- establishing ADIs for chemicals likely to be present as impurities in pharmaceutical manufacturing (Dolan et al. 2005)
- use as a screening tool for risk assessment of air toxics (Drew & Frangos 2007)
- (more recently in Australia) setting concentrations that would be unlikely to pose a human health risk for chemicals likely to be present in recycled water (NRMMC, EPHC, NHMRC 2008).

The following description of the TTC approach is taken from the *Australian guidelines for water recycling* (NRMMC, EPHC, NHMRC 2008).

In establishing TTCs for chemicals that are not carcinogens, an evaluation of toxicological databases undertaken for non-carcinogenic endpoints is used (Munro et al.1996; 1999; Kroes et al. 2000; 2004). In these evaluations, some 900 non-carcinogenic organic chemicals were assigned to three 'classes' based on their chemical structure, presence of structural alerts for toxicity and known metabolic pathways, according to the classification scheme of Cramer et al. (1978). The Cramer classification scheme divides chemicals into three classes according to their predicted toxicity as judged from structural alerts and metabolism:

- *Class I:* substances of simple chemical structure with known metabolic pathways and innocuous end products that suggest a low order of toxicity
- *Class II:* chemical structures that are intermediate they are chemicals that are less innocuous they may contain reactive functional groups but do not contain the structural features suggestive of toxicity
- *Class III:* chemicals for which structural features or likely metabolic pathways permit no strong presumption of safety, or may even suggest significant toxicity.

The 5th percentile NOEL (no observed effect level) of each of the three Cramer classes was divided by an uncertainty (safety) factor of 100 to yield TTC values that are somewhat higher than those created by the FDA for carcinogens. No formal stratification of toxicological endpoints was used in establishing NOAELs for the three Cramer chemical classes. The NOAELs are:

- *Class I:* 3 mg/kg/day (equates to a TTC of 30 µg/kg bw/day)
- *Class II:* 0.9 mg/kg/day (equates to a TTC of 9 µg/kg bw/day)
- *Class III:* P 0.15 mg/kg/day (equates to a TTC of 1.5 µg/kg bw/day).

In applying the TTCs to derivation of drinking-water guidelines, a more conservative approach has been applied to reflect the use of safety factors used in the ADWG (NHMRC, NRMMC 2004). These guidelines apply a safety factor of 1,500 to organic chemicals (95th percentile). To achieve this, an additional safety factor of 15 has been applied in converting TTCs (which already include a safety factor of 100) to drinking-water guidelines.

5.13.1 Can the TTC approach be applied to carcinogens?

A generic approach has been developed for potentially genotoxic carcinogens using the TTC approach (NRMMC, EPHC, NHMRC 2008).

The FDA (1995; CFR 2001) regulatory TTC is based on a carcinogenic potency database of more than 500 chemicals examined in more than 3,500 experiments. The FDA (1995; CFR 2001) and other leading researchers (Munro et al.1996; 1999) have concluded that, if no toxicological data is available to derive a health-based guideline for a chemical, intakes of 1.5 µg/person/day (0.02 µg/kg bw/day for a body weight of 70 kg) are unlikely to result in appreciable health risk, even if the substance was later found to be a carcinogen. According to Munro (1990), a daily intake at the TTC of 0.02 µg/kg bw corresponds to a 96 per cent probability that the lifetime risk of cancer would be less than one in a million (1×10^{-6}).

The TTC that is protective of cancer endpoints is termed a 'generic TTC', to differentiate it from the TTC developed for non-cancer endpoints and using the Cramer classification. The TTC estimate of 0.02 µg/kg bw/day is conservative, erring on the side of safety, because of the numerous compounding conservative assumptions used to derive the low-dose cancer risk estimates (Barlow et al. 2001; Kroes et al. 2004).

5.14 QSAR AND READ ACROSS TECHNIQUES

Better understanding of structure–activity relationships (SAR), especially when combined with quantitative information (quantitative structure–activity relationship – QSAR) may facilitate prediction of toxicological properties of chemicals without testing, or where no testing has been done to establish the toxicological profile of a new chemical. There will also be consequent benefits in terms of lower costs, shorter testing time frames and less use of animals. QSAR may also be useful in complementing the increasing use of *in vitro* and *in silico* technologies to provide insights into toxicological properties of chemicals without using live animals. As well as facilitating chemical and drug development by industry, regulatory recognition of QSAR is also growing in importance. For example, it has been suggested that up to 10 per cent of new chemical notifications in the UK include QSAR data, and this proportion is expected to grow over time.

The implementation of the REACH (Registration, Evaluation, and Authorization of Chemicals) program in Europe, as well as the increasing number of high production volume (HPV) chemicals requiring assessment in OECD programs, should provide impetus for the further development and use of SAR and QSAR techniques.

SARs already utilised in regulatory toxicology include:

- recognition of structural elements that act as alerts for particular types of toxicological behaviour (e.g. epoxides or other reactive metabolic intermediates which that confer DNA- and protein-interactive capabilities)
- recognition of common structural elements in chemical classes that are consistent with known patterns of toxicity (e.g. organophosphonate groupings that enable phosphorylation of the active site on acetylcholinesterases)
- grouping of chemicals based on recognisable structural features that lead to common toxicological properties (e.g. dioxin-like chemicals and others that interact with aryl hydrocarbon (Ah) or peroxisome proliferator (PPAR) receptors)
- computational systems that use a combination of features of the molecule (electronic, physico-chemical, size, hydrophobicity, etc.) to predict properties (e.g. EPIWIN)
- knowledge-based or rule-based systems that compare many parameters of a dataset and enable predictions of the properties of chemicals that share common structural features. One such commercially available system is DEREK, a computer-based SAR program (Sanderson and Earnshaw, 1991), although its utility is mainly limited to predicting sensitisation and carcinogenic properties.

Another alternative approach when data on a specific chemical is lacking is to use 'read across' techniques to make informed predictions about the toxicity profile from a known, and closely related chemical. Read across is primarily useful for hazard prediction. It has limited capabilities for predicting quantitative dose–response behaviour. It relies on there being a high-quality toxicological dataset for the reference compound.

5.15 UNCERTAINTY AND SENSITIVITY ANALYSIS

5.15.1 General

At the completion of a risk assessment, it may become apparent that there are inherent limitations to the outcomes, such as:

- information gaps (e.g. effects of mixtures, low-level and variable exposures over time, relative contributions of lifestyle factors versus other environmental hazards, variations in sensitivity)
- poor exposure information (e.g. complex mixtures of hazards with complex behaviours in the environment, limited knowledge about the actual or potential population and sensitive sub-populations geographic, variations in exposure)
- limitations of toxicological and epidemiological research (e.g. small populations, limited exposure information, multifactorial causes of many diseases)
- 'background noise' affecting research into common diseases or symptoms, population heterogeneity, and the fact that it is expensive and time consuming.

Some of these limitations may be apparent before beginning the risk assessment process. For example:

- the large number of combinations of hazards, exposures and health states leading to complexity that cannot be readily resolved
- complex causality for many of the health conditions addressed in the EHRA
- confidentiality of health and commercial information preventing full disclosure
- the atmosphere of fear, antagonism and distrust being so charged that it inhibits meaningful dialogue between the stakeholders.

In formulating an EHRA report it is crucial that all uncertainties and knowledge gaps be acknowledged and guide the development of risk management options (see Chapter 7). It is also important that these uncertainties be managed in a consistent and scientifically defensible way, and that there is a clear explanation of how 'scientific judgement' may have been applied to the management of these uncertainties. This may include careful description of definitions of default parameter inputs or using more complex probabilistic approaches to defining bounding values, or intervals within which the risk assessor expects the best estimates of risk to lay.

It may be important to carry out proper sensitivity and uncertainty analyses so the level of effort expended in an EHRA can be appropriately matched to the precision of the desired outcomes (NRC 2008). If the outcomes or advice to the risk manager will not be materially affected by adopting more simplistic approaches, it may be wasteful of scarce resources to use more sophisticated methodologies (e.g. deterministic versus Monte Carlo assessment of exposures). Similarly, the sophistication of analytical techniques used to measure environmental concentrations should be matched to the level of precision required in the EHRA.

5.15.2 Uncertainty analysis

Uncertainty in health risk assessment is the lack of knowledge about the correct value such as a specific exposure measure or estimate. Uncertainty is

distinguished from variability, which refers to true differences in attributes due to diversity or heterogeneity; variability cannot be reduced by further measurement or study, although it can be better characterised (NRC 2008).

Both uncertainty and variability contribute to uncertainty in the estimation of risk and should be adequately assessed in a risk assessment. Such consideration needs to be done transparently so that all users of the risk assessment can understand the approach taken.

An analysis of the uncertainty in the risk assessment is important because of the following:

- Information from different sources carries different kinds of uncertainty and knowledge of these differences is important when uncertainties are combined for characterising risk.
- The risk assessment process, with risk management input, involves decisions regarding the collection of additional data (versus living with uncertainty). In the risk characterisation, a discussion of the uncertainties will help to identify where additional information/data could contribute significantly to reducing uncertainties in the risk assessment.
- A clear and explicit statement of the strengths and limitations of a risk assessment requires a clear and explicit statement of related uncertainties (US EPA 1995b).
- Characterising uncertainty in a risk assessment informs the stakeholders about the range of possible risks from an exposure. Risk estimates may sometimes diverge widely (NRC 2008).
- Characterising the uncertainty in a risk assessment associated with a given decision informs the decision maker about the range of potential risks that may result from the decision (NRC 2008).

Uncertainty analysis is generally a qualitative process; however, in some cases it can be semi-quantitative or quantitative.

The first step should be a consideration of the conceptual site model and what aspects of that model are uncertain and how that uncertainty has been accounted for.

The second most important part of the uncertainty assessment is an evaluation of the uncertainty and variability in the data available relating to the site, situation or activity being assessed. Data will always be limited. However, the risk estimates based on even quite limited data can be fit for purpose if the exposure concentrations are a long way below (or above) toxicity reference values which indicate that the risks are very low (or very high). Decision making based on such uncertain but quite clear results is straightforward. Where risks are close to or slightly above the relevant toxicity reference values or 'target risk' level (the 'grey' zone), the issue of the uncertainty and variability in the data becomes much more important and so the uncertainty assessment needs to be more detailed.

When assessing risks, uncertainty can arise from missing or incomplete information, be incorporated into the scientific theory behind the model used to make predictions, and factors affecting a particular parameter, for example, errors in sampling. Such uncertainty has the potential to cumulatively overestimate or underestimate risk during an assessment. An assessment of uncertainty is a part of the health risk assessment process and consequently must be addressed for each step of the risk assessment and for its cumulative effect from all of the steps.

There are three broad types of uncertainty (US EPA 1992):

- *Scenario uncertainty:* uncertainty arising from missing or incomplete information such as descriptive errors, aggregation errors, errors in professional judgement, and incomplete analysis.
- *Parameter uncertainty:* uncertainty affecting a particular parameter such as measurement errors, sampling errors, variability, and use of generic or surrogate data.
- *Model uncertainty:* uncertainty in scientific theory affecting the ability of a model to make predictions.

NRC (2008) provides a detailed evaluation of the techniques currently provided for in US EPA guidance and concludes that although a number of usable methodologies are provided, it is unclear what level of detail is required to capture and communicate key uncertainties. A further comment is that quantitative methods suffer from the difficulty in sensibly quantifying all uncertainties, and that the apparent precision of quantitative analysis for some uncertainties may distract attention from other, possibly equally important but unquantifiable, uncertainties.

In most health risk assessments, it is unlikely that quantitative uncertainty analysis will provide value given the effort required to undertake it. A clear qualitative analysis is considered sufficient in most cases to provide the communication of the effects of uncertainty that is necessary.

NRC (2008) and IPCS (2008) provide useful guidance on the principles to be adopted for uncertainty analysis; these have been adapted for specific relevance to the enHealth document.

- Risk assessments should provide qualitative (as a minimum) or quantitative description of uncertainty and variability consistent with available data. The information required to conduct detailed uncertainty analysis may not be available in many situations.
- Sensitive sub-populations should be considered to the extent that they are not covered by the selected toxicity criteria (generally they will be).
- The uncertainty analysis should seek to communicate which uncertainties are most important to the conclusions of the risk assessment.
- The level of detail in the uncertainty analysis should be commensurate with the scope of the risk assessment.
- Uncertainty analysis should be expressed in terms that can be understood by the risk manager and other stakeholders.
- Uncertainty and variability should be kept conceptually separate.

The combination of uncertainty in the scientific data and assumptions (the 'inputs') and inability to validate assessment results directly or to isolate and evaluate the impact of a resulting decision (the 'outputs') creates a situation in which decision makers, the scientific community, the public, industry and other stakeholders have little choice but to rely on the overall quality of the many processes used in the conduct of risk assessment to provide some assurance that the assessment is aligned with societal goals (NRC 2008).

5.15.3 Sensitivity analysis

Sensitivity analysis is an important final step in the risk characterisation process, especially where modelling has been used to determine important components of the EHRA (see Section 8.7.4). It provides a quantitative estimate of the effect of uncertainty and/or variability in the input parameters on the results of the risk assessment and it should be undertaken when a risk assessment is conducted using a deterministic exposure model.

While a single value must be entered for each parameter in a deterministic model, it is unlikely that reasonable inputs for each parameter can be limited to a single value. This may be due to uncertainty and/or variability. A range of reasonable values will be defined as appropriate for a given input parameter. Sensitivity analysis is the process of changing variables used as input parameters one at a time to determine how such changes influence the final output. Variables are changed within a defined range while leaving the others constant and determining the effect on the output – the risk estimate. The procedure involves fixing each uncertain quantity, one at a time, at its credible lower bound and then its upper bound (holding all other at their medians), and then computing the outcomes for each combination of values (US EPA 1992). It can be used to test the effects of both uncertainty and variability in input values. The substitution of input parameters should be informed by knowledge of the upper and lower bounds of the expected parameter distributions.

Sensitivity analyses can be used to identify the most important input variables (or groups of variables) that are critical to the outcome of the risk assessment. It follows that variation of some inputs may have inconsequential effects. Sensitivity analysis can develop bounds on the distribution of exposure or risk. A sensitivity analysis can also estimate the range of exposures or risk that result from combinations of minimum and maximum values for some parameters and mid-range values for others (US EPA 1989). Effort may then be directed to the collection of additional data for these important variables; as additional data is collected, the uncertainty in the 'true' value is reduced, and it may be possible to define a smaller range for a given parameter. The uncertainty in the results of the risk assessment may therefore be reduced.

All risk assessments where conclusions are derived using modelling should incorporate a sensitivity analysis and describe the variability in the model outputs generated by plausible variation in the inputs. Note that some input variables may be connected and unable to vary independently. Monte Carlo models, where inputs are described by probability distribution functions, provide probability distribution function outputs.

The Monte Carlo method reduces the requirement for sensitivity analysis but may not eliminate it, depending on the model used.

5.16 INTERPLAY OF SCIENTIFIC JUDGEMENT AND SCIENCE POLICY

The interplay between these processes and the importance of providing appropriate explanation of assumptions, the use of scientific judgement, and the overlay of 'science policy' considerations is illustrated in the ebb and flow of regulatory actions and interpretations surrounding the presence of chloroform in drinking water and its surrogacy as an indicator of disinfection by-products (Box 1).