資料４－１

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不確実係数（抜粋）

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Chapter 8. Chemical aspects

8.2 Derivation of chemical guideline values

Guideline Values are derived for many chemical constituents of drinking-water. A Guideline Value represents the concentration of a constituent which does not result in any significant risk to health over a lifetime of consumption.

There are two principal sources of information on health effects resulting from exposure to chemicals that can be used in deriving guideline values. The first is investigation in human populations. The value of such studies for many substances is limited, owing to lack of quantitative information on the concentration to which people are exposed or on simultaneous exposure to other agents. However, for some substances such studies are sometimes the primary basis on which guidelines are developed. The second, and most frequently used source of information is toxicity studies using laboratory animals. The limitations of toxicology studies include the relatively small number of animals used and the relatively high doses administered, which creates uncertainty as to the relevance of particular findings to human health. This is because there is a need to extrapolate the results to the low doses to which human populations are usually exposed. In most cases, the study used to derive the guideline value is supported by a range of other studies, including human data, and these are also considered in carrying out a health risk assessment.

In order to derive a guideline value to protect human health, it is necessary to select the most suitable study or studies. Data from well-conducted studies, where a clear dose-response relationship has been demonstrated, are preferred. Expert judgement was exercised in the selection of the most appropriate study from the range of information available.

8.2.1 Approaches taken

To approaches to the derivation of Guideline Values are used: one for "threshold chemicals" and the other for "non-threshold chemicals" (mostly genotoxic carcinogens). It is generally considered that the initiating event in the process of genotoxic chemical carcinogenesis is the induction of a mutation in the genetic materials (DNA) of somatic cells (i.e. cells other than ova or sperm), and that there is a possibility of risk at any exposure (i.e. no threshold). On the other hand, there are carcinogens that are capable of producing tumours in animals or humans without exerting a genotoxic activity, but acting through an indirect mechanism. It is generally believed that a threshold dose exists for non-genotoxic carcinogens.

In deriving Guideline Values for carcinogens, consideration was given to the potential mechanism/s by which the substance may cause cancer, in order to decide whether a threshold or non-threshold approach should be used (see 8.2.1 for Threshold chemical effect and 8.2.6 Non-threshold chemicals).

The evaluation of the potential carcinogenicity of chemical substances is usually based on long-term animal studies. Sometimes data are available on carcinogenicity in humans, however mostly from occupational exposure.

On the basis of the available evidence, IARC categorises chemical substances with respect to their potential carcinogenic risk into the following groups:

Group 1: the agent is carcinogenic to humans
Group 2A: the agent is probably carcinogenic to humans
Group 2B: the agent is possibly carcinogenic to humans
Group 3: the agent is not classifiable as to its carcinogenicity to humans

Group 4: the agent is probably not carcinogenic to humans

According to IARC, these classifications represent a first step in carcinogenic risk assessment, which leads to a second step of quantitative risk assessment where possible. In establishing guideline values for drinking-water, the IARC evaluation of carcinogenic compounds is taken into consideration where available.

8.2.2 Threshold chemicals

For most kinds of toxicity, it is generally believed that there is a dose below which no adverse effect will occur. For chemicals that give rise to such toxic effects, a tolerable daily intake (TDI) should be derived as follows, using the most sensitive endpoint in the most relevant study, preferably in drinking water:

$$TDI = (NOAEL \text{ or } LOAEL) / UF$$

Where: NOAEL = no-observed-adverse-effect-level
LOAEL = lowest-observed-adverse-effect-level
UF = Uncertainty factor

The guideline value (GV) is then derived from the TDI as follows:

$$GV = (TDI \times bw \times P) / C$$

Where:

bw = body weight (see Annex 2)
P = fraction of the TDI allocated to drinking-water
C = daily drinking-water consumption (see Annex 2)

Tolerable daily intake

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 over a lifetime without appreciable health risk.

Over many years, JECFA and JMPR have developed certain principles in the derivation of acceptable daily intakes (ADIs). These principles have been adopted where appropriate in the derivation of TDIs used in developing guideline values for drinking-water quality.

ADIs are established for food additives and pesticide residues that occur in food for necessary technological purposes or plant protection reasons. For chemical contaminants, which usually have no intended function in drinking-water, the term "tolerable daily intake" is seen as more appropriate than "acceptable daily intake", as it signifies permissibility rather than acceptability.

As TDIs are regarded as representing a tolerable intake for a lifetime, they are not so precise that they cannot be exceeded for short periods of time. Short-term exposure to levels exceeding the TDI is not a cause for concern, provided the individual's intake averaged over longer periods of time does not appreciably exceed the level set. The large uncertainty factors generally involved in establishing a TDI (see below) serve to provide assurance that exposure exceeding the TDI for short periods is unlikely to have any deleterious effects upon health. However, consideration should be given to any potential acute effects that may occur if the TDI is substantially exceeded for short periods of time.

No-observed-adverse-effect-level and lowest-observed-adverse-effect-level

The NOAEL is defined as the highest dose or concentration of a chemical in a single study, found by experiment or observation, that causes no detectable adverse health effect. Wherever possible, the NOAEL is based on long-term studies, preferably of ingestion in drinking-water. However, NOAELs obtained from short-term studies and studies using other sources of exposure (e.g., food, air) may also be used.

If a NOAEL is not available, a LOAEL may be used, which is the lowest observed dose or concentration of a substance at which there is a detectable adverse health effect. When a LOAEL is used instead of a NOAEL, an additional uncertainty factor is normally applied (see below).

Uncertainty factors

The application of uncertainty factors has been widely used in the derivation of ADIs for food additives, pesticides and environmental contaminants. The derivation of these factors requires expert judgement and careful consideration of the available scientific evidence.

In the derivation of guideline values, uncertainty factors are applied to the NOAEL or LOAEL for the response considered to be the most biologically significant.

In relation to exposure of the general population, the NOAEL for the critical effect in animals is normally divided by an uncertainty factor of 100. This comprises two 10-fold factors, one for interspecies differences and one for interindividual variability in humans (see Table 8.2). Extra uncertainty factors may be incorporated to allow for database deficiencies and for the severity and irreversibility of effects.

Table 8.2 Source of uncertainty in derivation of guideline values

Source of uncertainty	Factor
Interspecies variation (animals to humans)	1 - 10
Intraspecies variation (individual variations within species)	1 – 10
Adequacy of studies or database	1 – 10
Nature and severity of effect	1 – 10

Factors lower than 10 were used, for example, for interspecies variation when humans are known to be less sensitive than the animal species studied. Inadequate studies or databases include those where a LOAEL was used instead of a NOAEL and studies considered to be shorter in duration than desirable. Situations in which the nature or severity of effect might warrant an additional uncertainty factor include studies in which the end-point was malformation of a foetus or in which the end-point determining the NOAEL was directly related to possible carcinogenicity. In the latter case, an additional uncertainty factor was usually applied for carcinogenic compounds for which the guideline value was derived using a TDI approach.

The total uncertainty factor should not exceed 10,000. If the risk assessment would lead to a higher uncertainty factor, then the resulting TDI would be so imprecise as to lack meaning. For substances for which the uncertainty factors were greater than 1,000, guideline values are designated as provisional in order to emphasise the higher level of uncertainty inherent in these values.

The selection and application of uncertainty factors are important in the derivation of guideline values for chemicals, as they can make a considerable difference to the values set. For contaminants for which there is sufficient confidence in the database, the guideline value was derived using a smaller uncertainty factor. For most contaminants, however, there is greater scientific uncertainty, and a relatively large uncertainty factor was used. Hence, there may be a large margin between the guideline value and the concentration of the substance which would actually cause adverse health effects. This flexible approach to the use of uncertainty factors enables the particular attributes of the chemical and the data available to be considered in the deriving the guidelines. Where uncertainty factors have been used on calculating the guideline value, it is presented as part of the rationale for guideline derivation.

Allocation of intake

Drinking-water is not usually the sole source of human exposure to the substances for which guideline values have been set. In many cases, the intake of chemical contaminants from drinking-water is small in comparison with that from other sources such as food and air. Guideline values derived using the TDI approach take into account exposures from all sources by apportioning a percentage of the TDI to drinking-water. This approach ensures that total daily intake from all sources (including drinking-water containing concentrations of the substance at or near the guideline value) does not exceed the TDI.

Wherever possible, data concerning the proportion of total intake normally ingested in drinking-water (based on mean levels in food, air and drinking-water) or intakes estimated on the basis of consideration of physical and chemical properties were used in the derivation of the guideline values. Where such information was not available, an arbitrary (default) value of 10 per cent for drinking-water was used. This default value is, in most cases, sufficient to account for additional routes of intakes (i.e., inhalation and dermal absorption) of contaminants in water. In some cases a specific discussion has been made of the potential for exposure from intake through inhalation and dermal uptake in bathing and showering where the allocation of the ADI to drinking water is greater than 10%.

It is recognised that exposure from various media may vary with local circumstances. It should be emphasised, therefore, that the derived guideline values apply to a typical exposure scenario or are based on default values that may nor be applicable for all areas. In those areas where relevant exposure data are available, authorities are encouraged to develop context-specific guideline values that are tailored to local circumstances and conditions. For example, in areas where the intake of a particular contaminant in drinking-water is known to be much greater than that from other sources (i.e., air and food), it may be appropriate to allocate a greater proportion of the TDI to drinking-water to derive a Guideline Value more suited to the local conditions. In addition, in cases in which guideline values are exceeded, efforts should be made to assess the contribution of other sources to total intake, if practicable, exposure from these sources should be minimised.

Significant figures

The calculated TDI is used to derive the guideline value, which was then rounded to one significant figure. In some instances, ADI values with only one significant figure set by JECFA or JMPR were used to calculate the guideline value. The guideline value was generally rounded to one significant figure to reflect the uncertainty in animal toxicity data and exposure assumptions made.

8.2.3 Non-threshold chemicals

In the case of compounds considered to be genotoxic carcinogens, guideline values were normally determined using a mathematical model. Although several models exist, the linearised multistage model was generally adopted in the development of these guidelines. Other models were considered more appropriate in a few cases. Guideline values presented are the concentrations in drinking-water associated with an estimate upper bound excess lifetime risk of 10^{-5} (or one additional cancer per 100,000 of the population ingesting drinking-water containing the substance at the guideline value for 70 years).

It should be emphasized that guideline values for carcinogenic compounds computed using mathematical models must be considered at best as hypothetical and a rough estimate of the upper bound cancer risk. These models do not usually take into account a number of biologically important considerations, such as pharmacokinetics, DNA repair, or protection by the immune system. They also assume the validity of extrapolation of very high dose exposures in test animals to very low dose exposures in humans. As a consequence, the models used are conservative (i.e. err on the side of caution).

8.2.4 Data quality and peer review

The assessment of the toxicity of drinking-water contaminants has been primarily made on the basis of published reports from peer reviewed open literature, reviews by recognised international bodies or national reviews recognised to be of high quality, information submitted by governments and other interested parties, and to a limited extent, unpublished proprietary data. In the development of the guideline values, existing international approaches to developing guidelines were carefully considered. In particular, previous risk assessments developed by the International Programme on Chemical Safety (IPCS) in Environmental Health Criteria monographs, the International Agency for Research on Cancer (IARC), the Joint FAO/WHO Meetings on Pesticide Residues (JMPR), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) were reviewed. These assessments were relied upon except where new information justified a reassessment but the quality of new data was critically evaluated before it was used in any risk assessment. The primary use of unpublished proprietary data has been in the evaluation of pesticides. Current revisions and future assessments of pesticides will only take place through

WHO/IPCS/JMPR/JECFA processes.

8.2.5 Quality of data for derivation of guideline values

WHO has endeavoured to provide as much assistance as possible to users of the Guidelines by developing guideline values wherever possible. On occasion this has required the use of very large uncertainty factors and guideline values that are designated as provisional. One situation where this occurs is when the quality of health-effects data relevant to guideline derivation is lower than what is generally available to other chemicals. It is suggested that a formal guideline value for a substance in such circumstances might not be appropriate or even necessary. Instead where data are considered to be highly uncertain, it would be appropriate to provide a health-based number in the summary for use in cases where needed, but not propose a formal health based guideline value. The substance would be listed as having been considered but would not have an associated guideline value. An example of the successful use of such an approach is iron.

In terms of the quality of data and peer review of such data required to develop a health based guideline value, the following are some general considerations. However, it is not expected that all these will be available:

- The studies have undergone international peer review (such as by IPCS, JECFA or JMPR) or high quality national peer review
- Oral studies are preferred (in particular, drinking-water studies), with the pure substance with appropriate dosing regime and a good quality pathology.
- A sufficiently broad database to be reasonably comfortable that potential toxicological end-points of concern have been identified.
- The quality of the studies is such that they are considered reliable, for example, there has been adequate consideration of confounding factors in epidemiological studies.
- There is reasonable consistency between studies; the endpoint and study used to derive a guideline value do not contradict the overall weight of evidence.
- For inorganic substances there is some consideration of speciation in drinking-water.
- There is appropriate consideration of multi-media exposure.