Table 10: Environmental health criteria derived from a threshold approach

Toxicity reference value	Units	Description or definition
Acceptable daily intake (ADI)	mg/kg/day	The daily intake of a chemical that, during a lifetime, appears to be without appreciable risk, on the basis of all the facts known at the time (WHO 1994a). The term ADI is generally used for chemicals such as pesticides, which may be present in foods within their maximum residue level (MRL) because of their permitted uses in agriculture. The ADI and RfD are conceptually the same; the terminology differs because of development by different authorities.
Tolerable daily intake (TDI)	mg/kg/day	An estimate of the intake of a substance that can occur over a lifetime without appreciable health risk (WHO 1994a). This is conceptually the same as the ADI and RfD but used when the substance is an unintended contaminant in food or an environmental medium such as air, water or soil. This terminology avoids the implication that the contaminant is 'accepted'.
Reference dose (RfD) (US terminology)	mg/kg/day	An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive sub-groups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
Reference concentration (RfC) (US terminology)	mg/m^3	An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive sub-groups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Note that the US EPA envisages that, while the RfD or RfC are generally only used for non-cancer endpoints, it may be necessary to derive both an RfD (or RfC) and a non-threshold cancer risk slope factor where both cancer and non-cancer endpoints need to be considered in the risk assessment. The only exception is where a carcinogenic response drives the risk assessment, but it is considered that a non-threshold approach is warranted because of the proposed mode of action.

The time base may be altered from daily intake to weekly or monthly intakes where the exposure pathways or toxicokinetic behaviour of the chemical warrant a longer period of averaging. For example, the term 'tolerable monthly intake' (TMI) is applied to dioxins because of the very long half-life for elimination and the use of body-burden estimates in humans and animals to adjust intakes (Joint FAO/WHO Expert Committee of Food Additives – JECFA 2002; OCS 2004).

Sometimes the word 'provisional' is attached to the term (e.g. the provisional tolerable weekly intake – PTWI). This is generally done when further data is required to establish an acceptable or tolerable intake but a temporary GV is required by the risk managers. A provisional ADI or TDI may incorporate an additional SF in the calculation because of the inherent uncertainty.

There are other sets of health-based guideline values derived from occupational health and safety (OHS). These include threshold limit values (TLV), short-term exposure limits (STEL) permissible exposure limits (PEL), to be used in an environmental health risk assessment. While they are often derived using comparable methodology, extrapolating from animal toxicity studies, human exposure studies and epidemiological studies, they are based on the protection of workers (who are on average healthier than the whole community) during the course of a normal working shift and a normal working lifetime. They may use different levels of protection and safety factors than used for the general community, such as tolerating relatively minor adverse effects. It would be unusual for OHS-based guideline doses to be used in an environmental health risk assessment, although the risk assessor may need to be aware of potentially conflicting situations where it may not be clear whether the risk estimates of an EHRA should be applicable to both the general community and/or to workers within an exposure scenario.

5.6 DETERMINATION OF NO(A)ELs, ADIs (RFD) AND TDIs FOR HUMANS

The determination of an acceptable or tolerable daily intake (ADI or TDI) involves establishing an overall NOAEL for a chemical that is generally the lowest NOAEL in the most sensitive species.

This approach of using the lowest NOAEL is justified unless there is evidence of one or more of the following:

- from pharmacokinetic/metabolic studies that the most sensitive species shows a different toxicokinetic behaviour than humans and is therefore less relevant as a predictor of human toxicity than another toxicity test species
- that the toxic effect that has the lowest NOAEL is not relevant for humans, or
- that the lowest NOAEL is derived from an inadequate or invalid study.

Thus it is emphasised that the full database must be used and all relevant findings correlated when determining the most appropriate health endpoint.

It is important to note also that in public or occupational health risk assessments, establishing a NOAEL is likely to be influenced by a consideration of the relevant route(s) of exposure and experimental design.

The selection of the NOAEL can be significantly influenced by:

- the selection of doses used in the study – the 'real' NOAEL is likely to lie somewhere between the apparent NOAEL and LOAEL doses (if there is a relatively wide margin between doses used in the study, a higher NOAEL might have been obtained if doses had been more appropriately spaced)
- the number of test subjects in the dose levels – a smaller number of test animals per dose in a study compromises the statistical power of being able to discriminate between dose levels that produce an 'effect', compared with those where the incidence of disease or toxicity is comparable to the 'controls' or untreated animals
- the extent to which disease or toxicity associated with administration of the test agent can be discriminated from disease processes that occur naturally during ageing. This is particularly true of neoplastic responses, where it may be difficult to 'score' the number of neoplasms at different stages of the life span of the test animals, where the progression through a series of pathological changes is not well delineated. Where the progression of toxicity is time related and possibly reversible if exposure ceases, the duration of treatment becomes a more critical factor in the experimental design.

An ADI or TDI is derived from the NOAEL (or LOAEL) as follows:

$$\text{ADI or TDI} = \frac{\text{NOAEL}}{\text{SF}}$$

These exposure limits are derived by first determining the NOAEL or, if the NOAEL cannot be determined, taking the LOAEL and dividing the value by factors to account for:

- inter-species differences (extrapolating from animals to humans)
- intra-species differences (differing sensitivities between individuals)
- the severity of the adverse effect
- the quantity and quality of the scientific data.

The general approach to calculating an ADI/TDI follows the principles initially outlined in the IPCS *Environmental health criteria monograph* No. 104 (WHO 1990). The uncertainty inherent in extrapolation between and within species has generally been dealt with by using safety (uncertainty) factors.

Historically, the most common overall factor used by a number of regulatory bodies is 100, comprised of 10 to account for uncertainties in inter-species extrapolation, and 10 to account for intra-species variability. An additional factor of 10 is sometimes used if the NOAEL was not established in the study and the LOAEL used instead, if the study used to determine the ADI/TDI must be based on a relatively short-term study (e.g. 28–90 days) or if a large toxicological database has not been assessed. Application of additional factors needs careful consideration for new industrial chemicals, where the available toxicological databases may be less comprehensive than those for new agricultural chemicals, proposed food additives or medicines (human and animal). The overall factor can range from 10 to 10,000, depending on the source and quality of data, the biological relevance of the endpoint, and the hazard assessment (carried out on a case-by-case basis). In general terms only, a safety factor of 10 would apply when appropriate human data were available.

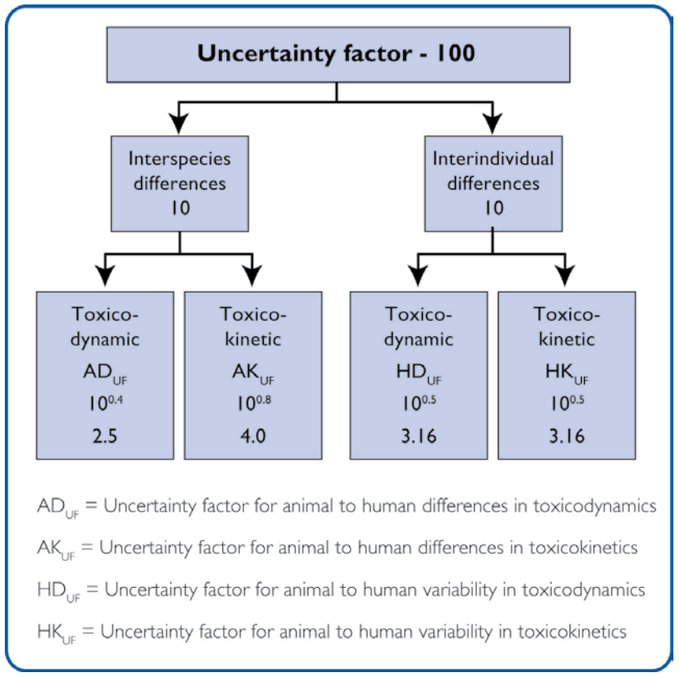
From the data available on humans and experimental animals, it appears that inter-species and intra-species differences are, in general, less than 10, hence the often-used overall safety factor of 100 for these two factors is conservative and adequately protective of public health (Johannsen 1990; Renwick & Walker 1993).

One of the outcomes of an IPCS program (IPCS 2005) to develop chemical-specific adjustment factors (CSAFs) was to further refine the breakdown of the conventionally used 100x safety factor by incorporating figures based on inter-species and intra-species toxicokinetic and toxicodynamic variation. The IPCS proposal for the default CSAFs is set out in Figure 23.

The IPCS program recommends using chemical-specific data to replace default values where adequate data is available, and outlines the nature of data on toxicokinetic and toxicodynamic variation that could be used. The program recognises that the combined uncertainty factor (CUF) based on CSAFs could be less than, or more than, the common default value of 100, but notes that this should be made transparent to the risk manager. It still recognises the need to add additional uncertainty factors when the quality of the studies is deficient or where significant data gaps occur.

The decision on the magnitude of factors to use is predominantly based on expert or informed judgement. While this approach to selecting the number and magnitude of the safety factors can appear to be somewhat arbitrary, improved knowledge of the biological processes that cause inter- and intra-species variation (e.g. metabolic and other pharmacokinetic rate differences) have generally supported the choice of the default safety factors.

Figure 23: Proposed subdivision of default uncertainty factors to be used in risk assessment



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It is generally accepted that if the magnitude of the overall safety factor approaches or exceeds 5,000, this is effectively an admission that there is insufficient knowledge of the environmental hazard under consideration and that the underlying data may be unsuitable to support a risk assessment. US EPA practice has been to not recommend an RfD/RfC if the combined uncertainty factor exceeds 3,000 (NRC 2008). Where a precautionary approach requires the application of such large uncertainty factors in setting a health-based guideline value, it is inevitable that when better information becomes available, the consequent change in the numerical value (often an increase) can reduce community confidence in its health-protectiveness.

However, Gaylor et al. (1999), when commenting on the possible use of a benchmark dose approach (using BMD_{10}) as a point of departure, recommended the use of a default uncertainty factor of 10,000 for irreversible adverse effects (e.g. cancer) with a smaller default uncertainty factor of 1,000 for reversible adverse effects. The argument was based on the fact that BMD_{10} approximates the LOAEL dose in conventional threshold-type risk assessments.

This update of enHealth guidance on EHRA commends the IPCS approach to selecting and justifying CSAFs and recommends that it be adopted in EHRA practice in Australia when relevant data is available.

5.7 TOXICOLOGICAL REFERENCE VALUES DERIVED USING A NON-THRESHOLD APPROACH

The two toxicological reference values that may be developed using a non-threshold approach are:

- *cancer slope factor (CSF)*: This is the plausible upper-bound estimate of the probability of a carcinogenic response per unit of intake over a lifetime; it is expressed in units $(mg/kg/d)^{-1}$
- *unit risk factor (URF):* This is an expression of carcinogenic potency in concentration terms, expressed as the probability of cancer per unit of an exposure medium (e.g. per μg/L of water, per $\mu g/m^3$ of air *or ppm).*

The CSF is used in EHRA to estimate the upper-bound probability that cancer will develop over a lifetime of exposure to a chemical at a specific level of intake. It is the slope of a linear extrapolation from the upper-bound estimate of a POD dose to zero.

The URF can be derived directly from inhalation or drinking-water studies depending on which media is being assessed. Where such data is not directly available, these unit risks can be derived by converting an oral CSF with units of $mg/kg/d^{-1}$ to a concentration of the substance in air, water or other media. These extrapolations often assume default intake rates for the specified media (e.g. an inhalation rate of $20m^3$ per day of air, or ingestion of 2 L/day of water and a body weight of 70 kg).

The conversion equation most commonly used is:

Inhalation URF $(\mu g/m^3)^{-1}$ =

$$\frac{\text{CSF } (mg/kg/d)^{-1} \times 20\ m^3/d}{70\ kg\ BW \times 1000\ \mu/mg}$$

(BW = body weight)

Where different default values are used (e.g. those recommended in the *Australian exposure factor guidance* document – see Chapter 4), it may be necessary to adjust CSFs derived by the US EPA or in Integrated Risk Information System (IRIS) databases.

Recent US EPA (2009a) guidance (RAGS-F) indicates that inhalation risks should be assessed by calculating an exposure-adjusted air concentration, which is then used in EHRA risk characterisation equations. This means that exposure estimates are no longer adjusted based on inhalation rate or body weight, and the only difference in risk estimates between a child and an adult is the exposure time.

The application of these risk factors is to calculate the probability of a finite increase in cancer risk over a lifetime, according to the equation:

Increased lifetime cancer risk (ILCR) = chronic daily intake (mg/kg/d) × CSF $(mg/kg/d)^{-1}$

or

Increased lifetime cancer risk (ILCR) = exposure concentration × URF

The outcomes of cancer risk estimates based on CSF or URF calculations are the prediction of an increased lifetime risk of developing cancer. The intake estimate (or exposure concentration) must be averaged over the lifetime of expected exposure (default 70 years). The ILCR must be clearly presented so that the cancer estimate over 70 years cannot be misrepresented as an estimate of annual cancer risk.

To convert a lifetime to an annual risk estimate is approximated by a simple division by the standardised lifetime duration (70 years in most jurisdictions). In reality for cancer, incidence will be greater in the later part of the 70-year window.

The step-wise process for deciding on the dose–response data to adopt for the EHRA of carcinogens (or potential carcinogens) is set out in Figure 15 (Section 3.10.3). This decision-making process recommends use of a BMD approach to selecting a POD for risk assessment, once a decision has been made on classification of the COPC as a carcinogen and a carcinogenic risk assessment approach is warranted. Where appropriate BMD data is not available, alternative dose–response data should be sourced, which may include the use of CSF (for genotoxic carcinogens) and ADI/TDI (for non-genotoxic carcinogens).

5.8 AGE-SPECIFIC ADJUSTMENT FACTORS

The US EPA has directed particular attention to the possibility that early-life exposure to a carcinogen may exacerbate risk to the extent that the default approach based on a whole-of-life CSF or URF may not be sufficiently protective (US EPA 2005a). The guidance is consistent with reviews of animal carcinogenicity bioassays relevant to the assessment of early-life susceptibility to carcinogens (Hattis et al. 2004; 2005). US EPA guidance on early-life exposure to carcinogens for which a mutagenic mode of action (MoA) has been reasonably established has been summarised in the 2005 supplemental guidance (US EPA 2005c) and incorporated into the most recent RAGS-F guidance (US EPA 2009a p. 23).

The guidance indicates that an additional safety factor should to be applied to mutagenic carcinogens as follows:

- tenfold adjustment for exposures during the first 2 years of life
- threefold adjustment for exposures from ages 2 to <16 years of age
- no adjustment for exposures after turning 16 years of age.

Carcinogens identified by the US EPA as having a mutagenic mode of action (as of 2005) are discussed in US EPA 2005a. This list includes benzo(a)pyrene, and the additional safety factors recommended by the US EPA have accordingly been incorporated into the derivation of HILs for benzo(a)pyrene in the revision to the contaminated sites NEPM (NEPC 2010).

5.9 COMBINING RISK ESTIMATES

Where there are several exposure pathways, the incremental lifetime cancer risk (ILCR) estimate is simply summed for each of the relevant pathways to get a combined risk estimate (see Section 5.4). However, some caution should be exercised in adopting this simple summation approach (US EPA 1989). Since the CSF is an upper 95th percentile estimate of cancer potency, simple addition of 95th percentiles is strictly not correct. Such an approach can add unnecessary conservatism to the aggregate risk estimate. The CSF are not weighted according to the strength of evidence that underpins their categorisation. All classes of carcinogenic categorisation are given equal weight, including those where either human or animal data (or both) drive the categorisation.

There may be different CSF estimates for a single chemical where the cancer data relates to different tumour sites. The EHRA usually uses the CSF that predicts the highest risk. If cancer potency and/or the type of tumour produced differs according to the route of exposure, the aggregate risk may need to reflect this difference.

For example, in the case of benzo(a) pyrene (BaP), the representative carcinogenic polycyclic aromatic hydrocarbon (PAH), the CSF used for carcinogenic risk assessment in the