

## 4. Carcinogenic potential

### 4.1. *Weight of evidence for carcinogenicity*

Within the scientific literature, reports vary in their quality and some reports contradict each other. The International Agency for Research on Cancer (IARC) was the first organisation to develop a weight of evidence scheme for cancer agents. A panel of international experts systematically evaluates the evidence of carcinogenicity, classifies each agent and publishes a summary of the evidence which includes the rationale used to support the agent's classification. IARC is an agency of the World Health Organization (WHO).

Although the IARC ranking continues to be highly respected, other agencies have developed similar ranking schemes. Of these, the one published by the USEPA (1986) is probably the most influential. In 1996, USEPA replaced its ranking scheme based on letter ranks with a new descriptive scheme, which takes into account a wider range of data (see appendix A). The USEPA's 1986 scheme is still widely used, in part because the evaluations based on this earlier ranking scheme continue to be reported in the Integrated Risk Information System (IRIS) database. The ranking schemes by IARC and USEPA (1986) are quite similar. Although both organisations place a greater emphasis on good human epidemiological data than on animal data, USEPA has traditionally placed heavier emphasis on animal data than IARC. Even though the new USEPA (1996) ranking scheme has been in use for a few years, the number of agents ranked by this scheme is relatively small and thus it is not yet as widely used as the older scheme.

In Canada, Health Canada has developed a carcinogen-ranking scheme under the Canadian Environmental Protection Act (CEPA, 1994a) based on the IARC ranking scheme. CEPA's scheme consists of more categories and subcategories and is not very compatible with those of IARC and USEPA. CEPA distinguishes between genotoxic and non-genotoxic carcinogens, and gives the latter group a lower ranking when epidemiological evidence is inadequate.

Some US states, including California, have their own rankings. So do many European countries (see Moolenaar, 1994). A comparison of the key ranking schemes is summarised in table 4.1.1. Further details about the various ranking schemes are available in Appendix A.

**Table 4.1.1 Comparison of three well known weight of evidence classification schemes for carcinogens**

Strength/Type of Evidence	Weight of Evidence Classification		
	USEPA <sup>1</sup>	IARC (WHO) <sup>2</sup>	CEPA <sup>3</sup>
Strong human evidence	A	1	I
Some human + animal evidence	B1	2A	III B?
Little or no human evidence, strong animal evidence	B2	2B	II?
Weak evidence from human and animal data	C		III (except IIIb)?
Little evidence for or against carcinogenicity	D	3	VI
Good evidence for absence of carcinogenicity	E	4	V, (IV?)

Based on definitions obtained from the following sources.

1. USEPA (1986)
  2. IARC Monographs website
  3. CEPA (1994a)
- ? – Indicates imperfect fit

The carcinogenicity ranking of the selected contaminants is presented in table 4.1.2. In general, when ranking is available from more than one agency, there is a good agreement between the ranks assigned by the three agencies. The exception is tetrachloroethylene.

There is no consensus in the scientific community and regulatory agencies with respect to whether tetrachloroethylene induces cancer effects in humans. The judgement regarding tetrachloroethylene carcinogenicity ranges from probably carcinogenic to humans (IARC, 1995a; Cal EPA, 1991) to unlikely to be carcinogenic to humans (CEPA, 1996). Most agencies' positions lie somewhere between those of IARC and CEPA. For example, the European Union (Beck, 2000) considers tetrachloroethylene not classifiable as to its carcinogenicity. On the other hand, US EPA's official position (cited in ATSDR, 1995) is that tetrachloroethylene is on the continuum between group B2 (*probable human carcinogen*) and group C (*possible human carcinogen*).

There is a general agreement that the human data are by themselves insufficient to definitively identify tetrachloroethylene as a carcinogen. There is also a good agreement on the toxicity and carcinogenicity of tetrachloroethylene in rodents. The key area of contention for tetrachloroethylene relates to whether rodent data can be directly applied to humans.

The following excerpt from a CEPA (1993d) report summarises CEPA's position on tetrachloroethylene.

Generally, a substance for which there is adequate evidence of carcinogenicity in 2 species of laboratory animals (as observed in the NTP carcinogenesis bioassay for tetrachloroethylene) would be categorized in Group II (probably carcinogenic to humans) ...

Since the observed increase in the incidence of renal tumours in male rats and hepatic tumours in male and female mice exposed to tetrachloroethylene are likely species-specific responses, both of which appear to be induced by mechanisms that are not relevant to humans or, at least, for which humans are likely to be much less sensitive, the results considered most pertinent in assessing the weight of evidence for carcinogenicity are the small increases in the incidence of spontaneously occurring mononuclear cell leukemias in a single species (i.e., male and female F344 rats) in the NTP bioassay, in which the incidence of this tumour in the non-exposed (control) rats was higher than that observed in historical controls (NTP, 1986). The proportion of animals with this tumour in the high-dose group of males and females was 74% and 58%, respectively, compared to 56% and 36% in the concurrent control groups and 29% and 19% in historical controls (NTP, 1986).

On the basis of this argument, CEPA (1993b) assigned to tetrachloroethylene the ranking of III (*Possibly Carcinogenic to Humans*), and later downgraded the ranking (Health Canada, 1996) to IV (unlikely to be carcinogenic to humans).

The route of exposure is an important issue that has to be considered in determining the weight of evidence for carcinogenicity. Some compounds (e.g. dioxins) exert their effect once they are absorbed and distributed throughout the general body tissues. For such contaminants, the difference in carcinogenicity by different routes of exposure is most likely a function of the level of absorption and distribution (i.e. bioavailability), depending on the route of exposure.

Other compounds (e.g. PAHs such as benzo[a]pyrene (B[a]P)) are also activated near the site of uptake. Although such compounds may be carcinogenic at some distance from the site of entry if the dose is big enough, the effects are demonstrable at lower doses near the site of uptake and metabolism. Thus orally administered PAHs may induce skin tumours, they have been shown to induce tumours of the digestive track at lower doses. The reverse is true when PAHs are applied to the skin (MOE 1997).

Some metals appear to be carcinogenic when inhaled. Although they may have other toxic effects when they are taken up by another route, the evidence for carcinogenicity is either absent or not very strong. Most cancer ranking schemes do not provide separate ranking for each route of exposure, although some information may be provided in the text accompanying the ranking. Table 4.1.2 presents the original ranking by the three agencies for the selected contaminants. For these substances, the carcinogenicity ranking describes well the health impact resulting from inhalation exposure but does not describe as well the impact resulting from oral exposure. ToxProbe Inc. approximated the ranking for oral exposure. ToxProbe does not recommend using the ToxProbe ranking for oral exposure out of context from this document. The only purpose of this exercise is to demonstrate the route-specific difference in the weight of evidence

classification for carcinogenicity. A more thorough ranking exercise would be required for any other purpose.

In general, with the exception of tetrachloroethylene, there is a consensus that all the substances of interest are either classified as human carcinogens or probable human carcinogens by inhalation exposure. Oral ingestion is also a major concern for benzene, dioxins and PAHs.

**Table 4.1.2 Weight of evidence classification for carcinogenicity by inhalation route. The weight of evidence conclusion for other routes of exposure is sometimes different.**

	General ranking including inhalation			Oral
	USEPA <sup>1</sup>	IARC (WHO) <sup>2</sup>	CEPA <sup>3</sup>	ToxProbe (based on USEPA <sup>1</sup> ), oral
1,3-Butadiene	B2 <sup>7</sup>	2A	Highly likely human carcinogen	B2 <sup>4</sup>
Asbestos	A	1	NA	Human <i>inadequate</i> + animal <i>limited</i> (C <sup>5</sup> )
Benzene	A	1	I	A <sup>4</sup>
Cadmium	B1	1	II	C – D <sup>5</sup>
Chromium (VI)	A	1	I	D <sup>5</sup>
Dioxins	Likely human carcinogen <sup>8</sup>	1	NA	Likely human carcinogen <sup>8</sup>
Formaldehyde	B1	2A	NA	D <sup>5</sup>
PAHs (B[a]P)	B2	2A	II	B2 <sup>4</sup>
Tetrachloroethylene	NA	2A	IV	NA
Trichloroethylene	Withdrawn (was B2)	2A	II	Withdrawn

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|--|--|
| <ol style="list-style-type: none"> <li>1. IRIS database</li> <li>2. IARC Monographs</li> <li>3. Priority Substances List Reports</li> <li>4. not differentiated from inhalation</li> </ol> | <ol style="list-style-type: none"> <li>5. ToxProbe Inc. interpretation based on material in IRIS</li> <li>6. for explanation see text</li> <li>7. US EPA (1998a) draft reassessment considers 1,3-butadiene as a known human carcinogen.</li> <li>8. USEPA (2000) classifies 2,3,7,8-TCDD as a human carcinogen, but other 2,3,7,8-TCDD-like compounds as “likely” human carcinogens. All complex environmental mixtures of 2,3,7,8-TCDD and dioxin-like compounds are characterized as “likely” human carcinogens. The draft report is currently under review.</li> </ol> |
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## 4.2. Genotoxicity

Some carcinogens are believed to induce cancer effect even at very minute doses, although the probability of adverse effects at low doses is low. There is no safe level of exposure for these chemicals. As the level of exposure increases, so does the risk. At low dose levels, the increase is linear. This means that if the level of exposure increases by two-fold, the risk is also expected to increase proportionately two-fold. These cancer-inducing compounds are referred as non-threshold carcinogens. The mechanism by which they induce their effect requires a genotoxic event that results in an irreversible mutation in the DNA of a somatic cell and is called *initiation* and the carcinogens acting by this mechanism are called initiators.

In contrast, some carcinogens are thought not to induce an adverse effect, until a certain minimal exposure (threshold exposure) is reached. Above the threshold, the severity of the effect increases in proportion to the exposure level. These carcinogens are referred to as threshold carcinogens. They are thought to induce cell proliferation and allow for clonal expansion of the initiated cells and a mutation is not required. This step is called *promotion* and the carcinogens acting by this mechanism are called *promoters*. The next step in the development of cancer is called progression and is thought to involve further genotoxic events.

The carcinogens, which act by all the above mechanisms are called *complete carcinogens*. It is outside the scope of this report to provide a detailed review of the mechanism of carcinogenicity. Good reviews are available from Farber (1987) and from Barrett and Wiseman (1987).

Since initiators must be able to trigger a mutagenic event while the same is not true for promoters, the absence of mutagenic properties in a carcinogenic agent together with proven ability to induce cell proliferation is taken as evidence that the agent is a promoter. Conversely, highly mutagenic agents are treated as initiators. The rating of evidence for mutagenicity of selected contaminants is listed in table 4.2.1. The comparative ranking of promoting properties of carcinogens is not available, but the evidence is good for asbestos, formaldehyde and benzo[a]pyrene. Dioxins and similar compounds are not genotoxic. They exert their carcinogenic action through binding to and subsequent activation of the Ah receptor.

Initiators tend to be considered of greater concern with regards to environmental exposure. This is because these carcinogens are expected to pose some (small) risk even at very low concentrations, such as those usually found in the environment. In contrast, the level of exposure associated with cell proliferation tends to be relatively higher. Thus even though an exposure to promoters may have occurred, there may not be any adverse effect if the exposure is low enough. This is why CEPA's weight of evidence ranking scheme tends to rank promoters lower than initiators (see above). In the occupational setting, where exposures tend to be higher than environmental levels, promoters are more likely to pose a significant risk. Furthermore, thresholds of some non-genotoxic carcinogens (dioxins, for example) can be quite low and exposure may exceed the carcinogenic threshold in the environmental setting.

In most cases, considering the non-threshold effects of a chemical rather than its threshold effects in the risk assessment process is a more conservative approach and is more protective of human health. However, where the situation is uncertain, it is prudent to assess both threshold and non-threshold effects. Some agencies (USEPA and especially California Environmental Protection Agency) are particularly conservative and use the non-threshold model to provide an additional margin of safety to their calculations.

USEPA has been criticized for its policy of always assuming a non-threshold mechanism for carcinogens. This policy has now been revoked, and USEPA is now considering a wide range of data in its effort to determine what is more appropriate, to assume a threshold or a non-threshold mechanism. USEPA assessments seem to continue the use of the no threshold model even for non-mutagenic carcinogens.

As illustrated in table 4.2.1, most of the selected carcinogens are mutagenic and are considered initiators. The exceptions are dioxins, tri-and tetrachloroethylenes.

**Table 4.2.1 Mutagenicity evaluation**

	Evaluation by Agencies		
	USEPA <sup>1</sup>	WHO <sup>2</sup>	CEPA <sup>3</sup>
1,3-Butadiene	Implied mutagenic	Genotoxic metabolite	Genotoxic
Asbestos <sup>4</sup>	Not Stated – implied genotoxic	Not stated. Conflicting data summarised	NA
Benzene	Genotoxic, probably through epigenetic mechanisms	Implied genotoxicity	Genotoxic
Cadmium	Inconclusive	Mostly positive studies cited	Generally genotoxic
Chromium (VI)	Genotoxic	Genotoxic	Generally genotoxic
Dioxins	Not directly genotoxic	Not direct-acting genotoxic agents	NA
Formaldehyde	Genotoxic	Comprehensively genotoxic	NA
PAHs (B[a]P)	Genotoxic	Genotoxic	Genotoxic
Tetrachloroethylene	NA	Mostly negative studies cited	Not genotoxic
Trichloroethylene	NA	Mostly negative studies cited	Weakly mutagenic

1. IRIS database
2. WHO Air Guidelines for Europe
3. CEPA's Priority Substances List Reports
4. Since the USEPA and WHO evaluations, there is increasing evidence strongly suggesting that asbestos is genotoxic, causing damages to the chromosomes (ATSDR, 1995a). There is also evidence indicating that asbestos could be mutagenic, causing large DNA deletions, which may not be easily detected (ATSDR, 1995a).

### 4.3. Types and sites of cancer encountered

Different carcinogens have a tendency to induce tumours at different sites and different cancers types. Table 4.3.1 below summarizes the site and the type of tumour induced by the selected contaminants. The list is not necessarily complete and only the best-documented tumours are included in the table. Note that for some contaminants, the site and the type of tumour depend on the route of exposure.

**Table 4.3.1 Sites and types of tumours**

	<b>Cancer types</b>	<b>Reference</b>
1,3-butadiene	Cancer of lymphohaematopoietic system (leukemia, lymphosarcoma and reticulum cell sarcoma)	ATSDR (1992)
Asbestos	Lung cancer (cancer of the lung tissue itself) and mesothelioma (a cancer of the thin membrane that surrounds the lung and other internal organs)	ATSDR (1995)
Benzene	Acute myeloid leukemia (AML - leukemia characterized by proliferation of myeloid tissue in bone marrow and spleen and an abnormal increase in the number of white blood cells called granulocytes and cells which give rise to myelocytes and myeloblasts in the circulating blood)	ATSDR (1997)
Cadmium	Lung cancer	ATSDR (1993a)
Chromium (VI)	Lung cancer	ATSDR (1993b)
Dioxins	Best human evidence is for all cancers combined, lung cancer and soft tissue sarcoma, liver cancers in animals	USEPA (1994b)
Formaldehyde	Nasal and nasopharyngeal tumours	IPCS (1989a) ATSDR (1999)
PAHs (B[a]P)	Oral: mainly stomach tumours Inhalation: mainly lung tumours Dermal: mainly skin tumours	ATSDR (1995d)
Tetrachloroethylene	Weak evidence for cancer in humans	CEPA (1993d)
Trichloroethylene	No consistent pattern as to the type of cancer	CEPA (1993a)

#### 4.4. Other effects

Examination of adverse health effects other than cancer for the selected contaminants falls outside the scope of this report. However, it is important to bear in mind that the selected agents have other toxic effects other than cancer and that these effects may play an important role in the overall toxicity of the agent. The non-cancer effects may be particularly important in occupational settings, where exposures tend to be higher than environmental exposures. Table 4.4.1 provides a brief summary of the major toxic effects, other than cancer, of the selected agents.

**Table 4.4.1. Major toxic effects (other than cancer) of selected agents**

	<b>Most important health effects</b>	<b>reference</b>
1,3-Butadiene	Cardiovascular, hematopoietic (blood formation), reproductive and developmental effects, and respiratory diseases	ATSDR (1992)
Asbestos	Asbestosis - scar-like tissue in the lungs and in the membrane that surrounds the lungs	ATSDR (1995)
Benzene	Hematological effects might occur in humans after inhalation, oral, or dermal exposure; effects on red blood cells, white blood cells, platelets; bone marrow damage leading to aplastic anemia	ATSDR (1997)
Cadmium	Kidney damage after oral or inhalation exposure; also respiratory effects, but non-occupational exposure to cadmium is unlikely to be high enough to cause these effects; respiratory effects tend to be reversible with discontinuation of exposure	ATSDR (1993a)
Chromium (VI)	By inhalation: nasal septum ulceration and perforation, and other irritating respiratory effects, asthma By dermal exposure: dermatitis, skin ulcers By inhalation, oral, dermal: possible respiratory, cardiovascular effects, gastrointestinal and hematological effects, liver and kidney effects,	ATSDR (1993b)
Dioxins	Chloracne, reproductive and developmental toxicity, immunotoxicity	USEPA (1994b)
Formaldehyde	Inhalation: upper respiratory tract irritation, dysplasia and squamous metaplasia of the respiratory and olfactory epithelia Oral: papillomas in the forestomach of rats Dermal: skin irritation at high doses	IPCS (1989a)
PAHs (B[a]P)	Hematological, developmental and dermal effects	ATSDR (1995d)
Tetrachloroethylene	Acute effects: reversible neurological effects such as headache, dizziness, nausea, difficulty in speaking, and sleepiness Long-term: neurological and neurobehavioral effects, lung congestion, kidney effects, liver effects	ATSDR (1995c)
Trichloroethylene	Neurotoxicity, liver and kidney damage	CEPA (1993a)

## **4.5. Carcinogenic potency**

### **4.5.1. Threshold versus non-threshold dose-response effects**

As discussed in section 4.2, many cancer-inducing compounds and some other toxicants are non-threshold toxicants. There is no safe level for these chemicals. As the level of exposure increases, so does the risk.

At low dose levels, the increase is linear. In contrast, most non-cancer inducing chemicals and some carcinogens are thought not to induce an adverse effect, until a certain minimal exposure (threshold exposure) is reached. Above the threshold, the severity of the effect would increase as the exposure level increases. For example, atropine will cause widening of the pupil at a certain concentration. Below that concentration, atropine is thought to have no effect on the pupil. These toxicants are referred to as threshold toxicants.

The distinction between threshold and non-threshold effects is needed, because the approach to assessing the risk for the two groups of chemicals is different. For chemicals with a threshold, the purpose of the dose-response assessment is to identify this threshold at which no adverse effect is expected. No observable adverse effect level (NOAEL) or a benchmark dose is determined either experimentally or in a human epidemiological study. For threshold toxicants, NOAEL is a measure of toxic potency. The more potent the threshold toxicant is, the lower the dose at which no adverse effect is detected. By applying an appropriate safety factor that accounts for the uncertainties in the estimation of the threshold, the reference dose (RfD), which is also called tolerable daily intake (TDI), is determined.

Since there is no “safe” level for non-threshold chemicals, it is necessary to establish a level of exposure for each chemical that is deemed operationally as “tolerable”. Such a level is called risk-specific dose (RsD).

“Tolerable” risk levels differ not only from chemical to chemical but also from organisation to organisation, circumstance to circumstance and they are often controversial. What is tolerable depends usually on an individual’s perspective. Generally for environmental exposures, a tolerable risk has been operationally defined as the probability of an adverse event ranging from one in 10,000 to one in a million. Most organisations use RsDs at one in a million risk for human health. This is the risk level that will be used in this report.

RsD is affected not only by the level of risk deemed tolerable, but also by the potency of the non-threshold effect of the toxicant. Potency is generally expressed as the initial slope of the dose-response curve. This slope estimates the increase in risk as exposure is incrementally increased. The higher the potency, the greater the increment of risk resulting from a given increment of exposure and the steeper the slope of the dose-response curve is. The RsD is derived from this slope.

The decision as to whether to treat an agent as a threshold or non-threshold toxicant often has a large impact on its potency estimate. Non-threshold estimates tend to be far more conservative in many circumstances.

### **Potency Estimates**

Carcinogenic potency by inhalation, oral and dermal routes is summarized in tables 4.5.1 and 4.5.2. In the case of dioxins and PAHs, the cancer potency estimates developed by the four organisations differ significantly. These differences are discussed in section 4.5.1 and 4.5.2, as well as in appendix A. The four agencies listed in tables 4.5.1 and 4.5.2 have not developed a cancer potency for tetrachloroethylene (perchloroethylene). California Environmental Protection Agency (CalEPA) (1991), on the other hand, estimated a lifetime cancer unit risk of  $8 \times 10^{-3} (\text{mg}/\text{m}^3)^{-1}$  for tetrachloroethylene. The use of this estimate is not recommended, given the many questions related to the carcinogenicity of this agent in humans (see section 4.1). Some of these questions relate to the inadequacy of carcinogenic evidence in humans and the relevance of the mechanism of tumour induction in animals to humans.

Most agencies do not develop cancer potencies for dermal exposure, although MOE (1997) did develop dermal potencies for PAHs. Procedures and uncertainties associated with estimating dermal potencies from oral potencies are discussed in section 4.5.3 and the potency estimates are provided in table 4.5.2.

As indicated in table 4.5.1, carcinogenic PAHs and chromium (VI) appear to be the most potent carcinogens by inhalation exposure among the initiators, followed by asbestos and cadmium. 1,3-butadiene and benzene are about 3 to 4 orders of magnitude less potent than PAHs and chromium (VI). Oral and dermal potency factors are available only for a few of the substances. Other than inhalation, dermal exposure to carcinogenic PAHs is of great concern while oral exposure to PAHs is of lesser importance. However, these comparisons are done without taking into consideration the weight of evidence supporting the identification of a chemical as a carcinogen. For example, while benzene is classified as a human carcinogen, PAHs are probably carcinogenic to humans. The orders could have been different if the weight of evidence classification could be factored into the comparison.

Among substances (e.g. dioxins and related compounds, trichloroethylene and tetrachloroethylene) for which the evidence for mutagenicity is weak, i.e. their potentials for initiation are low, dioxins and related compounds are likely the most potent carcinogens. However, it is difficult to compare dioxins and related compounds against the other substances. Dioxins and related compounds are promoters whereas the other substances are tumour initiators. Some are complete carcinogens, such as B[a]P. Since the action of a promoter requires prior tumour initiation, an adverse effect may not occur ensuing exposure to a promoter, especially if the level of exposure is low. In contrast, initiators are expected to pose some (small) risk even at very low concentrations. As a result, promoters tend to be considered of lesser concern than initiators with regards to environmental exposure. On the other hand, dioxins and related compounds are very potent as promoters. The levels at which dioxins and related compounds likely exert their tumour promotion properties are lower than the levels at which other substances start to significantly initiate tumour formation (i.e. levels associated with an added cancer risk of one in a million for initiators). This is true for all routes of exposure.

**Table 4.5.1. Inhalation Potency of selected carcinogens, expressed as unit risks ( $\mu\text{g}/\text{m}^3$ )<sup>-1</sup> except for asbestos (fibres/mL)<sup>-1</sup>. The recommended values are in bold face.**

	Sources			
	MOE <sup>(1)</sup>	USEPA <sup>(2)</sup>	WHO <sup>(3)</sup>	CEPA <sup>(4)</sup>
1,3-Butadiene		2.8 x 10 <sup>-4</sup> , <b>6.3 x 10<sup>-6</sup></b> <sup>(7)</sup>	NA	5.8 x 10 <sup>-6</sup> <sup>(6)</sup>
Asbestos		<b>2.3 x 10<sup>-1</sup> (f/mL)<sup>-1</sup></b> <sup>(8)</sup>	NA	NA
Benzene		<b>4.1 x 10<sup>-6</sup> (geom. m)</b>	6 x 10 <sup>-6</sup>	3.3 x 10 <sup>-6</sup> <sup>(5)</sup>
Cadmium		<b>1.8 x 10<sup>-3</sup></b>	NA	9.8 x 10 <sup>-3</sup> <sup>(5)</sup>
Chromium (VI)		<b>1.2 x 10<sup>-2</sup></b>	4 x 10 <sup>-2</sup>	7.6 x 10 <sup>-2</sup> <sup>(5)</sup>
Dioxins	No values given here. Issues are too complex to be summarized in a table. Please refer to section 4.5.1.			
Formaldehyde		1.3 x 10 <sup>-5</sup> , <b>2.8 x 10<sup>-7</sup></b> <sup>(9)</sup>	NA	NA
PAHs (B[a]P/B[a]Ps)	<b>1.5 x 10<sup>-3</sup>/</b> <b>2.3 x 10<sup>-2</sup></b>	NA	8.7 x 10 <sup>-2</sup> (B[a]Ps)	3.1 x 10 <sup>-5</sup> (B[a]P) <sup>(5)</sup>
Tetrachloroethylene		NA	NA	NA
Trichloroethylene		NA	4.3 x 10 <sup>-7</sup>	<b>6.1 x 10<sup>-7</sup></b>

<sup>(1)</sup>-MOE Scientific Criteria Documents

<sup>(2)</sup>-IRIS database

<sup>(3)</sup>-WHO Air Guidelines for Europe

<sup>(4)</sup>-CEPA's Priority Substances List Reports

<sup>(5)</sup>-Calculated from TC<sub>05</sub> value reported by CEPA (unit risk = 0.05/TC<sub>05</sub>)

<sup>(6)</sup>-Calculated from TC<sub>01</sub> value reported in CEPA (2000a) report for 1,3-butadiene. Based on human data

<sup>(7)</sup>-US EPA (1998a) draft Health Risk Assessment of 1,3-Butadiene.

<sup>(8)</sup>-The potency of asbestos is equivalent to 7.7 x 10<sup>-3</sup> ( $\mu\text{g}/\text{m}^3$ )<sup>-1</sup>.

<sup>(9)</sup>-USEPA (1991) draft Formaldehyde Risk Assessment Update.

B[a]Ps represents a potency of a PAH-rich mixture, where the concentration or dose is expressed in terms of benzo[a]pyrene (B[a]P) content.

**Table 4.5.2. Oral and dermal potencies of selected carcinogens expressed as slope factors (mg/kg day)<sup>-1</sup>. The recommended values are in bold face.**

	Sources			
	MOE oral <sup>(1)</sup>	USEPA oral <sup>(2)</sup>	CEPA oral <sup>(3)</sup>	Dermal
1,3-Butadiene		NA	NA	
Asbestos		NA	NA	
Benzene		<b>2.9 x 10<sup>-2</sup></b>	NA	<b>3 x 10<sup>-4</sup></b> <sup>(4)</sup>
Cadmium		NA	NA	
Chromium (VI)		NA	NA	
Dioxins	No values given here. Issues are too complex for a table. Please see section 4.5.1.			
Formaldehyde		NA	NA	
PAHs (B[a]P/B[a]Ps)	<b>0.18/2.9</b>	7.3	NA	<b>8.4/ 95</b> <sup>(1)</sup>
Tetrachloroethylene		NA	NA	
Trichloroethylene		NA	<b>1.5 x 10<sup>-4</sup></b> (geom. mean)	<b>1.0 x 10<sup>-5</sup></b> <sup>(4)</sup>

<sup>(1)</sup>-MOE Scientific Criteria Documents

<sup>(2)</sup>-IRIS database

<sup>(3)</sup>-CEPA's Priority Substances List Reports

<sup>(4)</sup>-Derived from oral potency. See section 4.5.3 for details

*B[a]Ps represents the potency of a PAH-rich mixture, where the concentration or dose is expressed in terms of benzo[a]pyrene (B[a]P) content.*

### 4.5.2. Estimating potency for dioxins

Assessment of the toxicity of polychlorinated dibenzo-p-dioxin (dioxin)/polychlorinated dibenzofuran (furan)/coplanar polychlorinated biphenyl (PCB) mixtures is usually conducted using toxic equivalency factors (TEFs). The concept of toxic equivalence is based on a common mechanism of action within this class of compounds (for listing of these compounds and their TEF values, see appendix B). TEFs are assigned to individual dioxins, furans and coplanar PCBs on the basis of how toxic they are in comparison with the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), the most potent dioxin. This approach first estimates the potency of TCDD and then expresses the environmental levels of other dioxin-like compounds as "TCDD equivalents" (TEQs). In order to estimate the toxicity of a mixture of dioxin-like compounds, the total number of TCDD equivalents in the mixture is multiplied by the potency of TCDD. The result is numerically equivalent to summing up the risks attributable to individual dioxin-like compounds in the mixture.

**Potency of TCDD**

Although dioxin-like compounds induce a wide range of effects, the dose-response assessments conducted by major regulatory agencies focus on cancer as the endpoint. However, there are major differences in the way these organisations establish the dose-response relationship and this difference has a major effect on the estimates of toxicity.

In the case of dioxin-like compounds, there is no consensus on whether to treat this family of compounds as threshold or non-threshold carcinogens. However, the arguments are complex and beyond the scope of this report. It should be noted that while US EPA (1994b, 1997a, 2000) assessed the potency of TCDD and thus of all the other compounds for which TEFs are developed as non-threshold carcinogens, WHO (1995b) and CEPA (1993c) treated these compounds as threshold carcinogens. This is probably the main reason for the large discrepancy among the exposure limits derived by the three agencies (see below for further details).

US EPA (2000)

US EPA (2000) assumed a non-threshold dose-effect relationship for dioxin-like substances. It conducted its dose-response assessment using three occupational studies (Fingerhut *et al.* 1991; Manz *et al.* 1991; Zober *et al.* 1990). The human data suggest an ED<sub>01</sub> (effective dose resulting in 1% excess risk) based on the average lifetime body burden in the range of 6-80 ng/kg for all cancers combined and 36-250 ng/kg for lung cancer. These estimates correspond to upper bound slope factors of  $8.6 \times 10^{-3}$  to  $2.5 \times 10^{-4}$  risk per pg TCDD/kg/day. Since there is no a priori reason to choose one specific study over the other, US EPA performed a meta-analysis by combining all data sets into a single large data set yielding a slope factor of approximately  $1 \times 10^{-3}$  per pg TCDD/kg/day. This value represents US EPA's most current upper bound cancer slope factor for estimating human cancer risk based on human data. The slope factor derived from animal data supports this estimate.

WHO (1995b)

WHO implicitly assumed a threshold for the effects of TCDD-like substances and developed a tolerable daily intake (TDI) of 10 pg/kg/day based on TCDD-induced liver cancer in rats, for which the NOAEL was 1000 pg/kg/day. 1000 pg/kg/day corresponds to 540 ng ( $10^9$ g) of TCDD/kg of liver wet weight in rats. In humans, such TCDD content in the liver is estimated to require an intake of 100 pg/kg/day of TCDD. The TDI is derived from this value by applying an uncertainty factor of 10. This factor is intended to account for the different sensitivity among individuals to TCDD.

In 1998, WHO revisited its risk assessment for dioxin and dioxin-like compounds. A TDI of 1 - 4 TEQ pg/kg/day was established for dioxins and dioxin-like compounds based on dioxin-induced developmental and reproductive effects in rats and monkeys. Lowest Adverse Effect Levels (LOAEL) ranging from 14 to 37 pg TCDD/kg/day were identified from a series of developmental and reproductive studies. These studies observed a decrease in sperm count, immune suppression and an increase in genital malformation in the offspring of exposed rats (Gray *et al.* 1997a, Gray *et al.* 1997b, Gehrs *et al.* 1997, Gehrs & Smailowicz,

1998). Endometriosis was observed in exposed monkeys in one study (Rier *et al.* 1993) while neurobehavioral effects were identified in the offspring of exposed monkeys in another study (Schantz and Boman, 1989). An uncertainty factor of 10 was applied to the LOAEL to arrive at the TDI. This factor accounts for the use of a range of LOAELs instead of a NOAEL, the possible differences in susceptibility to these compounds between humans and experimental animals, the potential differences in sensitivity within the human population and differences in half-lives of elimination for the compounds of a complex TEQ mixture. WHO assessment suggests that developmental effects may be more important than carcinogenic effects for dioxin and dioxin-like compounds.

#### CEPA (1993c)

CEPA has estimated the TDI to be 10 pg/kg/day. Their estimate is based on the assumption that dioxin-like substances are non-genotoxic and that a threshold (NOAEL) exists for their action at approximately 1000 pg of TCDD/kg/day. An uncertainty factor was applied to account for differences among individuals and for the severity of the observed effect. CEPA's assessment is recommended for use at the present time.

Note that the difference between the estimates derived by the USEPA (1997a) versus CEPA (1993c) and WHO (1995b) is approximately ten thousand fold at the risk level of one in a million. This discrepancy among the estimates of potency has not yet been resolved. Overall, ToxProbe recommends that dioxin-like contaminants be treated as having a threshold, consistent with the approaches taken by WHO and CEPA. At the proof review stage of this draft, the Science Advisory Report released a draft report (SAB, 2001) which recommends against reliance on the exclusive use of non-threshold extrapolation. That draft offers an excellent discussion of the issues involved.

### **4.5.3. Estimating potency for PAHs**

PAHs exist in the environment as a mixture and not as single compounds. As a result, all the available human toxicological data involve mixtures, rather than individual compounds. Quantitative experimental data are available for only a few of these compounds. Furthermore, only a few PAHs are on the routine monitoring lists. A risk assessment based on the few well-characterized PAHs is therefore likely to underestimate the risk from the entire PAH family by more than a hundred fold (For discussion and references, see MOE 1997).

The cancer risk due to a complex mixture of PAHs can be estimated by conducting a risk assessment on individual PAH, and the risk attributable to each selected PAH in the mixture can be added up to form an aggregate risk. Alternatively the toxicity of the complex mixture can be expressed in terms of the potency of a single "standard" compound with well-quantified potency. Such an expression of relative potency is called toxicity equivalent factor (TEF). The potency of the mixture is then estimated as the product of the number of TEFs and the potency of the "standard" compound on which the TEF is based. The two alternatives are numerically identical. This approach has been used to develop USEPA drinking water (USEPA, 1993a) and CEPA's air guidelines (CEPA, 1994b).

An alternative approach is to assess the carcinogenicity of the PAH fraction of the mixture as a whole. The quantity of PAH in the mixture and the potency of the mixture is estimated from the quantity of a “surrogate”, B[a]P in this case. It is therefore assumed that as the levels of B[a]P increase, so will the levels of other cancer-causing PAH and the potency of the mixture. In this approach, B[a]P is assigned not just its own potency, but the potency estimated for the whole PAH fraction. Although it has been shown that PAH profile differs depending on the source of emissions and the conditions of combustion, these differences are not sufficiently large to alter the outcome of the risk assessment (MOE, 1997). WHO (1996) and MOE (1997) have adopted this approach. The differences between CEPA’s potency estimates and the WHO and MOE estimates are partly due to the fact that the CEPA assessment assigned B[a]P only its own potency, while WHO and MOE assessments assigned B[a]P not only its own potency but the potency of the whole PAH fraction. WHO and MOE estimates differ by about an order of magnitude. Their values differ because the MOE estimate was based on the initial slope representing the best fit of the linearised multistage model to the data, while WHO used a more conservative 95% upper confidence limit (UCL) on that slope. MOE (1997) has also provided the UCL potency estimates. The difference in the oral potency estimate for B[a]P stems from the fact that MOE has extrapolated the oral cancer potency from human inhalation data, while CEPA has used the animal ingestion data as the starting point. In arriving at its approach, MOE (1997) has compared the two different sets of extrapolations and concluded that the route-to-route extrapolation it used is associated with a lower level of uncertainty. Please refer to Appendix A for further discussion.

#### **4.5.4. Estimating Dermal potency from Oral Potency**

USEPA (1996b) has demonstrated that extrapolation of exposure limits from oral to inhalation exposure may lead to a significant underestimation of the risk. Although no similar evaluation is possible for extrapolation from oral to dermal exposure, the possibility that the same result may hold true exists.

The use of oral dose response parameters, such as RfD or cancer slope factor, as dermal dose response parameters, after correcting for incomplete absorption by dermal exposure, is currently a common practice.

This practice implicitly assumes that the health effects elicited are related only to the total uptake and are not dependent on the route of exposure. This assumption may hold for some chemicals, such as lead and dioxins. Some other substances tend to have different potencies and act at different organ sites depending on the route of exposure. PAHs are good examples (MOE, 1997). They are activated to a significant extent by metabolism in the skin following dermal absorption before being delivered to the liver where metabolism of most xenobiotics takes place. Some substances may cause skin irritation, a phenomenon that is not normally taken into consideration in developing an oral exposure limit. These factors make dermal exposure significantly different from oral exposure. As a result, the use of oral dose response parameters in evaluating health risk from dermal exposure may significantly underestimate the risk (for example nickel, chromium VI).

USEPA (1989a, 1992b, 1998c) discusses another important issue: oral and dermal RfDs and slope factors are developed and used differently. Oral dose response parameters are usually developed in terms of the administered dose, rather than the delivered or absorbed dose. The administered dose represents the total intake of the test substance, not corrected for absorption. In contrast, the delivered or absorbed dose is the administered dose that has been corrected for uptake. The vehicle in which the test substance is delivered

is usually selected to minimally impede uptake. When an oral RfD or a slope factor is applied to an environmental situation, the actual absorption may be less complete compared to the experimental conditions, making the application of the uncorrected slope factor conservative. For example, absorption from the soil matrix may be less than absorption from a solution matrix administered by gavage in the laboratory. The oral slope factor when applied as a substitute for a dermal slope factor is usually corrected for bioavailability by assuming a 100% uptake. In effect, the administered dose is assumed to be equal to the absorbed dose. On the other hand, dermal exposure is usually described in terms of absorbed dose. These practices lead to an underestimation of the dermal uptake due to over-correction for oral bioavailability; the magnitude of the underestimation being inversely proportional to the true oral absorption of the chemical in question. The USEPA (1989a, 1992b) therefore recommends correcting the oral slope factor for bioavailability before extrapolation to dermal toxicity values, if defensible data allow for such a correction. If correction for bioavailability is impractical, the USEPA (1992b, page 10-10) recommends conducting route-to-route extrapolation from oral to dermal toxicity values only when *accompanied with a strong statement emphasizing the uncertainty involved*.

Following the USEPA assessment of bioavailability by dermal route for a number of substances in 1992, the USEPA regions (1995, 1998c) started to compile guidance on skin absorption factors for the Superfund Program. This report makes use of the skin absorption factors recommended by Risk Assessment Information System (RAIS, 2000). RAIS provides estimates of absorption factors for both the dermal and the oral routes. The availability of oral absorption factors allows for the conversion of oral potency expressed in the form of administered dose to the form of absorbed dose. The availability of dermal absorption factors allows for calculation of dermal absorbed dose using the oral absorbed dose. The extrapolation of dermal RfD from the oral RfD is illustrated below.

$$\text{RfD}_{\text{dermal}} = \text{RfD}_{\text{oral}} \times (f_{\text{oral}} / f_{\text{dermal}})$$

Derivation of dermal slope factor from oral slope factor can be achieved using the equation below.

$$\text{Slope}_{\text{dermal}} = \text{Slope}_{\text{oral}} \times (f_{\text{dermal}} / f_{\text{oral}})$$

The results are summarized in table 4.5.2. As discussed above, oral to dermal extrapolation does not take into account effects, which are observed only when individuals are exposed via the dermal route. The potencies for these dermal effects are generally not available and it is therefore important to recognize that this assessment may underestimate the level of health concern by dermal route of exposure.