guideline Q3C (R6) on impurities – support document 2: toxicological data for class 2 solvents

Step 5

Release for information | October 2018
### Q3C SUPPORT DOCUMENT 2
#### Document History

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<tr>
<td>Q3C Support Document 2</td>
<td>This document was originally the Appendix 5 of the Q3C Step 2 draft Guideline from 1996 which contained the summaries of the toxicity data from which the PDEs for Class 2 solvents were derived. The Appendix 5 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 5 as a Support Document on the ICH public website on 3 October 2018.</td>
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ACETONITRILE

Genotoxicity
Negative in most studies.
Ref. Schlegelmilch R et al., J. Appl. Toxicol. 1988 8 (3) 201-9

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.

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

For continuous exposure = \[
\frac{0.336 \times 6 \times 5}{x \times 7} = 0.06 \text{ mg / L}
\]

Daily dose = \[
\frac{0.06 \times 290}{0.425}
\]

\[
PDE = \frac{40.9 \times 50}{5 \times 10 \times 1 \times 10 \times 1}
\]
= 40.9 mg / kg

\[ = 4.1 \text{ mg / day} \]

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

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.

As above 200 ppm = 0.336 mg/L

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

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

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

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

PDE = \(\frac{190 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 10\)

Limit (ppm) = \(\frac{190 \times 1000}{3}\)
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 ppm = $\frac{1200 \times 41.05}{24.45} = 2015 \text{ mg} / \text{ m}^3 = 2.015 \text{ mg} / \text{ L}$

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

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

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

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. 14


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

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

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.

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

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

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

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

Limit (ppm) = \frac{9.0 \times 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)
24.45 m³ = 168 mg / m³ = 0.168 mg / L

For continuous exposure:

\[
\frac{0.168 \times 6.5 \times 5}{24 \times 7} = 0.033 \text{ mg / L}
\]

Daily dose = \[
\frac{0.033 \times 43}{0.028} = 50.7 \text{ mg / kg}
\]

\[
\text{PDE} = \frac{50.7 \times 50}{12 \times 10 \times 5 \times 1 \times 1} = 4.22 \text{ mg / day}
\]
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.


**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

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

**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.


NEL 60 mg/kg

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

\[
\text{PDE} = \frac{43 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = \frac{43.0 \times 1000}{10}
\]
= 43.0 mg / day

= 4300 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.


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.


NEL 590 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 6678-86

NEL is 450 ppm
= 0.52 mg / L

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

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

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.


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 Toxicity

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 haemopoietic system. No changes were observed at lower levels. NEL 54.5 mg/kg


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

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

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

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.


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

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

\[
\text{Limit} = \frac{17.8 \times 1000}{10} = 1780 \text{ ppm}
\]
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)


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

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

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

**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.

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

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

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

**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)

\[
PDE = \frac{19 \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 1.9 \text{ mg / day}
\]
Reproductive Toxicity


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.

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

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

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.

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

\[
\text{Limit} = \frac{70 \times 1000}{10} = 7,000 \text{ ppm}
\]

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.


697-705

\[
25 \text{ ppm} = \frac{25 \times 119.38}{24.45} = 122 \text{ mg} / \text{m}^3 = 0.12 \text{ mg} / \text{L}
\]
For continuous dosing = \( \frac{0.12 \times 7 \times 5}{24 \times 7} \) = 0.025 mg / L

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

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

Limit = \( \frac{8.6 \times 1000}{10} \) = 860 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

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

**Human** PDE = \( \frac{12.9 \times 50}{2 \times 10 \times 1 \times 1 \times 10} \)

Limit = \( \frac{3.2 \times 1000}{10} \) = 320 ppm
= 3.2 mg / day

= 320 ppm

No epidemiological data available.

**Conclusion**

The PDE for chloroform is 0.6 mg/day.
CYCLOHEXANE

Genotoxicity
Negative in in vitro studies.
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

\[
434 \text{ ppm} = \frac{434 \times 84.16}{24.45} = 1494 \text{ mg/m}^3 = 1.5 \text{ mg/L}
\]

\[
1.5 \times 6 \times 5 = 0.27 \text{ mg/L}
\]

For continuous exposure = \[
\frac{1.5 \times 6 \times 5}{24 \times 7}
\]

\[
0.27 \times 1440 = \frac{97.2 \text{ mg/kg}}{4}
\]

Daily dose =
\[
\frac{97.2 \times 50}{2.5 \times 10 \times 5 \times 1 \times 1} = 38.8 \text{ mg/day}
\]

\[
\text{Limit} = \frac{38.8 \times 1000}{10} = 3880 \text{ ppm}
\]
**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.


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.


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

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

Daily dose = \[
\frac{0.83 \times 290}{0.425} = 566 \times \frac{50}{5 \times 10 \times 2 \times 1 \times 1}
\]
= 566 mg / kg

= 284 mg / day
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

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

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

For continuous exposure \[
\frac{3.5 \times 6 \times 5}{x \times 7} = 0.625 \text{ mg/L}
\]

Assuming average rat wt = 0.425 kg

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

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

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

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

For continuous exposure = 1.25 mg / L

Assuming average mouse wt 28g

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

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

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

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.
22-28 154,500 ppm = 15633 mg/m³ = 15.6mg/L

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

Assuming average wt of 330 g

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

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

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

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

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

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.


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.


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.

250 mg/kg

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

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

**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.)

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

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

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

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

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

**Conclusion**

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.


*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.


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

For continuous dosing:

\[
\text{Daily dose} = \frac{1.25 \times 6 \times 5}{24 \times 7} = 0.223 \frac{\text{mg}}{\text{L}}
\]

\[
\text{PDE} = \frac{152 \times 50}{35}
\]
\[ 5 \times 10 \times 1 \times 1 \times 1 \]
\[ = 152 \text{ mg} / \text{kg} \]
\[ = 152 \text{ mg} / \text{day} \]

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

**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.

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

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

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

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

**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.


132-7

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

For continuous dosing

\[
\text{Daily dose} = \frac{1.07 \times 6 \times 5}{7} = 0.19 \text{ mg / L}
\]

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

\[
PDE = \frac{167 \times 50}{37}
\]
\[
5 \times 10 \times 1 \times 1 \times 1 = 167 \text{ mg} / \text{kg}
\]

\[
= 167 \text{ mg} / \text{day}
\]

\[
\text{Limit} = \frac{167 \times 1000}{10} = 16,700 \text{ ppm}
\]
Complete resorption in rabbits dosed orally at 500 microL/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.


\[
\text{NEL } 100 \mu L / \text{kg} = 100 \times 0.9429 = 94 \text{ mg / kg}
\]

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

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

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.


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

\[
\text{Animal Toxicity Limit} = \frac{32 \times 1000}{10}
\]
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.
21 ppm = \( \frac{25 \times 87.12}{24.45} \) = 89 mg / m\(^3\) = 0.089 mg / L

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

Daily dose = \( \frac{0.016 \times 290}{0.425} \) = 10.9 mg / kg

PDE = \( \frac{10.9 \times 50}{5 \times 10 \times 1 \times 1 \times 1} \) = 10.9 mg / day

Limit = \( \frac{10.9 \times 1000}{10} \) = 1,090 ppm

**Conclusion**

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
Williams GM Cancer Res. 1977 37 1845-51
Topham JC Mut. Res. 1980 74 379-87

**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

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

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.
1557-62

\[ 46 \div 4 \mu l / kg = 46.4 \times 0.9445 = 43.8 \text{ mg} / \text{kg} \]
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.


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.


Toxicity
PDE = 12
00 x 50
5 x 10
x 1 x 1
x 1

= 1200 mg / day

Limit = 1200
x 1000
10

= 120,000 ppm

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.

Rat eats 30 g/day

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

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

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

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

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

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

\[
\text{Limit} = \frac{56.7 \times 1000}{10} = 5,670 \text{ ppm}
\]
**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.
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
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

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

\[
PDE = \frac{922 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = \frac{3.84 \times 1000}{48}
\]
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).


\[
PDE = \frac{94 \text{ mg} / \text{kg} \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 9.4 \text{ mg} / \text{day}
\]

Limit ppm = \[
\frac{9.4 \times 1000}{10} = 940 \text{ ppm}
\]

**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

\[
PDE = \frac{1030 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 1030 \text{ mg} / \text{day}
\]

Limit = \[
\frac{1030 \times 1000}{10} = 103,000 \text{ ppm}
\]

**Toxicity**

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

\[
PDE = \frac{9.6 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 9.6 \text{ mg/day}
\]

\[
Limit = \frac{9.6 \times 1000}{10} = 960 \text{ ppm}
\]
**Human Results**

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


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.


**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.

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

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

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

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

For continuous exposure = \[
0.74 \times \frac{6}{24} = 0.185 \text{ mg} / \text{L}
\]
\[
\text{Daily dose} = \frac{0.185 \times 290}{0.33 \text{ kg}} = 163 \text{ mg / kg}
\]

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

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

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.


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

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

\[
\text{Daily dose} = \frac{0.148 \times 1440}{10}
\]

\[
PDE = \frac{53.3 \times 50}{2.5 \times 10 \times 1 \times 5 \times 10}
\]

\[
\text{Limit} = \frac{2.13 \times 1000}{55}
\]
= 53.3 mg / kg

= 2.13 mg / day

= 213 ppm
**Toxicity**

Rats fed 1.45% in diet for 2 years showed testicular oedema and atrophy.  
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  
\[
\text{PDE} = \frac{250 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = 25 \text{ mg/day}
\]
\[
\text{Limit} = \frac{25 \times 1000}{10} = 250 \text{ ppm}
\]
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.

Human Results

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


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.


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.

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

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.


NOEL 200 mg/kg

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

\[
\text{Limit} = \frac{200 \times 1000}{10} = 20,000 \text{ ppm}
\]
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
Continuous dosing $= \frac{1000 \times 2}{7} = 286 \text{ mg} / \text{kg}$

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

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

**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

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

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

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

\[ \text{Limit} = \frac{1000 \times 1000}{10} = 100,000 \text{ ppm} \]
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.


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

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

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.


Animal Toxicity
\[
PDE = \frac{750 \times 50}{12 \times 10 \times 1 \times 10 \times 10} = 3.12 \text{ mg/day}
\]

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

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
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%

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

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

**Human Results**

Single oral lethal dose estimated at 1.4 ml/kg  

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

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

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.
1557-62.

\[
\text{NEL} = 20 \mu \text{l/kg} = 20 \times 1.1334 = 22.7 \text{ mg/kg}
\]

\[
\text{PDE} = \frac{22.7 \times 50}{2.5 \times 10 \times 1 \times 10 \times 1} = 4.54 \times 1000
\]

Limit

10
= 4.54 mg / day

= 454 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


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

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

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

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

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

**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., Toxcol. Appl. Pharmacol. 1979 51 295-302

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

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

\[
\text{Daily dose} = \frac{0.875 \times 290}{0.33 \text{ kg}} = 769 \times 50
\]

\[
\text{PDE} = \frac{769 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 769 \times 1000
\]

\[
\text{Limit (ppm)} = \frac{769 \times 1000}{10}
\]
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.

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

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

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

\[
PDE = \frac{119 \times 50}{5 \times 10 \times 10 \times 1 \times 2} = \frac{5.95 \times 1000}{10} = 595 \text{ ppm}
\]

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.


For continuous dosing = \( \frac{200 \times 5}{7} = 143 \text{ mg} / \text{kg} \)
\[
PDE = \frac{143 \times 50}{5 \times 10 \times 10 \times 5 \times 1} = 2.86 \text{ mg/day}
\]
\[
\text{Limit} = \frac{2.86 \times 1000}{10} = 286 \text{ ppm}
\]
**Human Results**

Several reports of polyneuropathy in workers exposed to n-hexane by inhalation. Dose range 4 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  

**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.

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.

400 - 19. 6


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.


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

For continuous dosing = \[
\frac{6.55 \times 7}{24} = 1.91 \text{ mg/L}
\]
Daily dose = \( \frac{1.91 \times 290}{0.33 \text{ kg}} \) = 1678 mg / kg

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

Limit = \( \frac{167.8 \times 1000}{10} \) = 16,780 ppm
Animal Toxicity

Oral LD50 in rats 3.56 g/kg.

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

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

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

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.

Conclusion

The PDE for methanol is 30 mg/day.
2-METHOXYETHANOL

**Genotoxicity**

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

**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

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

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

\[
\text{Daily dose} = \frac{0.008 \times 1440}{4} = 2.88 \text{ mg/L}
\]

\[
PDE = 2.88 \times 50 = 144 \text{ mg/L}
\]
\[
\text{Limit} = \frac{1.15 \times 1000}{10} = 2.88 \text{ mg / kg}
\]

\[
= 1.15 \text{ mg / day}
\]

\[
= 115 \text{ ppm}
\]
**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

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

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

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

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

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

\[ \text{Daily dose} = \frac{0.056 \times 290}{0.425} \quad \text{PDE} = \frac{38.2 \times 50}{5 \times 10 \times 5 \times 1 \times 1} \]
\[
\text{Limit} = \frac{7.64 \times 1000}{10} = 38.2 \text{ mg/kg}
\]

\[= 7.64 \text{ mg/day}\]

\[= 764 \text{ ppm}\]
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.
49-54

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

For continuous dosing = \[
\frac{0.093 \times 6 \times 5}{x \times 7} = 0.017 \text{ mg} / \text{ L}
\]

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

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

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

**Human Results**

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

**Conclusion**

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


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

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

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

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

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

For continuous dosing \[
\frac{0.164 \times 8 \times 5}{x \times 7} = 0.039 \text{ mg} / \text{L}
\]

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

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

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%

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

Rat drinks 30 ml / day
i.e. consumes \[ \frac{250 \times 30}{100} = 75 \text{ mg/day} \]

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

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

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

**Human Results**

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

Refs. Davenport JG et al., Neurol. 1976 26 912-23
Wickersham CW and Fredericks EJ Conn. Med. 1976 40 311-12
Allen N et al., Arch. Neurol. 1975 32 209-18


**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.

Inhalation LC50 (2h) in mice 41,500 mg/m³.
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.

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

\[
\text{Daily dose } = \frac{0.82 \times 1440}{4}
\]

\[
PDE= 295 \times 50 \times \frac{2}{5} \times \frac{5}{1}
\]
\begin{align*}
0 \times 10 \times 5 \times 1 &= 295 \text{ mg / kg} \\
\text{Limit} &= \frac{11.8 \times 1000}{10} \\
&= 11.8 \text{ mg / day} \\
&= 1180
\end{align*}
Human
No relevant data.

Conclusion
The PDE for methylcyclohexane is 11.8 mg/day.
N-METHYL PYRROLIDONE

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.
NEL = 0.4 mg/L

\[
\text{For continuous dosing} = \frac{0.4 \times 6 \times 5}{24} \times 7 = 0.071 \text{ mg/L}
\]

Reproductive Toxicity

\[
\text{Daily dose} = \frac{0.071 \times 290}{\text{PDE}} = \frac{48.4 \times 50}{5 \times 10 \times 1 \times 1 \times 1} = 48.4 \times 1000
\]

Limit = 10
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

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

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

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

Limit = \( \frac{79 \times 1000}{10} \) = 7900 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.


**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)

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

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

Daily dose = \frac{0.042 \times 290}{0.425} = 28.7 mg / kg
\[
\text{PDE} = \frac{28.7 \times 50}{5 \times 10 \times 1 \times 10 \times 1} = 2.87 \text{ mg / day}
\]

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

\(\text{B6C3F1 mice given 188, 375, or 750 ppm by inhalation 6h/day, 5 days/week for 2 years.}\)

\(\text{Harderian gland adenoma and adenoma or carcinoma (combined) increased at intermediate and high levels. Incidence of Harderian gland carcinoma also increased at intermediate and high levels. Incidence of alveolar/bronchaleolar carcinoma in males at high level and females at intermediate level also increased. Female low and high level mice had increased hepatocellular adenoma and adenoma or carcinoma combined. Eosinophilic liver foci increased at intermediate and high levels. Degeneration and metaplasia of olfactory epithelium increased in all groups. Ref NTP Tech Report 461 NIH Pub No. 95-3377 (1995)}\)

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

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

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

\[
\text{PDE} = \frac{123 \times 50}{100} = 61.5 \text{ mg / kg}
\]
= 0.51 mg / day

\[
12 \times 10 \times 1 \times 10 \times 10
\]

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

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

Continuous exposure = \(\frac{138.8}{3}\) = 46.3 mg / kg

PDE = \(\frac{46.3 \times 50}{5 \times 10 \times 1 \times 1 \times 1}\) = 46.3 mg / day

Limit = \(\frac{46.3 \times 1000}{10}\) = 4630 ppm

Toxicity

Oral LD50 in mice 1440 mg/kg.

Oral LD50 in rats 1210 mg/kg.


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.

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


102-106

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

Limit = \[ \frac{1.6 \times 1000}{10} \] = 160 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 \( \geq 375 \) 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

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

Continuous exposure = \[ \frac{0.235 \times 6 \times 5}{24 \times 7} \]
\[
\text{Daily dose} = \frac{0.042 \times 43}{0.028} = 64.5 \text{ mg / kg}
\]

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

\[
\text{Limit} = \frac{1.08 \times 1000}{10} = 108 \text{ ppm}
\]
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.


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

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

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

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

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

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

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

Daily dose = \( \frac{0.05 \times 290}{0.425} \) = 34.1 mg / kg

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

Limit = \( \frac{3.41 \times 1000}{10} \) = 341 ppm

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

As above, continuous exposure = 0.05 mg / L

Daily dose = \( \frac{0.05 \times 1440}{4} \) = 341 ppm

PDE = \( \frac{18 \times 50}{2.5 \times 10 \times 2 \times 1 \times 5} \)
\[
\text{Limit} = \frac{3.6 \times 1000}{10} = 360 \text{ ppm}
\]

**Human**

Probable human oral lethal dose has been estimated to be 0.5-5 g/kg. Occupational exposure to very high levels has been reported, with gross conversion of haemoglobin to 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.
Ishidate M and Odoshima S. Mut. Res. 1977 48 337-54
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

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

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

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


Pyridine is a permitted direct food additive 11


**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 cerevisiae and in a rat micronucleus test.
Refs. Shimizu H et al., Sangyo Igaku 1985 27 (6) 400-419
Glaxo Wellcome R&D - Unpublished data
A positive result was obtained in a mouse lymphoma forward mutation assay

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

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

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

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

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

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

\[
\text{Daily dose} = \frac{0.118 \times 290}{0.425} \quad \text{PDE} = \frac{80.5 \times 50}{5 \times 10 \times 10 \times 1 \times 5}
\]
Limit = \frac{1.61 \times 1000}{10} = 80.5 \text{ mg/kg}

= 1.61 \text{ mg/day}

= 161 \text{ ppm}

Male Sprague-Dawley rats were exposed by inhalation to 2.8, 4 or 20 mg/m³ 23 h/day for 3 months. Females were also exposed at the high level. No adverse effects were seen.
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.


NOEL 200 mg/m$^3$ = 0.2 mg/L
\[
10 \times 10 \times 10 \times 1 \times 1
\]

\[
= 165 \text{ mg / kg}
\]

\[
\text{Limit} = \frac{8.25 \times 1000}{10}
\]

\[
= 8.25 \text{ mg / day}
\]

\[
= 825 \text{ ppm}
\]
Guinea pigs were exposed by inhalation to 20 or 159 mg/m³ 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/m³ = 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.
Inhalation LCLo in guinea pigs 275 ppm for seventeen 8h exposures.

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 \( \beta \)-tetralol formed; this appears to be a more significant metabolite in rabbits than in rats. Very limited evidence suggests that \( \beta \)-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

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

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

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 \( \alpha \)-2\( \mu \) 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.

\[
\text{Human} \quad \frac{243 \times 50}{5 \times 10 \times 10 \times 1 \times 1} = \frac{24.3 \times 1000}{10}
\]
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.


*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)

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

For continuous dosing = \[\frac{4.52 \times 6.5 \times 5}{x \times 7} = 0.874 \text{ mg/L}\]

Daily dose = \[\frac{0.874 \times 290}{0.425} \]

\[\text{PDE} = \frac{596 \times 50}{5 \times 10 \times 1 \times 1 \times 1} \]
= 596 mg / kg

= 596 mg / 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

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

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

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

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

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

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

\[
\text{Daily dose} = \frac{0.33 \times 290}{0.33 \text{ kg}}
\]

\[
PDE = \frac{290 \times 50}{5 \times 10 \times 1 \times 5 \times 1}
\]
= 290 mg / kg

= 58 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

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

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

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

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\(^3\).


\[
1000 \text{ mg} \text{ / m}^3 = \frac{130}{130}
\]
= 1 mg / L

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

Daily dose = \[ \frac{0.179 \times 290}{0.425} = 122 \text{ mg / kg} \]
\[
PDE = \frac{122 \times 50}{5 \times 10 \times 2 \times 1 \times 1} = 61 \text{ mg/day}
\]

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

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

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

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

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

**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.


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)

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

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

\[
\text{Limit} = \frac{714 \times 1000}{10} = 71,400 \text{ ppm}
\]
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 ppm = \( \frac{100 \times 131.4}{24.45} \) = 537 mg / m\(^3\) = 0.537 mg / L

For continuous exposure = \( \frac{0.537 \times 7 \times 5}{x \times 7} \cdot \frac{24}{24} \) = 0.112 mg / L

Daily dose = \( \frac{0.112 \times 290}{0.425} \) = 76 mg / kg

\[ \text{PDE} = \frac{76 \times 50}{5 \times 10 \times 1 \times 10 \times 10} \]

= 0.76 mg / day

\[ \text{Limit} = \frac{0.76 \times 1000}{10} \]

= 76 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

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

\[ \text{PDE} = \frac{643 \times 50}{12 \times 10 \times 1 \times 10 \times 10} \]

Reproductive Toxicity

\[ \text{Limit} = \frac{2.68 \times 1000}{10} \]
= 2.68 mg / day

= 268 ppm

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

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

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

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

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

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.

= 3.73 mg / day

= 373 ppm

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

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

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


**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.

Mohtashamipour 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)

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

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

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

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


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

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

**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)

**Conclusion**

\[
PDE = \frac{500 \times 50}{5 \times 10 \times 5 \times 1 \times 1} = 21.7 \text{ mg/day}
\]

\[
\text{Limit} = \frac{100 \times 1000}{10} = 10000 \text{ ppm}
\]
= 100 mg / day = 10,000 ppm

The PDE for xylene is 21.7 mg/day.