Canadian Environmental Protection Act

Priority Substances List

Supporting Documentation:

Health-Based Tolerable Daily Intakes/Concentrations and Tumourigenic Doses/Concentrations for Priority Substances

(Unedited Version)

Health Canada, August 1996

Preface

This document is a companion volume to the publication entitled: "Health-Based Tolerable Daily Intakes/Concentrations and Tumourigenic Doses/Concentrations for Priority Substances". Values contained in this volume and the afore-mentioned publication were developed on the basis of information reviewed for assessments conducted for compounds on the first Priority Substances List (PSL 1), under the *Canadian Environmental Protection Act*. Dates of cutoff for the literature surveys on which these values were based are specified.

It should be emphasized that the information presented here is restricted to that considered most relevant for the development of the above-mentioned values. For additional information concerning, for example, the basis for the classification of the carcinogenicity of the compounds or selection of the critical studies, readers are referred to the Assessment Reports for individual Priority Substances and/or their Supporting Documentation, copies of which are available from:

Environmental Health Centre
Health Canada
Room 104
Tunney's Pasture
Postal Locator 0801A
Ottawa, Ontario, Canada
K1A 0L2

A detailed description of the approach to assessment of Priority Substances under the *Canadian Environmental Protection Act* is also available. Summaries of all and complete versions of several of the Assessment Reports on Priority Substances are also available on the Internet World Wide Web Site:

http://www.hwc.ca/dataehd

Summaries of the assessments were also published in a special edition of the *Journal of Environmental Science and Health*, volume C12, issue number 2 (1994).

Any variations from values presented in the Assessment Reports are noted in the Supporting Documentation. For the following parameters, relevant values have been added, often for an additional medium of exposure, based on consideration of information reviewed at the time of completion of the assessments:

TC_{05}, bis(chloromethyl)ether
TDI, short chain chlorinated paraffins
TDI, 1,4-dichlorobenzene
TDI, dichloromethane
TDI, methyl methacrylate
TDI, methyl tertiary-butyl ether
TC_{05}, refractory ceramic fibres
TC, metallic nickel
TDI, nickel chloride
TDI and TC, nickel sulfate
TC, nickel oxide
TC, nickel subsulphide
estimate of TC_{05}: B(b)F, B(j)F, B(k)F, IND
TDI, tetrachloroethylene
TDI, 1,2,4-trichlorobenzene
TDI, 1,3,5-trichlorobenzene
TDI, xylenes

The manner of presentation of values for the inhalation route of exposure has been modified to be expressed as concentrations rather than doses for the following parameters:

chlorobenzene
1,4-dichlorobenzene
methyl methacrylate
methyl tertiary-butyl ether
styrene
tetrachloroethylene
toluene
1,2,4-trichlorobenzene
1,3,5-trichlorobenzene
xylenes

In a very small number of cases, uncertainty factors presented herein vary slightly from those presented in the published assessments for Priority Substances since neoplastic and non-neoplastic effects are addressed separately and to ensure consistency across all parameters:

aniline
chlorobenzene
hexachlorobenzene
pentachlorobenzene
1,2,3-trichlorobenzene

In one case (1,2-dichloroethane), calculations for risk values were refined.

In the development of values presented here, unless otherwise specified, conversions have been applied based on the following principles. Surface area to body weight conversions (animal to human) have been applied in the development of Tumourigenic Dose 05s (TD_{05}s) from data in animal species in cases where the compound is believed to be a direct acting carcinogen (or data are inadequate to assess the mechanism of action in this regard). Similarly, for Tolerable Concentrations or Tumourigenic Concentration 05s (TC_{05}s) for inhalation on the basis of neoplastic or non-neoplastic effects, respectively, in animal species, conversions (animal to human) for inhalation volume to body weight ratios have been incorporated, where the critical effect(s) are systemic. These conversions were based on variations in breathing rates and body weights between rodents and the age group of humans for which this ratio is greatest (i.e., 5 to 11 year olds).

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Aniline

CAS Reg. No. 62-53-3

Cut-off date for literature review: June 1993

Exposure: Insufficient data

Neoplastic effects:

Classification for carcinogenicity: Group III (possibly carcinogenic to humans) based upon classification scheme developed for this endpoint under *CEPA* (Gomes *et al.,* 1994; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.007 mg/kg b.w./day (7 μg/kg b.w./day)

LOAEL: 7.2 mg/kg b.w./day. Based upon increased splenic hemosiderin, extramedullary hematopoiesis and congestion in male CD-F rats after 104 weeks administration of aniline hydrochloride in diet (CIIT, 1982). Similar to TDI developed on basis of limited clinical study in humans (Jenkins *et al.,* 1972).

1000 uncertainty factor[1]:

x10 for intraspecies variation

x10 for interspecies variation

x10 for use of LO(A)EL rather than NO(A)EL

TC: inadequate data available

1 Uncertainty factor modified slightly from Assessment Report.

Arsenic and its inorganic compounds

Cut-off date for literature review: April 1992

Exposure:

Drinking water: 43 to 71%
Food: 25 to 50%
Soil: 0.5 to 8.7%
Ambient air: 0 to 0.2%

Intake near point sources:

Drinking water: 49 to 99%
Food: 0.4 to 50%
Soil: 0.4 to 5.7%
Ambient air: 0.1 to 1.5%

Data on food (Dabeka *et al.,* 1993) were obtained after the final date for consideration of information. They have been included owing to their importance to the estimation of exposure in Canada.

Neoplastic effects:

Classification for carcinogenicity: Group I (carcinogenic to humans), based upon classification scheme developed for this endpoint under *CEPA* (Hughes *et al.,* 1994a; Meek *et al.,* 1994a); this classification applies to the group of inorganic arsenic compounds as a whole.

$TC_{05\ (men)}$: 910 μg/litre drinking water (oral exposure, skin cancer)
$TC_{05\ (women)}$: 840 μg/litre drinking water (oral exposure, skin cancer)
Cohort of 40,421 individuals in 37 villiages in Taiwan; skin cancer; exposure principally *via* drinking water (Tseng *et al.,* 1968; Tseng, 1977); US EPA (1988) model adjusted to take into account rates of skin cancer and volumes of ingestion of Canadians.

TC_{05}: 10 $\mu g/m^3$ (inhalation; lung cancer) Cohort of 2802 employees at the Tacoma copper smelter in Washington (Enterline *et al.,* 1987).

TC_{05}: 7.8 $\mu g/m^3$ (inhalation; lung cancer) Cohort of 8044 employees at the Anaconda smelter in Montana (Higgins *et al.,* 1986).
A relative risk model was used to calculate TC_{05}s based upon data from these studies.

TC_{05}: 51 $\mu g/m^3$ (inhalation; lung cancer) Cohort of 3916 men at Ronnskar smelter in Sweden (Jarup *et al.,* 1989).

Comments:

Non-neoplastic effects not addressed since carcinogenicity considered critical endpoint in the assessment.

Benzene

CAS Reg. No. 71-43-2

Cut-off date for literature review: October 1991

Exposure:

Indoor air: 64 to 87%
Automotive related (over 12 years of age): 25%
Ambient air: 6.9 to 11%
Food: 0.7 to 2.7%
Drinking water: 0.6 to 4.5%

Data on indoor air (Otson *et al.,* 1992) were obtained after the final date for consideration of information. They have been included owing to their importance to the estimation of exposure in Canada.

Neoplastic effects:

Classification for carcinogenicity: Group I (carcinogenic to humans) based on the classification scheme developed for this endpoint under *CEPA* (Hughes *et al.,* 1994b; Meek *et al.,* 1994a).

TC_{05}: 15×10^3 $\mu g/m^3$ (15 mg/m^3)
Cohort of pliofilm workers described by Rinsky *et al.* (1987). Derivation of quantitative estimate of carcinogenic potency based upon acute myelogenous leukaemia. A linear quadratic absolute risk model was used to derive the TC_{05}.

Comments:

Non-neoplastic effects not addressed since carcinogenicity considered critical endpoint in the assessment. TD_{05} for ingestion not developed since intake relatively small *via* this route.

Bis (2-ethylhexyl) phthalate

CAS Reg. No. 117-81-7

Cut-off date for literature review: December 1992

Exposure:

Food: 84 to 94%
Indoor air: 5 to 15%
Drinking water: 0.2 to 4.2%
For those aged 0 to 4 years, childrens' products can account for 0.05 to 56%.

Neoplastic effects:

Classification for carcinogenicity: Group IV (unlikely to be carcinogenic to humans) based on the classification scheme developed for this endpoint under *CEPA* (Meek and Chan, 1994a; Meek *et al.,* 1994a). Classification in Group III (possibly carcinogenic to humans) might also be appropriate.

Non-neoplastic effects:

TDI: 0.044 mg/kg b.w./day

NOEL (for effects other than hepatic peroxisome proliferation): 44 mg/kg b.w./day. Mice, developmental study; dietary administration. Maternal toxicity and increased numbers of resorptions, malformed fetuses and dead fetuses at next highest dose (Wolkowski-Tyl *et al.*, 1984).

1000 uncertainty factor:

x10 for interspecies variation

x10 for interspecies variation

x10 modifying factor for potential teratogenicity

Comments:
No TC for inhalation developed since intake *via* this route is relatively small and data on toxicity following inhalation insufficient.

Bis(chloromethyl) ether

CAS Reg. No. 542-88-1

Cut-off date for literature review: June 1992

Exposure: no data

Neoplastic effects:

Classification for carcinogenicity: Group I (carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Liteplo and Meek, 1994a; Meek *et al.,* 1994a).

TC_{05} (not included in Assessment Report):

Leong *et al.* (1981) exposed male Sprague-Dawley rats to bis(chloromethyl) ether by inhalation for 6 hours/day, 5 days/week for 6 months, after which time exposure was terminated and the rats observed for a further 22 months. A multistage model was fit to the data (incidence of nasal esthesioneuroepitheliomas) using GLOBAL82 and a TC_{05} of 0.139 mg/m^3 was obtained. This was converted to a constant daily concentration by multiplying by:

6/24 and 5/7 (for conversion of 6 hours/day, 5 days/week to continuous exposure)

6/28 (animals were exposed for 6 months; 28 months is the lifetime of the rats in the critical study)

Using these conversion factors, a TC_{05} of 0.0053 mg/m^3 (5.3 $\mu g/m^3$) was obtained.

Cadmium, inorganic compounds

Cut-off date for literature review: September 1993

Exposure:

Food: 98-99%
Soil: 0.1 to 1%
Air: 0.1 to 0.6%
Drinking water: 0 to 0.4%

For areas near point sources:

Food: 81 to 92%
Drinking water: 0 to 14%
Soil: 0.5 to 8.4%
Air: 1.7 to 6.3%

Neoplastic effects:

Classification for carcinogenicity: Inorganic cadmium compounds have been classified as Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Newhook *et al.,* 1994a; Meek *et al.,* 1994a).

TC_{05} (rat, inhalation): 2.9 μg Cd/m^3
Based upon lung tumor incidence in an inhalation bioassay with rats (Takenaka *et al.,* 1983; Oldiges *et al.,* 1984); exposure to cadmium chloride for 23 hours/day, 7 days/week for 18 months; necropsy 13 months after end of exposure period. This TC_{05} was subsequently amortized to be constant over the lifetime of the rat, adjusted for the longer than standard lifetime duration of the experiment, and converted to an equivalent concentration in humans using standard values for the breathing volumes and body weights of rats and humans. The resultant TC_{05} estimated for humans is 5.1 μg Cd/m^3. TC_{05} values derived from lung tumor incidences observed in rats inhaling cadmium chloride, cadmium oxide dust, cadmium sulphate and cadmium sulphide (Oldiges *et al.,* 1989; Glaser *et al.,* 1990) are similar, ranging from 2.7 to 12.7 μg/m^3.

Chlorinated paraffins, short chain ($\leq C_{13}$)

Cut-off date for literature review: Chan and Meek (1994a) surveyed literature up to August 1992. The International Programme on Chemical Safety (IPCS, 1995, in press) completed a review in March 1995.

Exposure: no data

Neoplastic effects:

Classification for carcinogenicity: Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Chan and Meek, 1994a; Meek *et al.,* 1994a).

The IPCS (1995, in press) has concluded that chlorinated paraffins do not mediate carcinogenic effects *via* direct interaction with DNA, based upon a review of the literature up to March 1995.

Non-neoplastic effects:

TDI[2]: 0.01 mg/kg b.w./day (IPCS, 1995, in press)

NOEL: 10 mg/kg b.w./day. Based upon increases in liver and kidney weight and hypertrophy of the liver and thyroid at the next highest dose in a 13-week study in rats; determined in both dietary and gavage studies (Serrone *et al.,* 1987).

1000 uncertainty factor:

x 10 for interspecies variation

x 10 for intraspecies variation

x 10 for less than chronic study
[Non-neoplastic lesions induced in F344/N rats exposed by gavage for two years (NTP, 1986a) included necrosis, hypertrophy and angiectasis of the liver; erosion, inflammation, and ulceration of the glandular stomach and forestomach; and the formation of multiple cysts in the kidneys of males. The incidence of nephropathy was also increased in female rats.] (LOAEL = 312 mg/kg b.w./day).

Comments:

Inhalation not addressed since likely to be negligible route of intake, based upon physical/chemical properties; also, data on toxicity following inhalation insufficient.

2 Not included in Assessment Report

Chlorinated paraffins, medium chain (C_{14-17})

Cut-off date for literature review: Chan and Meek (1994a) surveyed literature up to August 1992. The International Programme on Chemical Safety (IPCS, 1995, in press) completed a review in March 1995.

Exposure: no data

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Chan and Meek, 1994a; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.006 mg/kg b.w./day

LOEL: 5.7 mg/kg b.w./day. Reproductive study in rats; dietary administration. (IRDC, 1985; Serrone *et al.,* 1987). Decrease (not significant) in body weight gain in male pups by day 21 of lactation, which continued after weaning (less pronounced in males).

1000 uncertainty factor:

x 10 for intraspecies variation

x 10 for interspecies variation

x 10 for lack of data on carcinogenicity and less than chronic study; no uncertainty factor incorporated for LOEL rather than a NO(A)EL owing to the minor nature of the effects observed at this concentration.

In a more recent review, the IPCS (1995, in press) has derived a TDI based upon a similar effect level, but using an uncertainty factor of 100 (for intraspecies and interspecies variation).

A TDI developed on the basis of a more recent study by Poon *et al.* (1995) would be similar.

Comments:

Inhalation not addressed since likely to be negligible route of intake based upon physical/chemical properties; also, data on toxicity following inhalation insufficient.

Chlorinated paraffins, long chain ($\geq C_{18}$)

Cut-off date for literature review: Chan and Meek (1994a) surveyed literature up to August 1992. The International Programme on Chemical Safety (IPCS, 1995, in press) completed a review in March 1995.

Exposure: no data

Neoplastic effects:

Classification for carcinogenicity: Group III (possibly carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Chan and Meek, 1994a; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.071 mg/kg b.w./day

LOAEL: 100 mg/kg b.w./day. Diffuse lymphohistiocytic inflammation in the liver and in the pancreatic and mesenteric lymph nodes in female rats; two-year gavage study, 5 days/week (NTP, 1986b; Bucher *et al.,* 1987).

5/7 for conversion of 5 days/week dosing to 7 days/week

1000 uncertainty factor:

x 10 for intraspecies variation

x 10 for interspecies variation

x 10 for use of LOAEL rather than NOAEL

The IPCS (1995, in press) has derived a TDI of 100 μg/kg b.w./day, based upon the same LOAEL. IPCS did not include an amortization factor of 5/7 in their derivation of the TDI.

Comments:

Inhalation not addressed since likely to be negligible route of intake based upon physical/chemical properties; also, data on toxicity following inhalation insufficient.

Chromium, total

Cut-off date for literature review: April 1993

Exposure:

Food: 5.7 to 80%
Soil: 2.5 to 67%
Water: 1.1 to 71%
Air: 0.1 to 0.8%

Neoplastic effects:

Classification for carcinogenicity: see hexavalent chromium

TC_{05} for inhaled chromium (total) is 4.6 $\mu g/m^3$ based upon data reported by Mancuso (1975); lung cancer, chromate production plant.

Comments:

Available data are insufficient to address non-neoplastic effects. Although ingestion is the principal route of exposure, data are inadequate to establish value for this route.

Chromium, hexavalent

Cut-off date for literature review: April 1993

Exposure:

Neoplastic effects:

Classification for carcinogenicity: Group I (carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Hughes *et al.,* 1994c; Meek *et al.,* 1994a).

TC_{05}:

Based upon previous studies on the production plant described by Mancuso (1975), in which the proportion of hexavalent chromium was reported. The indirectly estimated TC_{05} (for lung cancer) is 0.66 $\mu g/m^3$.

Dibutyl phthalate

CAS Reg. No. 84-74-2

Cut-off date for literature review: November 1992

Exposure:

Food: 58 to 82%
Indoor air: 18 to 42%
Drinking water: 0.7 to 4.2%
Soil: 0 to 0.3%

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Chan and Meek, 1994b; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.063 mg/kg b.w./day

NOEL: 62.5 mg/kg b.w./day in dietary developmental study in mice; fetotoxic and teratogenic effects observed at next highest dose (Hamano *et al.,* 1977).

1000 uncertainty factor:

x 10 for intraspecies variation

x 10 for interspecies variation

x 10 including modifying factor for severity of the effect at the LOAEL in the critical study (teratogenicity), inadequacies of the data base, lack of adequate data on chronic toxicity and carcinogenicity

Comments:

Inhalation not addressed since intake *via* this route small in comparison to ingestion; also, data on toxicity following inhalation insufficient.

1,2-Dichlorobenzene

CAS Reg. No. 95-50-1

Cut-off date for literature review: December 1991

Exposure:

Ambient air: 3.2 to 100%
Food: 12 to 97%
Drinking water: 0 to 2.5%

Neoplastic effects:

Classification for carcinogenicity: Group V (probably not carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Meek *et al.,* 1994a,c).

Non-neoplastic effects:

TDI: 0.43 mg/kg b.w./day

NOEL: 60 mg/kg b.w./day; tubular regeneration in kidney at next higher dose in male mice; 103-week gavage study; corn oil vehicle, 5 days per week (NTP, 1983b).

5/7 for conversion of 5 days/week dosing to 7 days/week

100 uncertainty factor:

x 10 for intraspecies variation

x 10 for interspecies variation

Comments:

Although inhalation is probably the most important route of exposure, data are inadequate to establish a tolerable concentration by this route.

1,4-Dichlorobenzene

CAS Reg. No. 106-46-7

Cut-off date for literature review: May 1992

Exposure: Indoor air: 13 to 100%
Food: 0 to 88%
Ambient air: 1.3 to 20%
Drinking water: 0 to 3%

Neoplastic effects:

Classification for carcinogenicity: Group III (possibly carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Meek *et al.,* 1994a,d).

Non-neoplastic effects:

TC: 0.095 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

450 mg/m^3, NOEL. Based upon increased liver and kidney weights, urinary protein and coproporphyrin observed at higher concentrations in rats; 76-week inhalation exposure, 5 hours/day, 5 days/week (Loeser and Litchfield, 1983).

5/24 and 5/7 for conversion of 5 hours/day, 5 days/week to continuous exposure

modified to account for ratio of the inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

500 uncertainty factor:

x 10 for interspecies variation

x 10 for intraspecies variation

x 5 for limitations of the study (eg., less than lifetime exposure)

TDI[3]: 0.11 mg/kg b.w./day

LOAEL, 150 mg/kg b.w./day; male rats; 103-week gavage administration, 5 days/week; increased severity of nephropathy and in the incidence of hyperplasia of the parathyroid (NTP, 1987).

5/7 for conversion of 5 days/week to 7 days/week

1000 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation

x10 for LOAEL rather than NOEL

3 Not included in Assessment Report

3,3'-Dichlorobenzidine

CAS Reg. No. 91-94-1

Cut-off date for literature review: October 1992

Exposure:

The likely distribution of 3,3'-dichlorobenzidine in the environment was predicted based upon the level III fugacity computer model of Mackay and Paterson (1991) applied to southern Ontario using worst-case assumptions. The results indicated that, at steady-state, >99% would be expected to be present in surface water.

Neoplastic effects:

Classification for carcinogenicity: Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Liteplo and Meek, 1994b, Meek *et al.,* 1994a).

TD_{05}s range from 0.74 to 1.4 mg/kg b.w./day. Based upon the increased incidence of mammary tumors, granulocytic leukemias and Zymbal gland carcinomas in rats; dietary study, one dose level, administered for less than 2 years (Stula *et al.,* 1975).

Comments:

Data inadequate to develop TC_{05} and exposure *via* this route expected to be negligible.

1,2-Dichloroethane

CAS Reg. No. 107-06-2

Cut-off date for literature review: May 1993

Exposure:

Indoor air: 50 to 80%
Ambient air: 10 to 40%
Drinking water: 2.5 to 25%

Neoplastic effects:

Classification for carcinogenicity: Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Hughes *et al.,* 1994d; Meek *et al.,* 1994a).

TD_{05}s range from 6.2 to 34 mg/kg b.w./day (IPCS, 1994)
Based upon increased incidence of squamous cell carcinomas of the stomach, hemangiosarcomas, fibromas of the subcutaneous tissue and adenocarcinomas and/or fibromas of the mammary gland in rats; gavage administration for 78 weeks; increased incidence of alveolar/bronchiolar adenomas, hepatocellular carcinomas, mammary gland adenocarcinomas and endometrial stromal polyp or sarcoma in mice; gavage administration for 78 weeks (NCI, 1978). Surface area to body weight correction not incorporated since it is likely that carcinogenicity is due to metabolite(s). The upper value of the TD_{05} differs from that reported by Hughes *et al.* (1994d), due to refinement of the calculation of carcinogenic potency.

Comments:

Although principal route of exposure is inhalation, data inadequate for establishment of potency by this route. Data also inadequate to address non-neoplastic effects.

Dichloromethane

CAS Reg. No. 75-09-2

Cut-off date for literature review: March 1993

Exposure:

Indoor air: 91 to 98%
Ambient air: 1 to 7%
Food: 0.7 to 2%
Drinking water: 0 to 1.6%

Neoplastic effects:

Classification for carcinogenicity: Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Long *et al.,* 1994a; Meek *et al.,* 1994a).

TD_{05}:

No evidence of carcinogenicity in two adequate studies in which dichloromethane was orally administered to mice (Serota *et al.*, 1986a) or rats (Serota *et al.*, 1986b).

TC_{05}:

PBPK modified TC_{05}s (inhalation, mice): 2200 mg/m^3 for adenomas and carcinomas (combined) of the lung in females; 14,200 mg/m^3 for adenomas and carcinomas (combined) of the liver in males (NTP, 1986c).

Non-neoplastic effects:

TDI[4]: 0.05 mg/kg b.w./day

NOEL: 5 mg/kg b.w./day. Rat, two-year drinking water study. Fully reversible cellular proliferation and partially reversible fatty change in the liver at next highest dose (Serota *et al.*, 1986b).

100 uncertainty factor:

x10 for intraspecies variation

4 Not included in Assessment Report

x10 for interspecies variation

Hexachlorobenzene

CAS Reg. No. 118-74-1

Cut-off date for literature review: April 1992

Exposure:

Food: 96 to 100%
Air: 0 to 1.8%
100% of total intake for suckling infants derived from breast milk

Neoplastic effects:

Classification for carcinogenicity: Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Newhook and Meek, 1994; Meek *et al.,* 1994a).

TD_{05}s range from 0.06 mg/kg b.w./day (hepatic neoplastic nodules in female rats) to 0.17 mg/kg b.w./day (parathyroid adenomas in male rats); dietary administration; two generations (Arnold *et al.,* 1985). Surface area to body weight correction incorporated due to lack of information about role of active metabolites in carcinogenicity.

Non-neoplastic effects:

TDI: 500 ng/kg b.w./day

Lowest NOELs: 0.05 mg/kg b.w./day, based primarily upon hepatic effects in two species (pigs, rats) observed at higher doses (den Tonkelaar *et al.,* 1978; Arnold *et al.,* 1985; Mollenhauer *et al.,* 1975, 1976); NOEL for alterations in calcium metabolism in rats slightly greater (Andrews *et al.,* 1988, 1989, 1990); LOELs ranged from 0.1 to 0.7 mg kg b.w./day for effects on liver, ovarian morphology, immune function and perinatal survival (Newhook and Meek, 1994).

100 uncertainty factor[5]:

x 10 for intraspecies variation

x 10 for interspecies variation

Comments:

Inhalation not addressed since ingestion principal route of exposure.

5 Uncertainty factor modified slightly from Assessment Report.

Inorganic fluoride

Cut-off date for literature review: July 1993

Exposure:

For 0-6 months:

Breast-fed:
Breast milk: 40 to 92%
Soil: 5.9 to 59%
Air: 0.4 to 2%

Formula-fed:
Formula: 98 to 100%
Soil: 0.2 to 1.7%
Air: 0 to 0.1%

7 months to 20+ years:

Intakes, non-fluoridated water source:
Food: 23 to 93%
Household products: 3.2 to 62%
Water: 3.3 to 23%
Soil: 0 to 1.2%

Intakes, fluoridated water source:
Food: 14 to 64%
Water: 33 to 64%
Household products: 2 to 37%
Soil: 0 to 0.7%

"When the results of studies of occupationally exposed workers and clinical investigations of individuals receiving fluoride for the treatment of osteoporosis are evaluated collectively, however, the available data indicate that evidence of skeletal fluorosis is likely to be observed at intakes greater than approximately 200 μg/kg bw/day fluoride. Although, the weight of evidence in ecological studies (Jacobsen *et al.*, 1990, 1992; Cooper *et al.*, 1991; Danielson *et al.*, 1992; Keller, 1991, and May and Wilson, 1991, both cited in Gordon and Corbin, 1992; Suarez-Almazor *et al.*, 1993) indicates that there may be an association between the consumption of "fluoridated" drinking water and an increased incidence of hip fracture (based on hospitalization rates) particularly among the elderly, these results should be interpreted with caution in view of the limitations of epidemiological investigations of this experimental design. Moreover, owing to the lack of data on individual exposure in such studies, it is difficult to derive meaningful conclusions concerning the exposure-response relationship for possible skeletal effects associated with exposure to fluoride.

"Confidence in this effect level is limited, due to the limitations of individual epidemiological and clinical studies in which the relationship between exposure to inorganic fluoride and effects on the skeleton have been examined, as well as those factors which can influence the development of skeletal fluorosis. It should be noted, as well, that this effect level is based, in part, on studies in sensitive subgroups of the population. Based on the limited available data, adverse effects upon haematopoietic, hepatic, or renal function are not expected to occur at such levels of intake, since adverse effects upon the bone marrow, liver, or kidney were not observed following the administration of approximately 390 μg/kg bw/day fluoride to osteoporotic patients over a period of 5 years (Hasling *et al.*, 1987). There are insufficient quantitative data available from studies in humans to conclude definitively that exposure to this level of inorganic fluoride would have no adverse effect upon human reproduction and development, or the central nervous and immune systems" (Liteplo *et al.,* 1994).

Provisional daily intake (for skeletal effects): 200 μg/kg b.w./day (dental effects not considered)

Value based on studies in humans. No additional factor for intraspecies variation incorporated since sensitive subgroups examined in available studies.

With respect to the effects of fluoride on human health, neither dental fluorsis nor the beneficial effects of fluoride in the prevention of dental caries have been assessed in this report.

Methyl methacrylate

CAS Reg. No. 80-62-6

Cut-off date for literature review: September 1992

Exposure:

No data. Based upon fugacity modeling, inhalation is predicted to be the principal route of exposure (Mackay and Paterson, 1981, 1982, 1991; Mackay *et al.,* 1985, 1992).

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Chan *et al.,* 1994; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI[6]: 0.05 mg/kg b.w./day

NOEL, 5 mg/kg b.w./day. Two-year drinking water study; female rats at next highest dose level (146 mg/kg b.w./day) had increased ratio of kidney weight to body weight (Borzelleca *et al.,* 1964).

100 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

6 Not included in Assessment Report

TC: 0.052 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

NOEL, 410 mg/m^3 (two species).
Hamsters, 18 months exposure, 6 hours/day for 5 days/week; decrease in body weight in both sexes and increase in mortality in males observed at next highest concentration (Rohm and Haas Company, 1977).
Rats, 2 years exposure, 6 hours/day for 5 days/week; decrease in body weight in females and mild rhinitis in the mucosa lining the turbinates of both sexes observed at next highest concentration (Rohm and Haas Company, 1979).

6/24 and 5/7 for conversion of 6hours/day, 5 days/week to continuous exposure

modified to account for ratio of the inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

1000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for some evidence of effects following inhalation at slightly lower levels although in much less extensive and well documented studies

Comments:

Inhalation expected to be principal route of exposure.

Methyl tertiary-butyl ether

CAS Reg. No. 1634-04-4

Cut-off date for literature review: October 1991

Exposure:

The likely distribution of methyl tertiary-butyl ether in the environment was predicated based upon the level III fugacity computer model of Mackay and Paterson (1991) applied to southern Ontario using worst-case assumptions. The results indicated that, at steady-state, the proportions found in the environment would be:

56% in air
43% in surface water
0.5% in soil

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Long *et al.,* 1994b; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI[7]: 0.01 mg/kg b.w./day

NOAEL, 100 mg/kg b.w./day
Rat, 90-day gavage study, daily administration; based upon increased relative kidney weight and decreased calcium and glucose (Robinson *et al.,* 1990).

10,000 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation

x100 for less than chronic study, lack of data on carcinogenicity and minimal effects observed at the NOAEL

7 Not included in Assessment Report

TC: 0.037 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

NOAEL (could also be considered a LOEL): 2915 mg/m^3
Based upon neurobehavioral effects in rats; 13-week inhalation study; 6 hours/day, 5 days/week (Dodd and Kintigh, 1989).

6/24 and 5/7 for conversion of 6 hours/day, 5 days/week to continuous exposure

modified to account for ratio of the inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

10,000 uncertainty factor of 10,000:

x10 for interspecies variation

x10 for intraspecies variation

x100 for less than chronic study, lack of data on carcinogenicity and minimal effects observed at the NOAEL

Mineral fibres: Refractory ceramic fibers (kaolin)

Cut-off date for literature review: May 1993

Exposure:

Inhalation the only relevant route of exposure.

Neoplastic effects:

Classification for carcinogenicity: Group II (probably carcinogenic to humans) based upon the classification scheme developed for the assessment of "toxic" under paragraph 11(c) of CEPA (Meek and Long, 1994; Meek *et al.,* 1994a).

TC_{05}[8] (pulmonary tumors): 110 fibers/ml. Chronic inhalation bioassay, Fischer 344 male rats; nose-only exposure for 6 hours/day, 5 days/week. Fibre characterization: length/diameter ≥ 3; arithmetic mean diameter: 0.98 um; arithmetic mean length: 22.3 um. (Bunn *et al.,* 1993; Hart *et al.,* 1992; Glass *et al.,* 1992; Hesterberg *et al.,* 1991; Mast *et al.,* 1993).

Estimate of potency: a multistage model was fit (pulmonary tumor incidence), using GLOBAL82. A TC_{05} of 110 fibers/ml was obtained. It was not possible to derive a TC_{05} based on the incidence of mesotheliomas.

8 Not included in Assessment Report

Monochlorobenzene

CAS Reg. No. 108-90-7

Cut-off date for literature review: May 1991

Exposure:

Ambient air: 39 to 81%
Drinking water: 20 to 61%

Neoplastic effects:

Classification for carcinogenicity: Group III (possibly carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Meek *et al.,* 1994a,b).

Non-neoplastic effects:

TDI: 0.43 mg/kg b.w./day

NOEL/NOAEL: 60 mg/kg b.w./day. For male rats and mice in 103-week gavage study; administration 5 days/week (NTP, 1983a; Kluwe *et al.,* 1985).

5/7 conversion of 5 days/week to dosing 7 days/week

100 uncertainty factor[9]:

x 10 for interspecies variation

x 10 for intraspecies variation

9 Uncertainty factor modified slightly from Assessment Report.

TC (provisional): 0.01 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

LOAEL: 341 mg/m^3. ["marginal toxic concentration"] Increased kidney weight and tubular and interstitial lesions in the kidney, lesions in the adrenal cortex and small changes in red cell parameters in male rats; 24-week limited inhalation bioassay (exposure for 7 hours/day, 5 days/week) (Dilley, 1977)

7/24 and 5/7 for conversion of 7 hours/day, 5 days/week to continuous exposure

modified to account for ratio of the inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

5000 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation

x5 for LOAEL rather than NOAEL; effects only marginally adverse

x10 for less than chronic and limited study (only one sex in protocol and two dose levels)

Comments:

TC is considered "provisional" due to limitations of study

Nickel and its compounds

Cut-off date for literature review: August 1993

Exposure to total nickel:

Food: 96 to 100%
Drinking water: 0.1 to 3.3
Soil: 0 to 1.1%
Ambient air: 0 to 0.2%

Intake near point sources:

Food: 61 to 90%
Drinking water: 7.8 to 34%
Soil: 0.9 to 6.2%
Ambient air: 0 to 0.1%

Available data were such that an estimate of exposure was limited to nickel and its compounds (*i.e.,* total nickel). In contrast, available epidemiological studies and reports of studies with laboratory animals were focused upon these specific nickel compounds, which are presented separately on the following pages:

(i) metallic nickel

(ii) oxidic nickel/sulphidic nickel/soluble nickel

(iii) soluble nickel:

(iv) nickel chloride

(v) nickel sulfate

(vi) oxidic nickel (nickel oxide)

(vii) sulphidic nickel (nickel subsulphide)

(i) Nickel and its compounds: Metallic nickel

Exposure: see "total nickel"

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA*. (Hughes *et al.,* 1994e; Meek *et al.,* 1994a).

Non-neoplastic effects:

Provisional TC[10]: 0.000018 mg/m^3 [0.018 μg/m^3]

LOEL: 0.1 mg/m^3. Minimal effects on the morphology and function of alveolar cells have been observed in rabbits exposed to concentrations of metallic nickel as low as 0.1 mg/m^3 for 6 hours/day, 5 days/week for up to 8 months (Camner and Johansson, 1992; Curstedt *et al.*, 1983; Johansson *et al.*, 1983; Lundborg and Camner, 1982). The nickel dust used in the study with the lowest reported effect level was 95% respirable and the duration of exposure was up to 8 months (exposure for 6 hours/day, 5 days/week); however, the protocol included only one dose group and controls (Johansson *et al.* 1983).

6/24 and 5/7 for conversion of 6 hours/day, 5 days/week to continuous exposure

1000 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation

x10 for inadequate data on carcinogenicity and less than chronic study and limitations thereof; no additional factor for LOEL rather than NO(A)EL since observed effects were minimal

10 Not included in Assessment Report

(ii) Nickel and its compounds: Oxidic nickel, sulphidic nickel, soluble nickel

Oxidic nickel: including nickel oxide, nickel-copper oxide, nickel silicate oxides and complex oxides

Sulphidic nickel: including nickel subsulphide

Soluble nickel: primarily nickel sulfate and nickel chloride

Exposure: see "total nickel"

Neoplastic effects:

Classification for carcinogenicity: each of oxidic, sulphidic and soluble nickel has been included in Group I (carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Hughes *et al.,* 1994e; Meek *et al.,* 1994a).

TC_{05}:
The estimates of the TC_{05} (inhalation) for lung cancer mortality for *combined* oxidic, sulphidic and soluble nickel ranged from 0.04 to 1.0 mg/m^3. Based upon the results at the mining, smelting and refining operations in Ontario and Norway (Doll *et al.,* 1990). Estimates of TC_{05}s for nasal cancer were greater than those for lung cancer.

(iii) Nickel and its compounds: Soluble nickel (primarily nickel sulfate and nickel chloride)

Exposure: see "total nickel"

Neoplastic effects:

TC_{05} (soluble nickel):

The TC_{05} for lung cancer mortality for soluble nickel was estimated to be 0.07 mg/m^3. Based upon data from a cohort in Norway (Doll *et al.,* 1990). Soluble nickel was considered to consist primarily of nickel sulfate and nickel chloride.

(iv) Nickel and its compounds: Soluble nickel (nickel chloride)

Exposure: see "total nickel"

Non-neoplastic effects:

TDI[11]: 0.0013 mg Ni/kg b.w./day (1.3 μg Ni/kg b.w./day)

LOAEL: 1.3 mg Ni/kg b.w./day. Nickel chloride, drinking water administration to rats. Increased proportion of dead pups per litter (George *et al.*, 1989; Smith *et al.*, 1993)

1000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for LOAEL rather than NOAEL; no additional factor for short-term since more sensitive endpoint than those observed in long term studies

11 Not included in Assessment Report

(v) Nickel and its compounds: Soluble nickel (nickel sulfate)

Exposure: see "total nickel"

Non-neoplastic effects:

TDI[12]: 0.05 mg/kg b.w./day

NOEL: 5 mg Ni/kg b.w./day. Two-year dietary study in rats, 3 dose levels and controls; increase in relative weight of heart and decrease in relative weight of liver at next higher dose (Ambrose *et al.,* 1976).

100 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation

TC[13]: 3.5×10^{-6} mg Ni/m^3

Lowest LOEL: 0.02 mg Ni/m^3 as nickel sulfate (Dunnick *et al.*, 1989); 10 male, 10 female F344/N rats per group; 6 hours/day, 5 days/week for 13 weeks; nickel sulfate hexahydrate at concentrations equivalent to 0, 0.02, 0.05, 0.1, 0.2 or 0.4 mg Ni/m^3; histopathology on control and high dose group and on target tissues of other animals at other concentrations; lung and nasal lesions at all doses; dose-related chronic active inflammation of the lungs; alveolar macrophage hyperplasia in all exposed animals; atrophy of olfactory epithelium at 0.2 mg Ni/m^3; at higher (not specified) concentrations, lymphoid hyperplasia of the bronchial lymph nodes.

6/24 and 5/7 for conversion of 6 hours/day, 5 days/week to continuous exposure

1000 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation

12 Not included in Assessment Report

13 Ibid

x10 for subchronic study

No additional factor for LOEL rather than NO(A)EL since observed effects were minimal

(vi) Nickel and its compounds: Oxidic nickel (nickel oxide)

Exposure: see "total nickel"

Non-neoplastic effects:

TC^{14}: 0.00002 mg Ni/m^3 [0.02 μg Ni/m^3]

LOEL: 0.02 mg Ni/m^3
Rat, 4-month continuous exposure, two dose levels and controls.
Minimal respiratory effects: significant dose-related increase in number of granulocytes and lymphocytes in the lungs, and an increase in size of macrophages, and in the number of macrophages with more than one nucleus (Spiegelberg *et al.*, 1984).

1000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for less than chronic study and minimal effects at the LOEL.

14 Not included in Assessment Report

(vii) Nickel and its compounds: Sulphidic nickel (nickel subsulfide)

Exposure: see "total nickel"

Non-neoplastic effects:

TC[15]: 1.8×10^{-5} mg Ni/m^3

NOEL (mice): 0.1 mg Ni/m^3
LOEL (rats): 0.1 mg Ni/m^3
In a comprehensive study in which rats and mice were exposed to nickel subsulphide by inhalation for 6 hours/day, 5 days/week at concentrations between 0.1 and 1.8 mg of Ni/m^3 for 90 days, alveolar macrophage hyperplasia was observed in rats at all concentrations and in mice at 0.2 mg of Ni/m^3 and above, while chronic active inflammation (and, in some mice, focal interstitial fibrosis) occurred at higher concentrations (Benson *et al.,* 1990; Dunnick *et al.,* 1989). There were biochemical changes in the lungs indicative of a cytotoxic and inflammatory response which correlated well with the degree of chronic active inflammation. Atrophy of the olfactory epithelium was observed at concentrations of 0.2 or 0.4 mg of Ni/m^3 in rats and mice, respectively. The LOEL was considered to be 0.1 mg of Ni/m^3 in rats, while this value was considered to be the NOEL in mice, based upon minimal respiratory effects.

6/24 and 5/7 for conversion of 6 hours/day, 5 days/week to continuous exposure

1000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for less than chronic study

No additional factor for LOEL in rats rather than NO(A)EL since observed effects were minimal

15 Not included in Assessment Report

Pentachlorobenzene

CAS Reg. No. 608-93-5

Cut-off date for literature review: March 1992

Exposure:

Food: 92 to 100%
Drinking water: 0 to 8%
Ambient air: 0 to 8%
100% of total intake for suckling infants derived from breast milk.

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Giddings *et al.,* 1994a; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.001 mg/kg b.w./day [1 μg/kg b.w./day]

LOEL: 5.2 mg/kg b.w./day; lowest dietary concentration at which compound-related effects were observed in male mice (NTP, 1991a); 13-week administration; minimal to moderate centrilobular hepatocellular hypertrophy and occasional necrosis of hypertrophied hepatocytes (considered to be secondary to the hypertrophy).

5000 uncertainty factor[16]:

x 10 for intraspecies variation

x 10 for interspecies variation

x 10 for less than chronic study

x 5 for lack of data on carcinogenicity [additional factor of 10 for LOEL rather than NOAEL not incorporated since observed effects at the LOEL were minimal]

Comments:

Inhalation insignificant route of exposure and data insufficient to develop tolerable concentration for this route.

16 Uncertainty factor modified slightly from Assessment Report.

Polychlorinated dibenzodioxins and polychlorinated dibenzofurans

Cut-off date for literature review: December 1989

Exposure:

Food: 84 to 100%
Soil: 0 to 10%
Air: 0 to 7.1%
Water: 0 to 2.4%
Consumer products: 0 to <1.8%

Classification for carcinogenicity: not addressed in Assessment

TDI[17]: 10 picograms per kilogram of body weight per day of toxic equivalents (TEQ)[18] averaged over a lifetime

" ...it is estimated that human intakes should be below 10 picograms per kilogram of body weight per day of toxic equivalents averaged over a lifetime. This estimate assumes that 2,3,7,8-substituted dioxins and furans are non-genotoxic carcinogens for which a threshold dose exists at approximately 1 nanogram toxic equivalents per kilogram of body weight per day[19]. The no-observed-adverse-effect-level for reproduction in rodents is also approximately 1 nanogram of 2,3,7,8-tetrachlorodibenzodioxin per kilogram of body weight per day[20]. Humans appear to be less sensitive to dioxins and furans than most laboratory species (especially rats and monkeys) and the effect threshold values in rodents were based on lifetime exposures. An uncertainty factor of 100 was applied to the no-observed-adverse-effect-level to obtain the 10 picogram toxic equivalents per kilogram of body weight per day value, to take account of variations in response between individuals and to account for the seriousness of the potential effects." (Government of Canada, 1990).

The carcinogenicity bioassay by Kociba *et al.* (1978) was used as the basis for assessing the health risk posed by dioxins and furans (Armstrong and Newhook, 1992). In this study, groups of 50 male and female Sprague-Dawley rats were fed diets containing 2,3,7,8-TCDD to yield doses of 0.001, 0.01 and 0.1 μg/kg b.w./day for up to two

17 The TDI is currently under review.

18 Based upon the International Toxicity Equivalency Factors (TEF) scheme proposed by NATO (1988), to estimate the toxicological significance of complex mixtures of PCDDs and PCDFs in terms of equivalent amounts of 2,3,7,8-TCDD. In this scheme, the toxicity of the mixture is estimated as the sum of the concentrations of individual 2,3,7,8-substituted PCDDs and PCDFs multiplied by the potency (expressed as TEFs) of each substance relative to that of 2,3,7,8-TCDD. (See Table, following page.)

19 Kociba *et al.* (1978)

20 Murray *et al.* (1979)

years. At the highest dose, there were significantly increased incidences of squamous cell carcinomas of the tongue and/or nasal turbinates/hard palate in both sexes, and squamous cell carcinomas of the lung and hyperplastic nodules and carcinomas in the liver of females. At 0.01 μg/kg b.w./day, there was a significant incidence of hyperplastic nodules in the liver of females. At 0.001 μg/kg b.w./day, there were no statistically significant increases in neoplasms or other effects of toxicological significance. In a three-generation study (Murray *et al.,* 1979), a dose of 0.001 micrograms/kg b.w./day did not adversely affect the reproductive ability of rats. This dose is considered the NOAEL for 2,3,7,8-TCDD.

Comments: Inhalation insignificant route of exposure and data insufficient to develop tolerable concentration for this route.

International Toxicity Equivalency Factors (NATO, 1988)

Dioxin/Furan	Equivalency Factor
2,3,7,8-tetrachlorodibenzodioxin	1
1,2,3,7,8-pentachlorodibenzodioxin	0.5
1,2,3,4,7,8-hexachlorodibenzodioxin	0.1
1,2,3,7,8,9-hexachlorodibenzodioxin	0.1
1,2,3,6,7,8-hexachlorodibenzodioxin	0.1
1,2,3,4,6,7,8-heptachlorodibenzodioxin	0.01
octachlorodibenzodioxin	0.001
2,3,7,8-tetrachlorodibenzofuran	0.1
2,3,4,7,8-pentachlorodibenzofuran	0.5
1,2,3,7,8-pentachlorodibenzofuran	0.05
1,2,3,4,7,8-hexachlorodibenzofuran	0.1
1,2,3,7,8,9-hexachlorodibenzofuran	0.1
1,2,3,6,7,8-hexachlorodibenzofuran	0.1
2,3,4,6,7,8-hexachlorodibenzofuran	0.1
1,2,3,4,6,7,8-heptachlorodibenzofuran	0.01
1,2,3,4,7,8,9-heptachlorodibenzofuran	0.01
octachlorodibenzofuran	0.001

Polycyclic aromatic hydrocarbons

Selection of PAHs for assessment was based upon adequacy of data.

Cut-off date for literature review: July 1993

Exposure:

Insufficient data to estimate exposure from all routes; inhalation only considered.

Neoplastic effects:

Classification for carcinogenicity: benzo(a)pyrene, benzo(b)fluoranthene, benzo(j)fluoranthene, benzo(k)fluoranthene and indeno(1,2,3-cd)pyrene are classified in Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Meek *et al.,* 1994a,e).

Benzo(a)pyrene

Cut-off date for literature review: July 1993

Exposure:

Insufficient data to estimate exposure from all routes; inhalation only considered.

Neoplastic effects:

TC_{05} = 1.6 mg B(a)P/m^3, based upon multistage modelling of respiratory tract tumors in hamsters; nose-only inhalation of B(a)P for up to 96 weeks (Thyssen *et al.,* 1981).

Benzo(b)fluoranthene
Benzo(j)fluoranthene
Benzo(k)fluoranthene
Indeno(1,2,3-cd)pyrene

Cut-off date for literature review: July 1993

Exposure: Insufficient data to estimate exposure from all routes; inhalation only considered.

Carcinogenic potencies of the other PAHs relative to B(a)P were estimated on the basis of multistage modelling of tumor incidence (epidermoid carcinomas) in Osborne-Mendel rats; PAHs were implanted into left lung (Deutsch-Wenzel *et al.,* 1983). The potencies for each PAH relative to that of B(a)P were calculated by dividing the dose calculated to be associated with a 5% increase in tumors for B(a)P by those for each compound. On this basis, relative carcinogenic potency factors are:

(a) Benzo(a)pyrene, relative potency: 1

(b) Benzo(b)fluoranthene, relative potency: 0.06

(c) Benzo(j)fluoranthene, relative potency: 0.05

(d) Benzo(k)fluoranthene, relative potency: 0.04

(e) Indeno(1,2,3-cd)pyrene, relative potency: 0.12

Calculation for carcinogenic potency:

PAH	TC_{05} for benzo(a)pyrene derived from inhalation bioassay in hamsters (Thyssen *et al.,* 1981)	Carcinogenic potency factor, relative to benzo(a)pyrene; derived from pulmonary implantation study in rats (Deutsch-Wenzel *et al.,* 1983)]		Carcinogenic Potency[21]
Benzo(b)fluoranthene	1.6 mg/m^3	÷ 0.06	=	26.7 mg/m^3
Benzo(j)fluoranthene		÷ 0.05	=	32.0 mg/m^3
Benzo(k)fluoranthene		÷ 0.04	=	40.0 mg/m^3

21 Not included in Assessment Report

Indeno(1,2,3-cd)pyrene		÷	0.12	=	13.3 mg/m^3

Styrene

CAS Reg. No. 100-42-5

Cut-off date for literature review: March 1993

Exposure:

Food: 33 to 88%
Indoor air: 8.9 to 40%
Ambient air: 0.6 to 39%
Drinking water: 0.4 to 3.4%

Neoplastic effects:

Classification for carcinogenicity:

Group III (possible human germ cell mutagen) and

Group III (possibly carcinogenic to humans),

based upon the classification scheme developed for these endpoints under *CEPA* (Newhook *et al.,* 1994b; Government of Canada, 1993; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.12 mg/kg b.w./day

NOAEL: 12 mg/kg b.w./day. Reproductive effects (decreased gestational survival, pup survival, pup weight at the next highest dose) in rats exposed in drinking water in a three-generation study (Beliles *et al.,* 1985)

100 uncertainty factor:

x 10 for interspecies variation

x 10 for intraspecies variation

TC: 0.092 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

LOEL: 260 mg/m^3. Effects on body weight, the results of behavioural testing, and neurotransmitter levels (the latter not statistically significant) in the cerebrum of rat pups exposed to styrene on days 7 to 21 of gestation, 6 hours/day (Kishi *et al.*, 1992a,b).

6/24 conversion of 6 hours/day to continuous exposure

modified to account for ratio of the inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

500 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation

x5 for use of a LOEL (the effects observed at this concentration were minimal)

Limited available data indicate that humans form less of the putative toxic metabolite, styrene-7,8-oxide, and hydrolyze it more quickly than experimental animals; however, available data were insufficient to take these differences into account in the development of the uncertainty factor, and the relevance of this metabolite to developmental and neurotoxic effects is not clear.

This tolerable concentration is within the range of that which would be derived on the basis of neurological effects in occupationally exposed populations.

1,2,3,4-Tetrachlorobenzene

CAS Reg. No. 634-66-2

Cut-off date for literature review: September 1992

Exposure:

Food: 50 to 100%
Ambient air: 0.2 to 50%
Drinking water: 1.3 to 6%
100% of total intake for suckling infants derived from breast milk

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Giddings *et al.,* 1994b; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.0034 mg/kg b.w./day [3.4 μg/kg b.w./day]

NOAEL: 34 mg/kg b.w./day. Significant compound-related effects were not observed at any dose in the only subchronic bioassay identified for this isomer in which the compound was administered orally (mixed with corn oil in the diet) to Sprague-Dawley rats (Chu *et al.,* 1984)

10,000 uncertainty factor:

x 10 for interspecies variation

x 10 for intraspecies variation

x 10 for less than chronic study

x 10 for limited database including lack of adequate data on carcinogenicity and chronic and reproductive toxicity

Comments:

Data insufficient to develop tolerable concentration for inhalation, although intake by this route might be significant.

1,2,3,5-Tetrachlorobenzene

CAS Reg. No. 634-90-2

Cut-off date for literature review: June 1992

Exposure:

Food: 45 to 80%
Ambient air: 0.1 to 50%
Drinking water: 0.5 to 1%
100% of total intake for suckling infants derived from breast milk.

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Giddings *et al.,* 1994b; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.00041 mg/kg b.w./day [0.41 μg/kg b.w./day]

NOAEL: 4.1 mg/kg b.w./day. Based upon incidence of histopathological lesions in the liver in female Sprague-Dawley rats in a subchronic dietary study (Chu *et al.,* 1984)

10000 uncertainty factor:

x 10 for interspecies variation

x 10 for intraspecies variation

x 10 for less than chronic study

x 10 for limited database including lack of adequate data on carcinogenicity and reproductive toxicity

Comments:

Data insufficient to develop tolerable concentration for inhalation, although intake by this route might be significant.

1,2,4,5-Tetrachlorobenzene

CAS Reg. No. 95-94-3

Cut-off date for literature review: June 1992

Exposure:

Food: 50 to 75%
Ambient air: 0 to 50%
Drinking water: 2.5 to 23%
100% of total intake for suckling infants derived from breast milk.

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Giddings *et al.,* 1994b; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.00021 mg/kg b.w./day [0.21 μg/kg b.w./day]

NOAEL (females), NOEL (males): 2.1 mg/kg b.w./day.
Male and female F344 rats, based upon thyroid follicular cell hypertrophy observed at higher doses in subchronic dietary study (NTP, 1991b)

10000 uncertainty factor:

x 10 for interspecies variation

x 10 for intraspecies variation

x 10 for less than chronic study

x 10 for limited database including lack of adequate data on carcinogenicity and reproductive toxicity

Comments:

Data insufficient to develop tolerable concentration for inhalation, although intake by this route might be significant.

Tetrachloroethylene

CAS Reg. No. 127-18-4

Cut-off date for literature review: April 1992

Exposure:

Indoor air: 61 to 99%
Food: 0 to 28%
Ambient air: 0.4 to 17%
Drinking water: 0 to 2.3%

Neoplastic effects:

Classification for carcinogenicity: Group IV (unlikely to be carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Liteplo and Meek, 1994c; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI[22]: 0.014 mg/kg b.w./day

14 mg/kg b.w./day is the NOEL in the longest-term adequate study in which tetrachloroethylene was administered in drinking water (Hayes *et al.,* 1986); rat, 90-day study; based upon effects on body weight gain, ratio of liver or kidney weight to body weight and serum 5-nucleotidase at the next highest dose

1000 uncertainty factor:

x10 for interspecies variation

x10 for intraspecies variation;

x10 for use of a subchronic study; available chronic studies in which effects were observed at all administered doses were considered inadequate as a basis for development of meaningful effect levels or comparison with those reported in subchronic studies.

22 Not included in Assessment Report

TC: 0.36 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

678 mg/m^3 is the LOAEL (reduced survival and hepatotoxic effects in males, lung congestion and nephrotoxic effects [in males and females]) in mice, in the longest-term study of adequate design in which tetrachloroethylene was administered by inhalation for 6 hours/day, 5 days/week over 103 weeks (NTP, 1986d).

6/24 and 5/7 for conversion of 6 hours/day, 5 days/week to continuous exposure

modified to account for ratio of the inhalation volume/body weight of mice [(0.04 m^3/day)/0.03 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

1000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for use of a LOAEL rather than a NOAEL; an additional factor for limitations of the study (eg., lack of assessment of biochemical and hematological effects) was not incorporated since, in general, in shorter term studies in which these end-points were examined, adverse effects have not been observed at concentrations less than the value used here as basis for development of the Tolerable Concentration.

Toluene

CAS Reg. No. 108-88-3

Cut-off date for literature review: June 1991

Exposure:

Air (indoor): 72 to 93%
Air (ambient): 1.5 to 19%
Self-serve gasoline station: 5.3 to 6.3%
Food (fish): 0.6 to 1.1%
Drinking water: 0 to 0.9%

Data on indoor air (Otson *et al.,* 1992) were obtained after the final date for consideration of information. They have been included owing to their importance to the estimation of exposure in Canada.

Neoplastic effects:

Classification for carcinogenicity: Group IV (unlikely to be carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Meek and Chan, 1994b; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI[23]: 0.22 mg/kg b.w./day

NOEL: 312 mg/kg b.w./day. Based upon increase in relative liver and kidney weight in male rats at next higher dose; 5 days/week for 13-weeks; gavage administration (NTP, 1990)

5/7 to convert 5 days/week to continuous exposure

1000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for subchronic study

23 Not included in Assessment Report

TC: 3.75 mg/m^3

NOEL: 150 mg/m^3. Based upon decrease in neurological function as measured by a variety of tests, an increase in neurological symptoms and irritation of the respiratory tract in an adequate clinical study in human volunteers (Andersen *et al.,* 1983).

6/24 for conversion of 6-hour daily dosing to continuous exposure

10 uncertainty factor for intraspecies variation

This Tolerable Concentration is similar to that which would be derived on the basis of effects in laboratory animals, the derivation of which is presented below.

TC: 2.2 mg/m^3

LOEL: 375 mg/m^3. Based upon decreased body weight in male and female mice; 14-week inhalation bioassay; dosing for 6.5 hours/day, 5 days/week (NTP, 1990).

6.5/24 and 5/7 for conversion to continuous exposure

modified to account for ratio of the inhalation volume/body weight of mice [(0.04 m^3/day)/0.03 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

100 uncertainty factor:

x 10 for interspecies variation

x 10 for intraspecies variation

NB: no factor introduced for a LOEL rather than a NOEL, since observed effect was a decrease in body weight without other evidence of toxicity. Although additional factor of 10 usually introduced for less than chronic study, NOEL in chronic studies was more than the LOEL used here.

Comments:

Inhalation most important route of exposure.

1,2,3-Trichlorobenzene

CAS Reg. No. 87-61-6

Cut-off date for literature review: May 1992

Exposure:

Indoor air: 79 to 93%
Ambient air: 7.4 to 10%
Food: 0 to 0.1%
Drinking water: 0 to 0.1%
4.2 to 13% of total intake for suckling infants derived from breast milk

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Giddings *et al.,* 1994c; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI: 0.0015 mg/kg b.w./day [1.5 μg/kg b.w./day]

NOEL: 7.7 mg/kg b.w./day. Rats were exposed to up to 146 mg/kg b.w./day in the diet for 13 weeks; there were significant increases in the liver to body weight ratio at the highest concentration in males; mild to moderate histopathological changes in the liver, thyroid and kidney, significant at the highest concentration and more severe in males (Côté *et al.,* 1988).

5000 uncertainty factor[24]:

x10 for intraspecies variation

x10 for interspecies variation

x10 for use of subchronic study

x5 for lack of adequate data on carcinogenicity

Comments:

24 Uncertainty factor modified slightly from Assessment Report.

Data insufficient to develop tolerable concentration for inhalation.

1,2,4-Trichlorobenzene

CAS Reg. No. 120-82-1

Cut-off date for literature review: May 1992

Exposure:

Indoor air: 50 to 100%
Ambient air: 1.6 to 5%
Food: 0.3 to 4%
Drinking water: 0 to 0.1%
16 to 30% of total intake for suckling infants derived from breast milk

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Giddings *et al.,* 1994c; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI[25]: 0.0016 mg/kg b.w./day [1.6 μg/kg b.w./day]

NOEL: 7.8 mg/kg b.w./day. Rats were exposed to 0.07 to 146 mg/kg b.w./day in the diet for 13 weeks. At the highest dose, there were significant increases in the relative liver weight and absolute and relative kidney weight in males. Histopathological changes in the liver and thyroid were significant only at the highest dose, and were more severe in males than females (Côté *et al.,* 1988).

5000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for use of subchronic study

x5 for lack of adequate data on carcinogenicity

25 Not included in Assessment Report

TC: 0.007 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

NOAEL: 223 mg/m^3. Based upon increased liver and kidney weight at next highest concentration in male rats in a 44-day inhalation bioassay; exposure for 7 hours/day, 5 days/week (Kociba *et al.,* 1981)

For 1,2,4-trichlorobenzene, the lowest concentration at which compound-related effects were observed following inhalation was 74.2 mg/m^3, which resulted in a slight reversible increase in urinary porphyrins in a 13-week study in rats; the NOEL in this investigation was 22.3 mg/m^3 (Watanabe *et al.,* 1978). It should be noted, however, that the effects observed were minor and transient; no effects were observed in other sub-chronic (some longer-term) inhalation studies in several species at concentrations at least an order of magnitude higher (223 mg/m^3 - Kociba *et al.,* 1981; 742 mg/m^3 - Coate *et al.,* 1977). In sub-chronic, developmental and reproductive studies in which 1,2,4-trichlorobenzene has been administered by gavage or ingested in drinking water or the diet, it has not induced adverse effects at doses below those upon which the TDI derived above is based (Goto *et al.,* 1972; Côté *et al.,* 1988; Kitchen and Ebron, 1983; Black *et al.,* 1988; Robinson *et al.,* 1981).

7/24 and 5/7 conversion of 7 hours/day, 5 days/week administration to continuous exposure

modified to account for ratio of the inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

5000 uncertainty factor:

x 10 for intraspecies variation

x 10 for interspecies variation

x 10 for less than chronic study

x 5 for lack of adequate data on carcinogenicity and chronic toxicity

Comments:

Inhalation probably the most important route of exposure.

1,3,5-Trichlorobenzene

CAS Reg. No. 108-70-3

Cut-off date for literature review: May 1992

Exposure:

Indoor air: 76 to 88%
Ambient air: 8 to 12%
Food: 1.2 to 9.4%
Drinking water: 0 to 0.1%
16% of total intake for suckling infants derived from breast milk

Neoplastic effects:

Classification for carcinogenicity: Group VI (unclassifiable with respect to carcinogenicity in humans) based upon the classification scheme developed for this endpoint under *CEPA* (Giddings *et al.,* 1994c; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI[26]: 0.0015 mg/kg b.w./day [1.5 μg/kg b.w./day]

NOEL: 7.6 mg/kg b.w./day. Rats were exposed to up to 146 mg/kg b.w./day in the diet for 13 weeks; there were significant increases in the liver to body weight ratio at the highest concentration in males; mild to moderate histopathological changes in the liver, thyroid and kidney, significant at the highest concentration and more severe in males (Côté *et al.,* 1988).

5000 uncertainty factor:

x10 for intraspecies variation

x10 for interspecies variation

x10 for use of subchronic study

x5 for lack of adequate data on carcinogenicity

26 Not included in Assessment Report

TC: 0.0036 mg/m^3 [3.6 μg/m^3] (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

NOEL: 100 mg/m^3. Based upon squamous metaplasia and hyperplasia in the respiratory epithelium of the nasal passages in rats at the next highest dose; 13-week inhalation bioassay, exposure for 6 hours/day, 5 days/week (Sasmore *et al.,* 1983).

6/24 and 5/7 conversion of 6 hours/day, 5 days/week administration to continuous exposure

5000 uncertainty factor:

x 10 for intraspecies variation

x 10 for interspecies variation

x 10 for less than chronic study

x 5 for lack of adequate data on carcinogenicity

Conversion for variation in breathing rates and body weights between rats and humans not incorporated since initial effects were not systemic.

Comments:

Inhalation probably the most important route of exposure.

Trichloroethylene

CAS Reg. No. 79-01-6

Cut-off date for literature review: October 1992

Exposure:

Indoor air: 85 to 97%
Food: 1 to 7.5%
Ambient air: 0.8 to 6.1%
Drinking water: 1 to 5.4%

Neoplastic effects:

Classification for carcinogenicity: Group II (probably carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Hughes *et al.,* 1994f; Meek *et al.,* 1994a).

Estimates of potency:

(1) Inhalation exposure: male Sprague-Dawley rats; 7 hours/day, 5 days/week for 104 weeks; Leydig cell tumors in testes (Maltoni *et al.*, 1986, 1988). Two TC_{05}s were calculated (multistage model):

(i) 112.6 ppm for the incidence data ("uncorrected")

Conversion factor, 1 ppm = 5.46 mg/m^3
amortization factors: 7/24 for hours of day; 5/7 for days of week

modified to account for ratio of the inhalation volume/body weight of humans aged 5 to 11 years [(12 m^3/day)/27 kg] to rats [(0.11 m^3/day)/0.35 kg].

TC_{05} for incidence data is: (112.6) (5.46) (7/24) (5/7) (0.11/0.35) (27/12) = 91 mg/m^3
(Presented as tumorigenic dose (μg/kg b.w./day) for inhalation in Assessment Report.)

(ii) 101.9 ppm for the "corrected" incidence (number of animals alive at the time of appearance of the first testicular tumor).

Conversion factor, 1 ppm = 5.46 mg/m^3
amortization factors: 7/24 for hours of day; 5/7 for days of week

modified to account for ratio of the inhalation volume/body weight of humans aged 5 to 11 years [(12 m^3/day)/27 kg] to rats [(0.11 m^3/day)/0.35 kg].

TC_{05} (corrected) is: (101.9) (5.46) (7/24) (5/7) (0.11/0.35) (27/12) = 82 mg/m^3
(Presented as tumorigenic dose (μg/kg b.w./day) for inhalation in Assessment Report.)

(2) Inhalation exposure: female ICR mice; 7 hours/day, 5 days/week for 104 weeks; pulmonary adenomas and carcinomas (Fukuda *et al.*, 1983); TC_{05} was 124.6 ppm.

Multistage model
Conversion factor, 1 ppm = 5.46 mg/m^3
amortization factors: 7/24 for hours of day; 5/7 for days of week

TC_{05} = (124.6 X 5.46 X 7/24 X 5/7) = 140 mg/m^3
(Presented as tumorigenic dose (μg/kg b.w./day) for inhalation in Assessment Report.)

(3) Inhalation exposure: female $B6C3F_1$ mice; 7 hours/day, 5 days/week for 78 weeks; pulmonary adenomas, adenomas and adenocarcinomas (Maltoni *et al.*, 1986, 1988). Conversion has to account for the fact that the duration was only 78 weeks, rather than 104. Two TC_{05}s were calculated (multistage model).

(i) TC_{05} for incidence data ("uncorrected") = 229.7 ppm

Conversion factor, 1 ppm = 5.46 mg/m^3
amortization factors: 7/24 for hours of day; 5/7 for days of week; 78/104 for short duration of study

TC_{05} = (229.7 X 5.46 X 7/24 X 5/7 X 78/104) = 200 mg/m^3

(ii) TC_{05} corrected for number of animals alive at the time of appearance of the first pulmonary tumor = 226.5 ppm

Conversion factor, 1 ppm = 5.46 mg/m^3
amortization factors: 7/24 for hours of day; 5/7 for days of week; 78/104 for short duration of study

TC_{05} = (226.5 X 5.46 X 7/24 X 5/7 X 78/104) = 190 mg/m^3
(Presented as tumorigenic dose (μg/kg b.w./day) for inhalation in Assessment Report.)

(4) Gavage administration: male Marshall rats; 5 days/week for 103 weeks; malignant interstitial cell tumours in testes (NTP, 1988). Multistage model was used to estimate potency; amortization (5/7) included in calculation:

TD_{05}: 200 mg/kg b.w./day (not corrected for body surface area since carcinogenicity likely due to metabolites)

Comments:

Non-neoplastic effects not addressed since carcinogenicity considered critical endpoint in the assessment.

Xylene, mixed isomers

CAS Reg. No. 1330-20-7

Cut-off date for literature review: June 1991

Exposure: Indoor air: 73 to 93%
Ambient air: 2 to 22%
Self-serve gasoline station: 4.4 to 6.4%
Drinking water: 0 to 0.6%

Neoplastic effects:

Classification for carcinogenicity: Group IV (unlikely to be carcinogenic to humans) based upon the classification scheme developed for this endpoint under *CEPA* (Meek and Chan, 1994c; Meek *et al.,* 1994a).

Non-neoplastic effects:

TDI[27]: 1.5 mg/kg b.w./day

NOAEL: 150 mg/kg b.w./day. Based upon dose-related increase in absolute and relative weight of liver in rats administered xylenes by gavage for 90 consecutive days (Condie *et al.,* 1988)

100 uncertainty factor:

x 10 for interspecies variation

x 10 for interspecies variation

No additional factor incorporated for less than lifetime exposure, since effects observed at higher doses in chronic study in rats were limited to reduced body weight at highest dose; the published report of this study did not include organ weight data (NTP, 1986e).

27 Not included in Assessment Report

TC (provisional): 0.18 mg/m^3 (Presented as tolerable daily intake (for inhalation) in Assessment Report.)

LOEL: 250 mg/m^3. Based upon (unspecified) maternal effects and fetal skeletal retardation in developmental study in rats; continuous exposure on days 7-15 of gestation; composition of administered compound not specified (Ungvary and Tatrai, 1985)

modified to account for ratio of the inhalation volume/body weight of rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg].

1000 uncertainty factor:

x 10 for interspecies variation

x 10 for interspecies variation

x 10 for LOEL rather than NOEL; limitations of critical study

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