

Appendix 4L

Toxicity assessment

1.1 Overview

Toxicity assessment involves an assessment of the possible effects associated with exposure to a given chemical and the level of exposure that may be without appreciable risk of adverse effects. Dose response factors are used to characterise the relationship between the level of exposure and the likelihood of adverse effects. An overview of the approach to toxicity and dose response assessment is presented in Section 4.4 of Module 4. Details of the effects associated with particular chemicals and the justification for the dose response factors selected is presented in this appendix, together with some background information on the classification of carcinogens.

1.2 Classification of carcinogens

The International Agency for Research on Cancer (IARC) first developed (in 1977) a system for qualitatively categorising carcinogens. This system was based on weight-of-evidence data which involves assessment of all toxicity data originating from human, animal and in-vitro studies to ascertain if the chemical is carcinogenic or not. A similar classification system was also produced by the USEPA in the late 70s and was modelled on the IARC system¹. Table 4L3 shows the carcinogenic classifications developed by the two agencies.

1.3 Toxicity and dose response assessment

1.3.1 General

While a range of terms have been used to describe dose response factors (e.g. tolerable daily intake, acceptable daily intake, unit risk), the relevant dose response factors may be defined as follows;

Slope Factor

A plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime. The slope factor is used to estimate an upper-bound probability of an individual developing cancer as a result of a lifetime of exposure to a particular level of a potential (genotoxic) carcinogen.

Chronic Reference Dose (RfD)

An estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive sub-populations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Chronic RfDs are specially developed to be protective for long-term exposure to a compound. The WHO use the term tolerable daily intake (TDI) which is analogous to the RfD. The TDI is an estimate of the amount of a substance in food or drinking-water, expressed on a body weight basis (mg/kg or µg/kg of body weight) that can be ingested daily over a lifetime without appreciable health risk.

The dose response factors adopted for each chemical of concern are summarised in Tables 4L2 and 4L3. The dose response factors presented in Tables 4L2 and 4L3 are derived from published sources;

¹ The USEPA have recently released proposed guidelines which revise the carcinogen classifications presented in Table 4L3. The proposed guidelines do not include the letter descriptions. The guidelines are not to be released as final (USEPA, 1996).

no effort has been made to confirm the appropriateness of individual factors or assumptions or to derive dose response factors specifically for this work.

Table 4L1 IARC and EPA Classification of Carcinogenic Risk to Humans⁽¹⁾

IARC				Evaluation of Agent Mixture or Occupation	EPA		
Classification grouping	Evidence from ⁽²⁾				Classification grouping	Evidence from ⁽²⁾	
	Humans	Animals	Other Relevant Data ⁽³⁾			Humans	Animals
1	S			is IS carcinogenic	A	S	
2A or or	L L I/ND	S S	Supp Supp	is PROBABLY carcinogenic	B1 B2 or	L I ND	S S
2B or or	L I/ND I	S L	Supp	is POSSIBLY carcinogenic	C	ND	L
3	I/ND	L		is NOT CLASSIFIABLE as to its carcinogenicity	D	Inadequate evidence or no data available	
4	No evidence for carcinogenicity			is PROBABLY NOT carcinogenic	E	No evidence for carcinogenicity	

Notes

1. Based on table from Fitzgerald 1 993
2. S - sufficient Supp - supportive L - limited ND - no data I - inadequate
3. Other relevant data include structure - activity considerations, pharmacokinetics and metabolism, toxicity, genetic nd related effects.

Dose response factors have been nominated by a range of agencies for the contaminants of most concern in the context of petroleum contaminated sites. The USEPA have nominated the most comprehensive range of dose response factors and these have been selected as a starting point for the derivation of Tier 1 Acceptance Criteria. The USEPA dose response factors were reviewed for consistency with the dose response factors implied in the NZDWS, and where the NZDWS suggest a significantly more stringent value this value was adopted.

Table 4L2 Comparison of dose response factors for carcinogens

Contaminant	Source	Slope Factor (mg/kg/d) ⁻¹	
		Ingestion	Inhalation
Benzene	USEPA ⁵	0.029	0.029
	RIVM (Dutch) ^{3,4}	0.016	0.016
	NZDWS ⁷	0.035	
	WHO (Air Guidelines) ^{3,6}		0.014
	Adopted	0.029	0.029
Benzo(a)pyrene	USEPA ⁵	7.3	7.3
	NZDWS/WHO ^{1,7} (drinking water)	0.5	
	RIVM ^{2,4}	0.05	
	Adopted	7.3	7.3

1. Inferred from supporting documentation
2. Inferred from unit risk.
3. Inferred from Tolerable Daily Intake
4. Swartjes & van der Berg, 1993
5. USEPA (1995)
6. WHO, 1987
7. MOH, 1995

The problems associated with chemical constituent ingested (i.e. via drinking-water or similar) arise primarily from their ability to cause adverse health effects after prolonged exposure. Of particular concern are the contaminants that have cumulative toxic effects (i.e. heavy metals) or carcinogenic effects.

The World Health Organization states that Tolerable Daily Intakes (TDI) should be regarded as representing intake for a lifetime. They are not so precise that they cannot be exceeded for short periods of time. Short term exposure exceeding the TDI is not a cause of concern provided the individuals intake over time does not appreciably exceed the level set. The large uncertainty factors generally involved in establishing TDI serve to provide assurance that exposures for short periods are unlikely to have any deleterious effects on human health.

Information from the TPHCWG has been used for the assessment of health effects associated with TPH.

Table 4L3 Comparison of dose response factors for non-carcinogens

Contaminant	Source	Oral Reference Dose	Inhalation Reference Dose
		(mg/kg/d)	(mg/kg/d)
Toluene	USEPA ⁸	0.2	0.11 ¹
	RIVM (Dutch) ³	0.43	
	NZDWS ⁷	0.22	
	Adopted	0.2	0.11
Ethylbenzene	USEPA ⁸	0.1	0.029 ²
	NZDWS (drinking water) ⁷	0.1	
	RIVM ¹⁰	0.14	
	Adopted	0.1	
Xylene	USEPA ⁸	2	0.09
	NZDWS ^{4, 7}	0.18	
	RIVM	0.01	0.09 ³
	Adopted	0.18	
C6 to C9 TPH	USEPA (n-hexane) ⁸	0.06-0.6	0.06
	MDEP (n-hexane)	0.06	
	TPHCWG (aliphatics)	5	5
	Adopted	5	5
C10 to C14 TPH	MDEP (n-nonane) ⁶	0.6	0.3
	TPHCWG (aliphatics)	0.1	
	Adopted	0.1	0.3
C15 to C36 TPH	MDEP (eicosane)	6	1.5
	TPHCWG	1.5 ⁵	
	Adopted	1.5	1.5
Naphthalene	USEPA ⁹	0.04-0.004	0.04 to 0.004
	RBCA ¹¹	0.004	
	RIVM ¹⁰	0.05	0.004
	Adopted	0.004	
Pyrene	USEPA ⁸	0.03	0.03
	RIVM	0.02	
	Adopted	0.03	

1. Equates to reference concentration of 0.4 mg/m³
2. Equates to a reference concentration of 0.1 mg/m³
3. Equate to a reference concentration of 0.3 mg/m³
4. Inferred from supporting information.
5. Based on a weighted mean of the dose response information for the C9 to C16 (oral RfD = 0.1 mg/kg/day) and C17 to C34 fractions (oral RfD = 2 mg/kg/day).
6. MDEP, 1994
7. MoH, 1995
8. USEPA, 1995
9. USEPA, 1991
10. Swartjes & van der Berg, 1993
11. ASTM, 1995

1.3.2 Benzene

This section discusses the health effects and dose response factors for benzene.

1.3.2.1 Health effects

Benzene is readily absorbed via oral and inhalation exposures with small amounts absorbed through the skin. The metabolism of benzene occurs mainly in the liver. The formation of toxic metabolites such as benzoquinone and mucoaldehyde is believed to be responsible for the adverse effects of benzene.

In human and experimental animals, exposure to benzene commonly caused haematological effects such as lymphocytopenia and aplastic anaemia. Epidemiological studies have established a causal relationship between the occupational exposure of benzene and the incidence of leukemia. Based on this information, benzene has been classified as a Class A (confirmed) human carcinogen by the USEPA.

Although not teratogenic, benzene has been found to cause embryotoxicity and geotoxicity at non-maternally toxic doses as low as 47 ppm (150 mg/m³) in rats. Benzene was found to cross the placenta in human, but no association with fetotoxicity and birth defects has been reported. Benzene has also associated with adverse effects on the immune system in animals. Benzene, as with many other hydrocarbons, has been associated with neurological affects.

1.3.2.2 Dose response factors

Benzene is considered a non-threshold toxicant by the USEPA due to its carcinogenicity. An oral slope factor value of 0.029 (mg/kg/day)⁻¹ has been assigned. The oral slope factor has also been applied to the assessment of inhalation exposure.

1.3.3 Xylenes

This section discusses the health effects and dose response factors for xylene.

1.3.3.1 Health effects

Xylene is readily absorbed through inhalation and rapidly metabolised in the liver. Exposure to xylene by oral and inhalation caused mild toxicity in experimental animals without significant adverse effects. Although developmental effects were observed at high doses, in animal studies evidence regarding the teratogenicity of xylene was not conclusive. In humans, exposure to xylene vapour causes irritation of the eyes, nose and throat and some light-headedness at concentration of 200 ppm and above. Neurobehavioural effects were also reported after a 5-6 hour exposure of 100 ppm. According to the USEPA, xylene is a Class D chemical i.e. it is not classifiable with regard to human carcinogenicity due to inadequate human and animal evidence.

1.3.3.2 Dose response factors

In derivation of the NZDWS, the Ministry of Health adopted an acceptable daily intake of 0.18 mg/kg/day, and in accordance with the approach outlined in Section 4.3.3, this value has been adopted for the purposes of deriving Tier 1 Acceptance Criteria¹. The NZDWS value was based on a NOAEL of 250 mg/kg/day for

¹ Xylene was the only contaminant for which there was a significant discrepancy between the USEPA and NZDWS dose response factors, with the NZDWS more stringent, and therefore the dose response factor suggested by the NZDWS was adopted for xylene. The NZDWS nominate a less stringent dose response factor for benzo(a)pyrene and therefore the USEPA value was retained. Each of the contaminants assessed using a non-threshold model by the USEPA is regarded as a genotoxic carcinogen and therefore the assumption of a non-threshold model was retained.)

decreased body weight in a 103 week gavage study in rats. An uncertainty factor of 1000 and a correction from 5-7 days per week exposure was applied.

The USEPA has nominated an oral RfD for xylenes of 2.0 mg/kg/day, using a safety factor of 100, based on the NOAEL for hyperactivity, decreased body weight and increased mortality in rats (same study as used in NZDWS).

The USEPA and NZDWS refer to the same original study, however the NZDWS (and the WHO) includes an additional safety factor of 10 to account for limitations associated with the toxicological endpoint.

For comparison, a tolerable daily intake of 0.01 mg/kg/day may be inferred from the derivation of soil acceptance criteria by the Dutch agencies.

1.3.4 Toluene

The health effects and dose response factor for toluene are discussed in this section.

1.3.4.1 Health effects

Toluene is mildly toxic by inhalation and can cause systemic effects in humans. Exposure to toluene causes irritation to the eyes and skin. High doses lead to impairment of co-ordination and reaction time, narcosis and coma. According to the USEPA, toluene is a Class D chemical i.e. not classifiable with regard to human carcinogenicity, due to inadequate human and animal evidence.

1.3.4.2 Dose response factors

The USEPA has set RfD values for toluene of

- mg/kg/day by oral route, with a safety factor of 1000, based on NOAEL for effects on liver and kidneys;
- mg/m³ by inhalation with a safety factor of 300, based on LOAEL for neurological effects observed in a small population of workers.

1.3.5 Ethylbenzene

The health effects and dose response factor for ethylbenzene are discussed in this section.

1.3.5.1 Health effects

Ethylbenzene is mildly toxic by skin contact and inhalation, and causes systemic effects in humans. It also causes irritation to the eyes, skin, nose and throat and respiratory tract at a concentration of 0.2%. The lowest acutely toxic concentration (TC₁₀) by inhalation reported in humans is 100 ppm.

According to the USEPA, ethylbenzene is a Class D chemical i.e. not classifiable with regard to human carcinogenicity due to inadequate human and animal evidence.

1.3.5.2 Dose response factors

The USEPA has set RfD values for ethylbenzene of:

- mg/kg day with a safety factor of 1000, based on NOAEL by oral route for liver and kidney toxicity observed in animals

- mg/m³ by inhalation, with a safety factor of 300, based on NOAEL for developmental toxicity in rats and rabbits.

1.3.6 Polycyclic aromatic hydrocarbons

Health effects for non-carcinogenic and carcinogenic PAHs are discussed in this section.

1.3.6.1 Non-Carcinogenic

Polycyclic aromatic hydrocarbons (PAHs) occur in the environment as complex mixtures of which only a few components have been adequately characterised. Only limited information is available on the relative toxicity of the “non-carcinogenic” PAHs.

PAH absorption following oral and inhalation exposure is inferred from the demonstrated toxicity of PAHs following these routes of administration. PAHs are also absorbed following dermal exposure. Acute effects from direct contact with PAHs and related materials are limited primarily to phototoxicity; the primary effect being dermatitis. PAHs have also been shown to cause cytotoxicity in rapidly proliferating cells throughout the body; the haematopoietic system, lymphoid systems, and testes are frequent targets. Some of the non-carcinogenic PAHs have been shown to cause systematic toxicity but these effects are generally seen at high doses. Slight morphological changes in the liver and kidney of rats have been reported following oral exposure to acenaphthene for 40 days.

Subchronic oral administration of naphthalene (50 mg/kg/day) to rats has resulted in decreased body weight gain. Mice subchronically exposed to fluoranthene developed adverse kidney, liver and haematological effects. Haematological and kidney effects have also been observed in mice following exposure to fluorene (125-500 mg/kg/day) and pyrene (127-917 mg/kg/day), respectively.

Many of the non-carcinogenic PAHs have been assigned similar Reference Doses (RfDs) by the USEPA and therefore pyrene has been selected as representative of the range of noncarcinogenic PAHs. Some PAHs have been assigned an RfD higher than that assigned to pyrene. However, this is not expected significantly to influence the overall assessment of risk as in most cases health effects associated with the carcinogenic PAHs are limiting. Naphthalene has also been considered given its relatively high volatility compared to other PAHs and the lower RfD (0.004 mg/kg/day) proposed. Refer to Table 4.5 for dose response factors for naphthalene and pyrene.

1.3.6.2 Carcinogenic

Of the 16 PAHs identified by the USEPA in their primary pollutants list seven are classified as probable human carcinogens (B2) i.e. benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenzo(ah)anthracene, and indeno(123-cd)pyrene. PAH compounds are extremely lipophilic and are generally rapidly absorbed upon inhalation, ingestion or dermal exposure. The basis for the carcinogenic classification of these compounds is varied.

For example, no human data are available for chrysene, however, it has been found to produce skin carcinomas as well as malignant lymphoma in mice, while benzo(a)pyrene has been shown to be carcinogenic to rodent and non rodent species, following exposure by all three major pathways. Lung cancer in humans has been associated with various mixtures of PAHs known to contain benzo(a) pyrene, although it cannot be determined if one particular PAH is responsible for these effects.

The carcinogenic potency of these compounds is most commonly determined using data from animal studies. The dose associated with a particular increased lifetime cancer risk, or the slope of the dose-risk relationship (slope factor) is estimated using the available human and animal data.

To calculate the slope factors associated with these compounds, toxic equivalence factors (TEFs) are used to normalise the slope factors for each compound with reference to benzo(a) pyrene. The TEFs are shown in Table 4. The TEFs nominated in Table 4 are based on USEPA guidance and have been developed for the individual members of the class based on their relative potency, compared to the most potent member of the class i.e. benzo(a) pyrene. The TEF approach takes into account the differing potencies of carcinogenic chemicals, allowing acceptance criteria to be determined in terms of benzo(a) pyrene equivalent concentration.²

Oral and inhalation slope factors nominated by the USEPA for the carcinogenic PAHs (normalised to benzo(a) pyrene using TEFs) range from $7.3 \text{ (mg/kg/d)}^{-1}$ for benzo(a) pyrene to $0.073 \text{ (mg/kg/day)}^{-1}$ for chrysene.

As indicated in Table 2, there is a significant difference between the estimates of cancer potency for benzo(a)pyrene prepared by the USEPA (oral Slope Factor = $7.3 \text{ (mg/kg/day)}^{-1}$) and the WHO (inferred oral slope factor = $0.5 \text{ (mg/kg/day)}^{-1}$, as presented in the NZDWS). The basis for this difference lies in the low dose extrapolation methods and data sets used. The WHO/NZDWS apply a two-stage birth-death mutation model to the incidence of fore-stomach tumours in mice, given the data available was inadequate for the linearised multistage model normally used. The USEPA Slope Factor is derived from the geometric mean of four low dose extrapolations based on four combinations of base study and extrapolation model, including the combination used by the WHO/NZDWS. The USEPA Slope Factor is most commonly adopted in Australia and New Zealand for the assessment of contaminated land, is used in the derivation of the ANZECC/NHMRC Health Investigation Levels and appears to be more robust in derivation (i.e.. based on more than one approach) and therefore has been adopted for the purposes of these guidelines.

Table 4L4 Toxic equivalence factors (TEF) for carcinogenic PAHs (USEPA, 1993)

Chemical	TEF
benzo(a)pyrene	1
benz(a)anthracene	0.1
benzo(b)fluoranthene	0.1
benzo(k)fluoranthene	0.1
chrysene	0.01
dibenz(l,h)anthracene	1
indeno(123-cd)pyrene	0.1

1.3.7 Petroleum hydrocarbons

A range of adverse health effects have been associated with petroleum products, however, in most cases the majority of the concern is associated with minority constituents such as polycyclic aromatic hydrocarbons and

² As a first approximation, as part of a Tier 1 assessment, the significance of soil contamination by carcinogenic PAHs may be assessed by using the TEFs. The products of the concentration of each carcinogenic PAH and its TEF may be summed to give a benzo(a)pyrene equivalent concentration, which may be compared with the relevant criterion nominated for benzo(a)pyrene. The benzo(a)pyrene equivalent concentration may be conceptualised as the concentration of benzo(a)pyrene that would give the same risk as the mixture of carcinogenic PAHs. This approach is based on the simplifying assumption that the differences in the fate and transport characteristics of each of the carcinogenic PAHs are of secondary importance and therefore this approach should only be used for a preliminary evaluation.

monocyclic aromatic hydrocarbons. The health effects of such substances are usually addressed separately, refer discussion in Section 3.

For the alkanes, alkenes and similar compounds that make up the majority of products, narcotic and nervous system effects are commonly associated with acute exposure (e.g. headaches). Low level long term dermal exposure has also been associated with adverse skin effects, e.g. dermatitis. There is very little information quantifying the exposure to petroleum hydrocarbons associated with such health effects; however, experience has shown that criteria based on aesthetic effects are also generally protective of human health.

Petroleum hydrocarbons are normally considered in terms of the concentration of various fractions or carbon ranges. For the purposes of deriving Tier 1 Acceptance Criteria three carbon ranges have been considered, as shown in the following discussion. Slight variations in the definition of petroleum hydrocarbon fractions exist in guidance issued by different organisations. Guidance from the TPHCWG has been used as the basis for the following discussion. Information from the Massachusetts Department of Environmental Protection has also been presented in Table 3.

Summary information regarding the range of health effects associated with petroleum hydrocarbons based on information presented by the MDEP (1994) is outlined as follows:

Light Fraction Alkanes (C₇ to C₉)

Central nervous system (CNS) effects are commonly associated with exposure to C₅ to C₉ compounds, which perturb the lipid membrane of the nerve cells. Animal studies indicated that narcotic activity increases as a function of the carbon chain length in the C₅ to C₈ range and decreases beyond C₉.

N-hexane is a representative compound in the C₅ to C₈ range of alkanes and is the most toxic of these alkanes. N-hexane is neurotoxic. It neurotoxicity has been shown to be caused by its metabolite, 2,5-hexanedione.

The health effects associated with other alkanes (i.e. pentane, heptane and octane) are mainly narcosis and irritation to the mucus membrane due to inhalation exposure. C₇ and C₈ alkanes are also found to be immunotoxic.

Mid-range alkanes (C₁₀ to C₁₅)

As discussed earlier, information on the toxicity of C₁₀ to C₁₅ hydrocarbons is limited and therefore n-nonane has been used as the basis for deriving criteria in this range³. While n-nonane was found to cause neurotoxicity, C₁₀ - C₁₃ compounds cause no pathological changes in animal by inhalation exposure. Using the mouse ear adena model, dodecane (C₁₂) was found to be non-irritating and tridecane (C₁₃) showed a delay-response. The strongest irritant amongst these alkanes is tetradecane (C₁₄) with hexadecane (C₁₆), octadecane (C₁₈) and eicosane (C₂₀) showing progressively decreased activity.

Heavy Fraction Alkanes (C₁₅ to C₃₆)

Eicosane, a C₂₀ alkane, is a representative compound for the C₁₅ to C₃₂ range by the MDEP. Eicosane can cause irritation and functional changes at the cellular level. These alkanes cause little neurotoxicity.

³ The selection of surrogate compounds at the lower end of the TPH range considered for both the C₆ to C₉ and C₁₀ to C₁₅ fractions is likely to result in conservative criteria (i.e.. risk will be overestimated).

Alkenes

Alkenes are not considered to be particularly toxicologically active and do not show neurotoxicity. Animal exposure to high levels of the smaller alkenes caused liver damage and hyperplasia of the bone marrow. Similar effects have not been reported in humans.

No RfD is available for alkenes, although the MDEP (1994) have assumed the heavier alkenes exhibit toxicity similar to the non-carcinogenic PAHs, e.g. pyrene.

The TPHCWG has reviewed toxicological information available for whole fuel products and for specific chemicals within each TPH fraction in order to determine representative dose response factors for each fraction. A summary of the reference doses proposed by the TPHCWG is presented in Table 4L5. In determining Reference Doses for TPH fractions for these guidelines, some modification of the TPHCWG information was required to remain consistent with the fractions adopted for these guidelines. The where TPH fractions span more than one fraction nominated by the TPHCWG a weighted mean approach was applied to determine the relevant Reference Dose. The Reference Doses adopted for the purposes of these guidelines are presented in Table 4L3.

Table 5 Fraction Specific Dose Response Factors for Total Petroleum Hydrocarbons

Carbon range	Aromatic RfD (mg/kg/day)	Critical effect	Aliphatic RfD (mg/kg/day)	Critical effect
C ₆ - C ₈ (Aliphatics)	0.20 - Oral	Hepatotoxicity	5.0 - Oral	Neurotoxicity
C ₇ - C ₈ (Aromatics)	0.10 - Inhalation	Nephrotoxicity	5.0 - Inhalation	
C ₉ - C ₁₀	0.04 - Oral	Decreased	0.1 - Oral	Hepatic and
C ₁₁ - C ₁₂	0.05 - Inhalation	bodyweight	0.3 - Inhalation	haematological
C ₁₃ - C ₁₆				changes
C ₁₇ - C ₂₁	0.03 - Oral	Nephrotoxicity	2.0 - Oral	Hepatic (foreign)
C ₂₂ - C ₃₄				body reaction) granuloma