

Part 2. Chemical and physical aspects

12. Chemical and physical aspects: introduction

12.1 Background information used

The assessment of the toxicity of drinking-water contaminants has been made on the basis of published reports from the open literature, information submitted by governments and other interested parties, and unpublished proprietary data. In the development of the guideline values, existing international approaches to developing guidelines were carefully considered. 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. The quality of new data was critically evaluated prior to their use in risk assessment.

12.2 Drinking-water consumption and body weight

Global data on the consumption of drinking-water are limited. In studies carried out in Canada, the Netherlands, the United Kingdom, and the United States of America, the average daily *per capita* consumption was usually found to be less than 2 litres, but there was considerable variation between individuals. As water intake is likely to vary with climate, physical activity, and culture, the above studies, which were conducted in temperate zones, can give only a limited view of consumption patterns throughout the world. At temperatures above 25°C, for example, there is a sharp rise in fluid intake, largely to meet the demands of an increased sweat rate (1).

In developing the guideline values for potentially hazardous chemicals, a daily *per capita* consumption of 2 litres by a person weighing 60 kg was generally assumed. The guideline values set for drinking-water using this assumption do, on average, err on the side of caution. However, such an assumption may underestimate the consumption of water per unit weight, and thus exposure, for those living in hot climates as well as for infants and children, who consume more fluid per unit weight than adults.

The higher intakes, and hence exposure, for infants and children apply for only a limited time, but this period may coincide with greater sensitivity to some toxic agents and less for others. Irreversible effects that occur at a young age will have more social and public health significance than those that are delayed. Where it was judged that this segment of the population was at a particularly high risk from exposure to certain chemicals, the guideline value was derived on the basis of a 10-kg child consuming 1 litre per day or a 5-kg infant consuming 0.75 litre per day. The corresponding daily fluid intakes are higher than for adults on a body weight basis.

12.3 Inhalation and dermal absorption

The contribution of drinking-water to daily exposure includes direct ingestion as well as some indirect routes, such as inhalation of volatile substances and dermal contact during bathing or showering.

In most cases, the data were insufficient to permit reliable estimates of exposure by inhalation and dermal absorption of contaminants present in drinking-water. It was not possible, therefore, to address intake from these routes specifically in the derivation of the guideline values. However, that portion of the total tolerable daily intake (TDI) allocated to drinking-water is generally sufficient to allow for these additional routes of intake (see section 4.1). When there is concern that potential inhalation of volatile compounds and dermal exposure from various indoor water uses (such as showering) are not adequately addressed, authorities could adjust the guideline value.

12.4 Health risk assessment

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 studies on human populations. The value of such investigations is often limited, owing to lack of quantitative information on the concentrations to which people are exposed or on simultaneous exposure to other agents. The second, and the one used most often, is toxicity studies using laboratory animals. Such studies are generally limited because of the relatively small numbers of animals used and the relatively high doses administered. Furthermore, there is a need to extrapolate the results to the low doses to which human populations are usually exposed.

In order to derive a guideline value to protect human health, it is necessary to select the most suitable experimental animal study on which to base the extrapolation. 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.

12.4.1 Derivation of guideline values using a tolerable daily intake approach

For most kinds of toxicity, it is generally believed that there is a dose below which no adverse effects will occur. For chemicals that give rise to such toxic effects, a tolerable daily intake (TDI) can be derived as follows:

$$TDI = \frac{NOAEL \text{ or } LOAEL}{UF}$$

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:

$$GV = \frac{TDI \times bw \times P}{C}$$

where:

- *bw* = body weight (60 kg for adults, 10 kg for children, 5 kg for infants),
- *P* = fraction of the TDI allocated to drinking-water,
- *C* = daily drinking-water consumption (2 litres for adults, 1 litre for children, 0.75 litre for infants).

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 daily over a lifetime without appreciable health risk (2).

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 (3, 4).

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 (3).

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 (4). 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 (5). 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 toxic effects that may occur if the TDI is substantially exceeded for short periods of time (4).

The calculated TDI was 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 (4). The guideline value was generally rounded to one significant figure to reflect the uncertainty in animal toxicity data and exposure assumptions made. More than one significant figure was used for guideline values only where extensive information on toxicity and exposure to humans provided greater certainty.

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. Whenever 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 used (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 a careful sifting of the available scientific evidence.

In the derivation of the WHO drinking-water quality guideline values, uncertainty factors were applied to the lowest NOAEL or LOAEL for the response considered to be the most biologically significant and were determined by consensus among a group of experts using the approach outlined below:

<i>Source of uncertainty</i>	<i>Factor</i>
Interspecies variation (animals to humans)	1-10
Intraspecies variation (individual variations)	1-10
Adequacy of studies or database	1-10
Nature and severity of effect	1-10

Inadequate studies or databases include those that used a LOAEL 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 fetus or in which the end-point determining the NOAEL was directly related to possible carcinogenicity. In the latter case, an additional uncertainty factor was applied for carcinogenic compounds for which a guideline value was derived using a TDI approach (see section 12.4.2). Factors lower than 10 were used, for example, for interspecies variation when humans are known to be less sensitive than the animal species studied.

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 uncertainty factors were greater than 1000, guideline values are designated as provisional in order to emphasize the high 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 relatively little uncertainty, the guideline value was derived using a small uncertainty factor. For most contaminants, however, there is great scientific uncertainty, and a large uncertainty factor was used. Hence, there may be a large margin of safety above the guideline value before adverse health effects result.

There is considerable merit in using a method that allows a high degree of flexibility. However, it is important that, where possible, the derivation of the uncertainty factor used in calculating a guideline value is clearly presented as part of the rationale. This helps authorities in using the guidelines, as the safety margin in allowing for local circumstances is clear. It also helps in determining the urgency and nature of the action required in the event that a guideline value is exceeded.

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 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 exposure 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% for drinking-water was used. This default value is, in most cases, sufficient to account for additional routes of intake (i.e., inhalation and dermal absorption) of contaminants in water.

It is recognized that exposure from various media may vary with local circumstances. It should be emphasized, therefore, that the derived guideline values apply to a typical exposure scenario or are based on default values that may not be applicable for all areas. In those areas where relevant data on exposure 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 minimized.

12.4.2 Derivation of guideline values for potential carcinogens

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, mostly from occupational exposure.

On the basis of the available evidence, IARC categorizes chemical substances with respect to their potential carcinogenic risk into the following groups (6) (for a detailed description of the classifications, see

box):

- 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.

Evaluation of carcinogenic risk to humans

IARC considers the body of evidence as a whole in order to reach an overall evaluation of the carcinogenicity for humans of an agent, mixture, or circumstance of exposure.

The agent, mixture, or exposure circumstance is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent, mixture, or exposure circumstance is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1. The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Group 2

This category includes agents, mixtures, and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures, and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

Group 2A. The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture, or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

Group 2B. The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.

This category is used for agents, mixtures, and exposure circumstances for which there is *limited*

evidence of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture, or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3. The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents, mixtures, and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.

Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents, mixtures, and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4. The agent (mixture) is probably not carcinogenic to humans.

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

In establishing the present guideline values for drinking-water quality, the IARC classification for carcinogenic compounds was taken into consideration. For a number of compounds, additional information was also available.

It is generally considered that the initiating event in the process of chemical carcinogenesis is the induction of a mutation in the genetic material (DNA) of somatic cells (i.e., cells other than ova or sperm). Because the genotoxic mechanism theoretically does not have a threshold, there is a probability of harm at any level of exposure. Therefore, the development of a TDI is considered inappropriate, and mathematical low-dose extrapolation is applied. 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 these nongenotoxic carcinogens.

In order to make the distinction with respect to the underlying mechanism of carcinogenicity, each compound that has been shown to be a carcinogen was evaluated on a case-by-case basis, taking into account the evidence of genotoxicity, the range of species affected, and the relevance to humans of the tumours observed in experimental animals.

For carcinogens for which there is convincing evidence to suggest a nongenotoxic mechanism, guideline values were calculated using a TDI approach, as described in section 12.4.1.

In the case of compounds considered to be genotoxic carcinogens, guideline values were determined using a mathematical model, and the guideline values presented in Volume 1 are the concentrations in

drinking-water associated with an estimated upper bound excess lifetime cancer risk of 10^{-5} (one additional cancer per 100 000 of the population ingesting drinking-water containing the substance at the guideline value for 70 years). Concentrations associated with estimated excess lifetime cancer risks of 10^{-4} and 10^{-6} can be calculated by multiplying and dividing, respectively, the guideline value by 10. These values are also presented in this volume [Volume 2] to emphasize the fact that each country should select its own appropriate risk level. In cases in which the concentration associated with a 10^{-5} excess lifetime cancer risk is not practical because of inadequate analytical or treatment technology, a provisional guideline value was set at a practicable level and the estimated associated cancer risk presented.

Although several models exist, the linearized multistage model was generally adopted in the development of these guidelines. Other models were considered more appropriate in a few cases.

It should be emphasized, however, that guideline values for carcinogenic compounds computed using mathematical models must be considered at best as a rough estimate of the cancer risk. These models do not usually take into account a number of biologically important considerations, such as pharmacokinetics, DNA repair, or immunological protection mechanisms. However, the models used are conservative and probably err on the side of caution.

To account for differences in metabolic rates between experimental animals and humans-the former are more closely correlated with the ratio of body surface areas than with body weights-a surface area to body weight correction is sometimes applied to quantitative estimates of cancer risk derived on the basis of models for low-dose extrapolation. Incorporation of this factor increases the risk by approximately one order of magnitude (depending on the species upon which the estimate is based) and increases the risk estimated on the basis of studies in mice relative to that in rats. The incorporation of this factor is considered to be overly conservative, particularly in view of the fact that linear extrapolation most likely overestimates risk at low doses; indeed, Crump et al. (7) concluded that "all measures of dose except dose rate per unit of body weight tend to result in overestimation of human risk." Consequently, guideline values for carcinogenic contaminants were developed on the basis of quantitative estimates of risk that were not corrected for the ratio of surface area to body weight.

12.5 Mixtures

Chemical contaminants of drinking-water supplies are present with numerous other inorganic and organic constituents. The guideline values were calculated separately for individual substances, without specific consideration of the potential for interaction of each substance with other compounds present. However, the large margin of safety incorporated in the majority of guideline values is considered to be sufficient to account for potential interactions. In addition, the majority of contaminants will not be present at concentrations at or near their guideline value.

There may, however, be occasions when a number of contaminants with similar toxicological effects are present at levels near their respective guideline values. In such cases, decisions concerning appropriate action should be made, taking into consideration local circumstances. Unless there is evidence to the contrary, it is appropriate to assume that the toxic effects of these compounds are additive.

12.6 Format of monographs for chemical substances

The format adopted for the monographs in this publication is shown below. All of the headings may not, however, be required in every monograph.

General description

- Identity
- Physicochemical properties
- Organoleptic properties

Major uses
Environmental fate

Analytical methods

Environmental levels and human exposure

Air
Water
Food
Estimated total exposure and relative contribution of drinking-water

Kinetics and metabolism in laboratory animals and humans

Effects on laboratory animals and *in vitro* test systems

Acute exposure
Short-term exposure
Long-term exposure
Reproductive toxicity, embryotoxicity, and teratogenicity
Mutagenicity and related end-points
Carcinogenicity

Effects on humans

Guideline value

References

1. International Commission on Radiological Protection. *Report of the Task Group on Reference Man*. New York, Pergamon Press, 1992 (ICRP No. 23).
2. *Evaluation of certain veterinary drug residues in food: thirty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva, World Health Organization, 1991 (WHO Technical Report Series, No. 815).
3. *Principles for the safety assessment of food additives and contaminants in food*. Geneva, World Health Organization, 1987 (Environmental Health Criteria, No. 70).
4. *Principles for the toxicological assessment of pesticide residues in food*. Geneva, World Health Organization, 1990 (Environmental Health Criteria, No. 104).
5. *Evaluation of certain food additives and contaminants: thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives*. Geneva, World Health Organization, 1989 (WHO Technical Report Series, No. 776).
6. International Agency for Research on Cancer. *Occupational exposures to mists and vapours from strong inorganic acids; and other industrial chemicals*. Lyon, 1992 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 54).
7. Crump K, Allen B, Ship A. Choice of dose measures for extrapolating carcinogenic risk from animals to humans: an empirical investigation of 23 chemicals. *Health physics*, 1989, 57(Suppl 1):387-393.