1 **ENDORSED FOR PUBLIC CONSULTATION**

2 **SCIENTIFIC OPINION**

3 Guidance on Default assumptions used by the EFSA Scientific Panels and 4 Committee, and EFSA Units in the absence of actual measured data[1]

5 **EFSA Scientific Committee**[2, 3]

6 European Food Safety Authority (EFSA), Parma, Italy

7 **ABSTRACT**

8 *(Max. 300 words, no paragraph breaks. Note that the abstract should end with the copyright)*

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11 **KEY WORDS**

12 (Max. seven key words are suggested)

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[1] On request from EFSA], Question No EFSA-Q-2010-00221, adopted on DD Month YYYY.

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SUMMARY

A number of assumptions and default values are usually applied at the various steps of the risk assessment process. These can be of a methodological nature, or to compensate for the absence of data, in which case the risk assessor may have to refer to default values to be able to perform the assessment. These default values should be scientifically justified and, where possible, be based on existing data.

The European Food Safety Authority (EFSA) asked the Scientific Committee to develop a guidance document and to propose harmonised values/procedures to be used as default by the EFSA Scientific Panels, Committee and Units where needed. An internal consultation was organised during the second half of 2009 to review the various default values used within EFSA. The Scientific Committee then identified areas where harmonised default values are needed, and reassessed the extent to which these default values were science-based, making use of the statistics derived from the EFSA Comprehensive European Food Consumption Database and other relevant data sets. Based on this analysis, harmonised default values listed in the table below and default procedures are recommended for the use within EFSA's Panels and Units in the absence of empirical data.

The Scientific Committee also considered the use of probabilistic distributions of uncertainty factors (UFs), as an alternative for multiplying various UFs, in establishing health-based guidance values. The Scientific Committee recommends that these probabilistic approaches to combine UFs are further investigated for its potential use in EFSA's risk assessments.

The Scientific Committee also recommends the following rules to be applied for rounding figures when establishing health-based guidance values:

- The degree of precision for measured values is determined by the precision of the analytical methodology
- When reporting derived values, then the degree of precision should take into account the precision of the components used in the derivation.
- Rounding figures should be done at the latest stage in the assessment, e.g. when establishing health-based guidance values
- Derived values, such as health-based guidance values, will be rounded to a single significant figure if the impact of rounding is less than 10%, and to two significant figures if the impact of rounding to one significant figure exceeds that percentage.

The Scientific Committee underlines that the purpose of this guidance document is harmonisation of default values used by EFSA's Scientific Panels, Committee and Units, and not standardisation: it is therefore always possible to deviate from the proposed default values, provided that the rationale for such deviation is described.

52 **Default Values proposed for use by EFSA Scientific Panels and Committee, and EFSA Units**

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Issue for harmonisation	Default value proposed		Remark
Body weight (Kg)	Adults: 70	Infants & children: 12	
Total solid food intake	No default value		
Total liquid intake (L)	Adults: 2	Children: no default values	For children, See http://www.efsa.europa.eu/en/efsajournal/doc/1459.pdf
Converting test compound concentrations in feed (mg/kg), into daily dose (mg/kg b.w. per day)	*Rat* Chronic studies: 0.05 Subacute studies: 0.12 Subchronic studies: 0.09	*Mice* Chronic studies: 0.15 Subacute studies: 0.2 Subchronic studies: 0.2	If a subacute or a subchronic study starts at a later age, then the conversion factor for chronic studies should be applied
Converting test compound concentrations in drinking water (mg/l), into daily dose (mg/kg b.w. per day)	*Rat* Chronic studies: 0.05 Subacute studies: 0.12 Subchronic studies: 0.09	*Mice* Chronic studies: 0.09 Subacute studies: 0.18 Subchronic studies: 0.15	If a subacute or a subchronic study starts at a later age, then the conversion factor for chronic studies should be applied
UF for inter-species extrapolation	No data on kinetics and/or dynamics available: 10	Variability in toxicokinetics: 4.0 Variability in toxicodynamics: 2.5	
UF for intra-human extrapolation	No data on kinetics and/or dynamics available: 10	variability in toxicokinetics: 3.16 variability in toxicodynamics: 3.16	
UF for Deficiencies in the data available for the assessment	No default UF		Consider the possibility/feasability of getting additional data first. If not feasible, use additional UF (value determined on a case-by-case basis).
UF for for duration of exposure extrapolation	Subchronic to chronic: 2	Subacute to chronic: no default UF	
UF to account for the absence of a NOAEL	No default UF		Use the BMD approach. If not possible, consider use of the LOAEL with an additional UF (value determined on a case-by-case basis)
UF to account for the severity and nature of the effect	No default UF	Genotoxic and carcinogenic compounds: Use the Margin of Exposure approach	Usually not needed. If exceptionally considered necessary, UF value determined on a case-by-case basis.

54 UF: Uncertainty Factor

55 **TABLE OF CONTENTS**

85

BACKGROUND AS PROVIDED BY EFSA

In the absence of empirical data, default values are often used to substitute for essential information to perform risk assessments in many of the different areas in the remit of EFSA. Default assumptions may be made at different steps in the risk assessment process, such as in consumer exposure assessment, in converting a feed concentration into a dose in experimental animals or in applying uncertainty factors for extrapolation of animal data to the human situation. In the framework of the transparency activities of the Scientific Committee, a need for harmonisation of the approaches to default assumptions used within EFSA has been identified and the Dietary and Chemical Monitoring (DCM – former DATEX) Unit was asked to prepare, in consultation with the EFSA Panels and Units, a "state of the art" document describing default assumptions presently in use within the remit of EFSA's activities.

The consultation was performed via a questionnaire addressed to all EFSA Panels and Units. The analysis of the responses revealed a considerable degree of similarity for many default assumptions used by the different EFSA Panels and Units in risk assessment. Some default assumptions more specific and of interest for a limited number of Panels and Units were also identified. Based on the current analysis, a fine tuning of similar default assumptions being used by several Panels and Units was recommended.

TERMS OF REFERENCE AS PROVIDED BY EFSA

Following the suggestion of the Scientific Committee for a self task on the topic of harmonisation of default assumptions used by the different EFSA Scientific Panels and Committee, and EFSA Units, the European Food Safety Authority requests the Scientific Committee to:

Develop by end December 2011 a guidance document proposing harmonised values/procedures to be used as default by the EFSA Scientific Panels and Committee, and EFSA Units where needed.

Taking into account the outcome of the DCM survey on default assumptions used by EFSA Scientific Panels and Units (areas with consensus, exceptions), the Scientific Committee is requested:

- To consider when default assumptions are needed
- Where default values are set (e.g. by legal requirements), to discuss whether they are scientifically justified and, if not, to propose some science-based default assumptions.
- To compile a table with values/procedures to be used as default within EFSA

ASSESSMENT

1. Introduction

A number of assumptions and default values are usually applied at the various steps of the risk assessment process. These can be of a methodological nature, such as considering the 95th percentile for representing the high consumption when assessing exposure, or to compensate for the absence of data, e.g. when deciding that results obtained from animal experiments can be extrapolated to humans.

In cases of insufficient or absence of numerical data, the risk assessor may have to refer to default values to be able to perform the assessment. These default values should be derived on the basis of existing data and be therefore scientifically justified.

An internal consultation was organised by the EFSA Dietary and Chemical Monitoring (DCM – former DATEX) Unit during the second half of 2009 to review the various default values used by the EFSA Scientific Panels, Committee and the EFSA Units. The findings highlighted several cases where different default values are used for a same parameter. Recommendation was therefore made to the Scientific Committee to consider whether further harmonisation in the use of default values within EFSA is possible.

When reviewing the default values reported by the EFSA Units, the Scientific Committee looked the extent to which they were science-based and could therefore be proposed for the use of EFSA Panels and Units. The Scientific Committee made use of the statistics derived from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) published on the EFSA website[4].

It is underlined that the purpose of this guidance document is harmonisation of default values used by EFSA Scientific Panels and Committee, and the EFSA Units, and not standardisation: it is therefore always possible to deviate from the proposed default values, provided that the rationale for such deviation is described.

2. Default values for human body weight

A default value of 60 kg has generally been used by the World Health Organisation (WHO) for calculation of Acceptable Daily Intakes (ADIs) and water quality guidelines (IPCS, 1987; WHO, 1994; WHO, 2009), and this value has been adopted in the work of some EFSA Panels. However, the WHO value is intended to apply worldwide, and is not necessarily representative of EU adult populations. The EFSA Pesticides Unit (PRAS - formerly the PRAPeR and PPR units) uses a default value of 60 kg for adult body weight based on the 5th percentile of the distribution of body weights of English adult males (ECETOC, 2001), presumably based on the assumption that use of the 5th percentile is a conservative approach.

Assumptions regarding body weight of humans may be required under a number of different circumstances, such as:

a) Dietary exposure data are available on a per person basis, and there is a need to convert to a body weight basis in order to compare with an ADI or an Acute Reference Dose (ARfD) (e.g. feed additives, pesticides…)

b) Tolerable Daily Intake (TDI) values, expressed on a body weight basis, need to be related to amount of food consumed on a per person basis at different ages, in order to assess safety of

[4] See http://www.efsa.europa.eu/en/datex/datexfooddb.htm

current or proposed maximum levels of a chemical in food (e.g. Specific Migration Limits for food contact materials).

c) Non-dietary pesticide exposure estimated per person on the basis of default assumptions is converted to body weight basis in order to compare with an Acceptable Operator Exposure Level (AOEL).

d) Dietary exposure resulting in human illness is reported on a per person basis and needs to be converted to a body weight basis in order to establish health-based guidance values (e.g. ARfDs for some marine biotoxins).

In situations (a), (b) and (c) above, the implication of underestimating body weight is conservative, i.e. it will result in overestimation of exposure, and hence of risk. In contrast, for situation (d) underestimating body weight is not conservative, since it would result in a higher health-based guidance value. Therefore it cannot be assumed that application of a low default value for body weight is always a worst case scenario. The Scientific Committee decided that a realistic estimate of typical body weight for the EU population would support a more proportionate approach to risk assessment. Typical body weight is best represented by the median of the distribution. Variation between individuals is allowed for by the application of uncertainty factors in setting health-based guidance values.

2.1. Default body weight value for adults

The Scientific Committee used the Comprehensive Database, which was built from existing national information on food consumption at a detailed level. Competent organisations in the European Union's Member States provided EFSA with data from those most recent national dietary surveys in their country, at the level of consumption by the individual consumer. This included food consumption data concerning infants (from 0 to less than 3 months, 3 to less than 6 months, 6 to less than 12 months old), toddlers (from 1 to less than 3 years old), children (from 3 to less than 10 years old), adolescents (from 10 to less than 14 years, 14 to less than 18 years old), adults (from 18 to less than 65 years old), elderly (from 65 to less than 75 years old and very elderly (75 years old and over), for a total of 32 different dietary surveys carried out in 22 different Member States.

Table 1 summarises the body weight data for adult subjects in the EFSA Comprehensive Database. All medians are higher than the currently applied default value of 60 kg, with the lowest median body weight for females aged 18-64 years (66kg). The median body weights for older females, and for all age groups of men are larger. Taking into account also that body weights are tending to increase, the Scientific Committee concluded that a default value of 70 kg is a closer approximation to the typical body weight of the EU adult population than the currently applied default value of 60 kg. The Scientific Committee therefore recommends that 70 kg be used by EFSA when there is a need to apply a default body weight value for adults.

196 **Table 1:** Body weight (kg) statistics for adult subjects in all surveys of the EFSA Comprehensive
197 database

Age (years)	Gender	N	Mean	StdDev	Median	P5	P95	% ≤ 70kg	% > 70kg
18-64	♀	22507	67.2	12.5	66.0	50.0	91.0	71.0	29.0
18-64	♂	18699	82.1	13.6	82.0	62.6	105.0	18.5	81.5
18-64	♀+♂	41206	74.4	15.0	73.0	52.6	100.0	52.9	47.1
65-75	♀	2343	70.6	12.1	71.0	53.0	92.0	49.0	51.0
65-75	♂	2066	82.2	11.5	82.7	65.0	103.0	14.6	85.4
65-75	♀+♂	4409	76.0	13.2	75.0	55.0	98.9	67.1	32.9
≥75	♀	1230	66.8	12.6	67.0	50.0	86.0	62.4	37.6
≥75	♂	1030	78.1	11.8	79.0	60.0	96.0	30.5	69.5
≥75	♀+♂	2260	71.4	13.6	70.4	50.0	92.0	52.2	47.8

198 N: number of individuals in the database
199 StdDev: standard deviation
200 Pxx: xxth percentile
201

202 ## 2.2. Default body weight value for children

203 Infants and young children have higher food intake than older children or adults expressed on a body
204 weight basis due to their higher energy requirement during rapid growth (see Table 2). The highest
205 total food intake seen in table 2 is for infants aged 3-6 months. However at this age the diets are
206 specialised, comprising mainly breast or formula milk, with possible gradual introduction of small
207 amounts of a limited number of foods. The age group with the next highest food intake is the
208 "toddlers" (aged 1-3 years), and at this age the food consumed is more similar to that of other age
209 groups. Therefore the 1-3 year age-group should be included in exposure assessments as they are
210 likely to have the highest dietary exposure expressed on a body weight basis.

211 **Table 2:** Total food (solid + liquid) consumption (g/kg b.w. per day) statistics for infants and
212 children in all surveys of the EFSA Comprehensive database

Age range	Total food consumption (g/kg b.w. per day)	Number of individuals in database
Infants [0-3 months[	103.0	205
Infants [3-6 months[	132.4	231
Infants [6-12 months[	106.9	441
Toddlers [1-3 years[	114.4	1679
Other children [3-10 years[	74.1	8833
Adolescents [10 - 14 years[	43.5	3291
Adolescents [14 - 18 years[	37.0	3935
Adults [18-65 years[	37.5	41206
Elderly [65-75 years[	36.7	4409
Very elderly (≥75 years)	32.7	2260

213

214 Table 3 summarises the body weight data for infants and children in the EFSA Comprehensive
215 Database. The body weights of girls and boys are very similar up to the age of 14 years and are
216 combined for statistical purposes in the table. The Scientific Committee recommends that, since the
217 dietary exposure of infants aged 1-3 years is likely to be higher than that of older children, a default
218 body weight of 12 kg based on the median body weight of 1-3 year olds could be used in a

conservative approach for all infants and children. However if deviation from the default value is required for assessments for specific age groups, the median values identified in table 3 should be applied.

The Scientific Committee noted that PRAS uses different age categories in their assessments, based on ECETOC Report No 79 (2001), and advised that their approach should be aligned with the age categories in the EFSA Database.

Table 3: Body weight (kg) statistics for infants and children in all surveys of the EFSA Comprehensive database

Age (years)	Gender	N	Mean	StdDev	Median	P5	P95
Infants (0-3 months)	♀+♂	205	4.8	1.4	4.8	3.2	6.4
Infants (3-6 months)	♀+♂	231	6.7	1.0	6.7	5.1	8.5
Infants (6-12 months)	♀+♂	441	8.8	1.2	8.7	7.0	11.0
Toddlers (1-3 years)	♀+♂	1679	11.9	2.2	11.6	8.7	15.9
Other children (3-10 years)	♀+♂	8833	23.0	7.1	21.6	14.0	36.3
Adolescents (10-14 years)	♀+♂	3291	43.2	10.5	42.0	29.0	62.0
Adolescents (14-18 years)	♀	2048	57.4	9.3	56.0	45.0	76.0
Adolescents (14-18 years)	♂	1887	65.3	11.9	65.0	47.0	87.0
Adolescents (14-18 years)	♀+♂	3935	61.2	11.3	60.0	45.0	83.0

Abbreviations: see table 1's footnotes

Conclusions:

- A body weight of 70 kg should be used as default for European adults.
- For dietary exposure assessment, a body weight of 12 kg should be used as default for European infants and children. If deviation from the default value is required for the assessment of specific age groups, the median values identified in table 3 should be used.

3. Default values for food intake

3.1. Daily total solid food intake by humans

Relevant empirical data for EFSA Panel risk assessments seem in most cases to be available from food consumption databases, e.g. the EFSA Comprehensive Database, and being already commonly used, they negate the need for default values. There are some examples of EFSA Panels, such as the Panel on Food Additives and Nutrient Sources Added to Food (ANS), which has been using until recently the concept of total solid food (i.e. Budget Method) as an initial step in the exposure assessment. However the ANS Panel will now base its exposure estimates on data from the EFSA Comprehensive Database coupled with maximum permitted use levels and, if available, maximum reported use levels or analytically determined use levels.

Rather than considering daily total solid food intake, intake values for specific food categories (i.e. those containing the substance in question) tend to be more relevant for the risk assessments performed by some EFSA Panels (e.g. the Panel on Additives and Products or Substances used in Animal Feed - FEEDAP) and in some cases the default values used are defined in EU legislation. For

example, Commission Regulation (EC) No 429/2008 of 25 April 2008[5] regarding feed additive applications provides theoretical daily human consumption figures for tissues and products and potential consumer exposure to the animal feed additives and/or metabolite(s) is calculated based on these consumption figures. However, this Regulation also states that 'in certain situations (e.g. some nutritional and sensory additives or additives intended for minor species) it may be appropriate to subsequently refine the human exposure assessment using more realistic consumption figures, but still keeping the most conservative approach. Where this is possible this shall be based on Community data.' Consequently, the FEEDAP Panel is reviewing the theoretical consumption figures to be used in exposure assessments and any modifications will be included in subsequent FEEDAP guidance documents for use by applicants.

Some EFSA Panels refer to guidance documents containing relevant default values specific for their risk assessments. For example, the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) use the Guidelines of the Scientific Committee on Food for the presentation of an application for safety assessment of a substance to be used in food contact materials prior to its authorisation (EC, 2001) which "… maintains the assumption that a person may consume daily up to 1 kg of food in contact with the relevant food contact material." The CEF Panel is currently reviewing this guideline and considering other approaches for this consumption estimate. Guidance documents for risk assessments used by EFSA Panels are available on the EFSA website (http://www.efsa.europa.eu/).

Conclusion:

As the various EFSA Panels have different considerations and methodologies for their risk assessments, it was concluded that a single default value for daily total solid food intake for adults for harmonised use across the EFSA Panels was neither needed nor justifiable. The SC recommends that EFSA Panels regularly consult the EFSA Comprehensive Database in order to check the relevance of default values used and to be fully aware of their impact on exposure estimates. The Scientific Committee considers that default values used in EFSA Guidance documents, which are considered to more accurately reflect consumption/exposure, should also be considered for inclusion in the respective legislation. The Scientific Committee did not consider possible default values for daily total solid food intake for children, as the EFSA Panels and Units did not report using such default values.

3.2. Daily total liquid intake by humans

A number of EFSA Panels use default values for total liquid intake in the absence of empirical data. In general, the default value of 2 L total liquid intake per day for adults is used (e.g. the EFSA Panel on Plant Protection Products and their Residues (PPR) follows EC guidance[6] which stipulates 2 L water consumption is used for calculating human exposure to substances of unknown structure for applying a Threshold of Toxicological Concern (TTC)). The EFSA Comprehensive consumption database contains data from different EU member states on daily total liquid intake, but due to different methodologies used to collect and report total liquid intake data in the various studies, these data sets cannot be aggregated in order to determine the relevance of a default value of 2 L for total liquid intake for European adults.

[5] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives

[6] Guidance Document on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated under Council Directive 91/414/EEC

In a recent opinion on dietary reference values for water, the Panel on Dietetic Products, Nutrition and Allergies (NDA) defined adequate intakes of total water for adults (≥14 years old) using a combination of observed intakes in population groups, desirable osmolarity values of urine and desirable water volumes per energy unit consumed (EFSA NDA Panel, 2010). The total water intake values include water from drinking water, beverages of all types, and from food moisture and only apply to conditions of moderate environmental temperature and moderate physical activity levels. Based on median potential renal solute loads calculated from dietary surveys from 4 European countries, the NDA Panel calculated that to achieve a urine osmolarity of 500 milli-osmoles (mosm)/L, male adults would need urine volumes of 2 L and female adults would need urine volumes of 1.6 L. The NDA panel calculated that this urine volume should be attained from a total water intake (i.e. drinking water, beverages of all kind, and from food moisture) of 2.5 L for males and 2 L for females. The NDA Panel recommended the same adequate intakes of total water for elderly adults as for adults, as despite reduced energy requirements the water requirement per energy unit from the diet becomes greater due to a decreased capacity for renal concentrating (EFSA, 2010). The NDA opinion (EFSA, 2010) also gives adequate intake levels of total water for children according to their age.

The calculated values in the NDA opinion are in line with the default value of 2 L used in WHO risk assessment guidance documents such as Environmental Health Criteria - EHC 240 on 'Principles and methods for the risk assessment of chemicals in food' (IPCS, 2009). EHC 240 refers to the WHO Guidelines on drinking water (WHO, 2008), in giving the default value of 2 L for total daily drinking water consumption for adults (60 kg bw). Earlier WHO EHC publications (IPCS, 1994, 1999) also reported that the WHO used 2 L for total daily drinking water consumption for adults in calculating water quality guidelines, but also referred to the International Commission on Radiological Protection (ICRP) Report 'Reference Man' (ICRP, 1974), with EHC 170 stating that the ICRP intake volumes should be used for exposure estimates. In this ICRP Report (1974), it is stated that daily fluid intake values (i.e. milk, tap water, other beverages etc. and excluding food) were derived by considering that 1 ml of water is required for each kilocalorie of energy expended (ICRP, 1974). The total daily fluid intakes reported for the ICRP Reference Man are 1950 ml for males (70 kg bw) and 1400 ml for females (58 kg bw), but it was highlighted that actual values for reference man may range from 1000 to 2400 ml/day at moderate temperatures (ICRP, 1974). Based on these values, EHC 170 and EHC 210 report a reference value of 1900 ml/day daily fluid intake (i.e. milk, tap water, other beverages) for adults (bw not stated).

Conclusion:

Considering the inherent variation in water intakes and in view of the similar values for total liquid intakes reported for adult males and adult females in the NDA opinion (EFSA, 2010) and the ICRP (1974) report, the Scientific Committee recommends using 2 L as a conservative default value for daily total liquid intake in adults to be used in risk assessments.

4. Factors for converting chemical compound concentrations in feed or drinking water into daily doses in experimental animal studies

In dietary risk assessment, health-based guidance values are usually established based on a range of experimental animal studies where the compound of interest is orally applied. This is either done by applying the compound by gavage, via drinking water or, more commonly, via feed. When using gavage application of the compound, the animals are dosed individually and the exact doses are known. However, in the latter two cases, accurate doses can be calculated only when both body weight (bw) and feed or water consumption are reported. Where accurate doses cannot be calculated because of the lack of measured body weights and food or water consumption, according to WHO (2009) approximate doses can be estimated using dose conversion factors for feeding studies. To convert a feed concentration into a dose, for rats and mice a factor of 0.05 and 0.15, respectively, is proposed by

WHO (e.g. 1 mg/kg in feed is equivalent to a dose of 0.05 and 0.15 mg/kg bw per day in rats and mice, respectively). In addition, for young rats, WHO proposes a conversion factor of 0.1, while for mice, no such distinction was made. These conversion factors were taken unchanged from WHO EHC 70 (IPCS, 1987), originating from Lehman (1954). No recommendations for conversion factors for toxicity studies where the compound is administered in the drinking water are available.

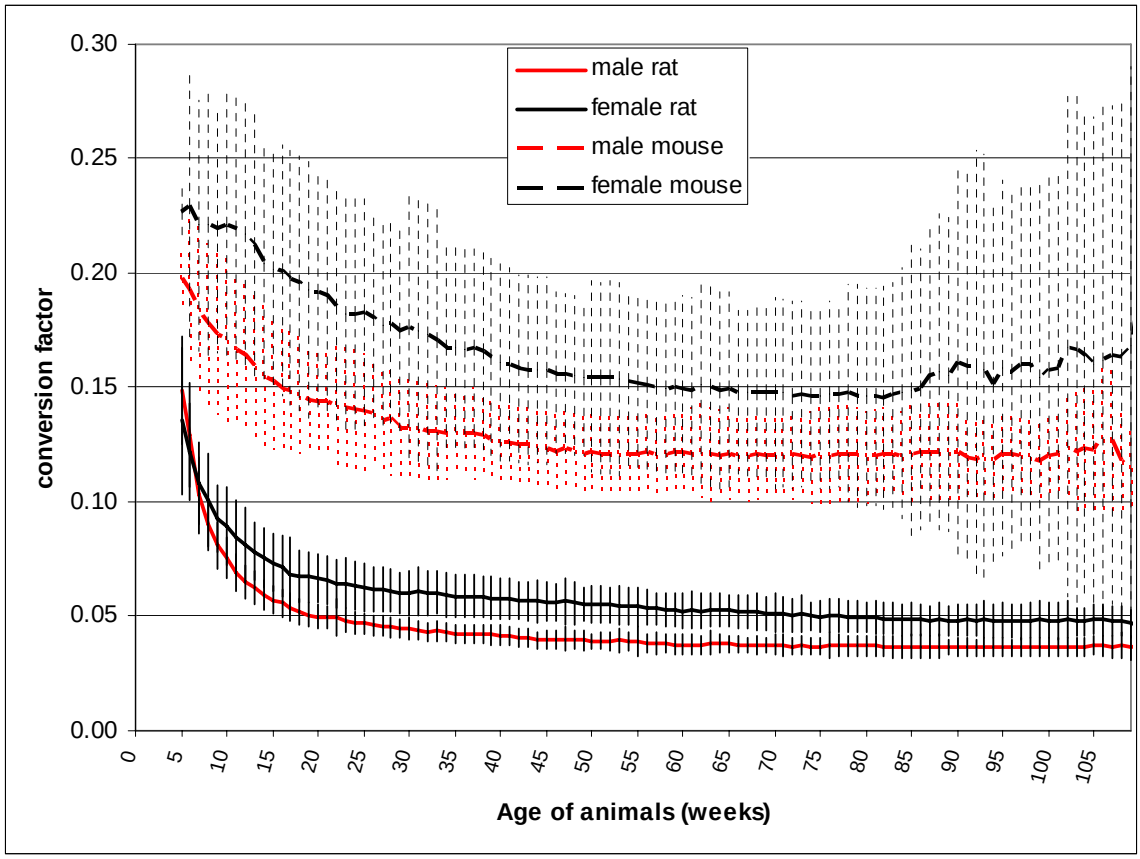
The most frequent situation where such a conversion is needed for assessing toxicological feeding studies is for studies in rats and mice. Although feeding studies with dogs are also frequently reported (e.g. for pesticide risk assessments), such conversion factors would not be needed as in these studies the dogs are fed individually and the actual doses are usually reported. For this reason the validity of the WHO default values for converting feed concentrations into a dose for rats and mice are explored.

4.1. Conversion factors for dietary administration of test compounds

To see whether the conversion factors proposed by WHO for rats and mice are supported by more recent data, factors for converting chemical compound concentrations in feed (e.g. mg/kg) into doses (e.g. mg/kg b.w. per day) in animal studies were calculated from long-term rat and mouse feeding studies, using control group mean weekly food consumption data and control group mean body weight data from 37 chronic rat and 38 chronic mouse studies. The reason for using only control group data is to avoid possible influence of compound administration on the feed consumption or potential effects on bw. Original data from dossiers submitted to the Swiss Federal Office of Public Health over the last 30 years on plant protection products (PPP) were used. These original studies formed also the basis for international evaluations establishing ADIs for these PPP (i.e. EFSA and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR)). All studies reported feed-consumption and body weight data on a weekly basis at least for the first 13 weeks of the study and thereafter every 4 weeks. The start of the studies (i.e. beginning of the treatment of the animals) was usually between weeks 5 and 8 of age and lasted for 104 weeks in rats but mouse studies were often terminated after 80 weeks. Consequently, data were available from 5 weeks onward. In the 37 chronic rat studies the following strains were used: Wistar: 18 studies, Sprague-Dawley: 9 studies, Fischer 344: 8 studies, and CD BR: 2 studies. In the 38 chronic mouse studies the following strains were used: CD-1: 28 studies, B6C3F1: 2 studies, C57BL: 7 studies, and NMRI: 1 study.

First, for each study, weekly conversion factors were calculated by dividing the listed weekly feed consumption by the respective weekly bw. Then, the means and their respective standard deviations of the calculated weekly conversion factors over all studies were calculated. The graphical plot of all weekly means and the respective standard deviations is shown in Figure 1.

As can be seen from Figure 1, a rapid drop of the conversion factor occurs over the first few weeks, especially in rats, and it levels off around week 20. Conversion factors calculated for week 5 were 0.15 and 0.14 in male and female rats and 0.2 and 0.23 in male and female mice, respectively. In general, the conversion factors for males are lower than those for females and the standard deviations in the mouse data were larger than those from rat data. The increase in the standard deviations seen after week 80 in the mouse studies is due to the rapidly decreasing number of studies lasting over the full period of 104 weeks. A similar pattern was observed already by Luijckx et al. (1994) based on eight 2-year carcinogenicity (feeding) studies in Fischer 344 rats performed by the U.S. National Toxicology Program (NTP) by using a slightly different approach.



Vertical bars indicate the standard deviation of the weekly mean. Note that the start of the treatment of the animals was usually between weeks 5 and 8 of age. Calculated with Microsoft® Office Excel 2003

Figure 1: Graphical plot of weekly means of factors for converting chemical compound concentrations in feed into daily doses for male and female rats and mice, respectively.

From these data, the mean of all weekly means were calculated, representing average conversion factors for chronic (i.e. 104 week) studies. Furthermore, the means for week 5 to 9 of age (4 weeks) and 5 to 17 (13 weeks) were also calculated, representing average conversion factors for subacute (i.e. 4 week) or subchronic (i.e. 13 week) studies. The resulting figures are listed for rats and mice in Table 4.

Table 4: Mean factors for converting concentrations of substances in feed into a daily dose for rats and mice for , subacute, subchronic and chronic study duration.

Study type (statistics)	Male rat	Female rat	Male mice	Female mice
Subacute	0.118	0.117	0.188	0.224
Subchronic	0.081	0.091	0.169	0.215
Chronic	0.045	0.058	0.130	0.167

For rats, there are no large differences between males and females in the mean conversion factors for feed concentrations into a dose. For mice, these differences between males and females are seemingly larger but the standard deviations are also larger. Therefore it is considered that no sex specific conversion factors are needed and only one single value for each species is selected. The mean values

for both sexes are 0.052 and 0.149 for rats and mice, respectively, which are close to the respective values proposed by WHO.

Conclusions:

Based on this analysis it is concluded that the conversion factors proposed by WHO of 0.05 and 0.15 for rats and mice respectively, are supported for chronic feeding studies by the data considered. The Scientific Committee recommends that within EFSA these conversion factors are used as defaults to calculate average doses in mg/kg bw per day from feed concentrations in mg/kg feed in the absence of measured actual data. However, it should be noted that the initial dose administered to rats during the first week is 3 times higher than the resulting calculated default dose. The respective ratio for mice is 1.5.

The Scientific Committee also recommends the following conversion factors to be used as defaults for shorter study durations: for subacute studies 0.12 and 0.2 for rats and mice, respectively, and for subchronic studies 0.09 and 0.2 for rats and mice, respectively.

As mentioned earlier, experiments start usually at week 5 to 7. If a subacute or a subchronic study starts at a later age, e.g. after week 25, then the conversion factor for chronic studies should be applied.

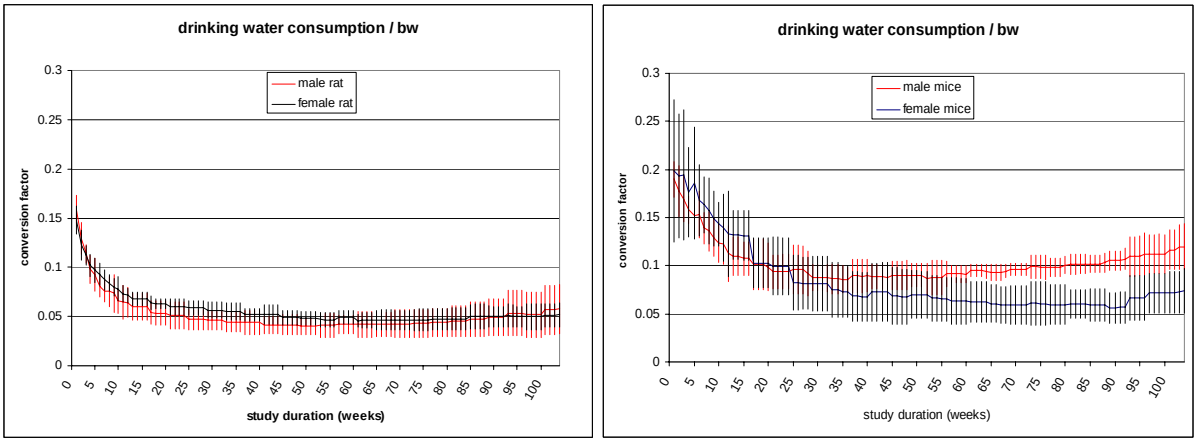
4.2. Conversion factors for administration of test compounds in drinking water

As mentioned before, so far there are no recommendations for conversion factors for toxicity studies where the compound is administered in the drinking water. To see whether default conversion factors for such studies can be derived from existing studies, the dossiers of long-term rat and mouse feeding studies used to derive conversion factors for feed were checked for the availability also of weekly drinking water consumption data. Surprisingly, no such data were found with the required level of detail. Therefore, published NTP long-term study reports were searched for studies where the compound was administered in the drinking water. Out of the 573 NTP studies published by December 2010, 20 studies were identified in which the compound was administered in drinking water. However, only in 8 studies out of these 20 studies, drinking water consumption and body weights were reported on a weekly basis for the first 13 weeks of the study and thereafter every 4 weeks. The remaining 12 studies did not report the required detailed drinking water consumption and body weights during the first weeks. As the body weight gain during the first weeks of a chronic study is largest and, therefore, any conversion factor is anticipated to change most during this phase, these studies were not considered suitable for the purpose of deriving conversion factors for different study phases. The 10 most recent NTP long-term study reports with dietary compound administration (2004-2010) were also searched for detailed data on drinking water consumption. As with the PPP dossiers, no such detailed data were identified. Equally, in the 5 most recent NTP gavage studies, in 2 NTP studies with dermal application and in one inhalation study, no detailed drinking water consumption data were identified.

All animals were 5 to 7 weeks old at the start of the study. In 7 of the selected studies, both Fischer344/N rats and B6C3F1 mice were used. In one study, only B6C3F1 mice were tested and in another study, a second rat strain (Wistar) was also tested besides the Fischer344/N rats.

Weekly factors for converting drinking water concentrations into daily doses in these 8 studies in rats and mice were calculated, using control group mean weekly drinking water consumption data and control group mean body weight data. The reason for using only control group data is again to avoid

possible influence of compound administration on the drinking water consumption or potential effects on body weight. As before with the feeding studies, the mean and the respective standard deviations of the calculated weekly conversion factors over all studies were calculated. The graphical plot of all weekly means and the respective standard deviations is shown in Figure 2.



Vertical bars indicate the standard deviation of the weekly means. Note that the x-axis relate to study duration in weeks and not to the actual age of the animals. Animals were 5 to 7 weeks old at the start of the study . Calculated using Microsoft® Office Excel 2003

Figure 2: Graphical plot of weekly means of factors for converting chemical compound concentrations in drinking water into daily doses for male and female rats (left plot) and mice (right plot).

As can be seen from Figure 2, again a rapid drop of the conversion factor occurs over the first few weeks, especially in rats, and it levels off around week 20. Conversion factors calculated for the first week of treatment (i.e. at an average age of the animals of 6 weeks) were 0.16 and 0.15 in male and female rats and 0.19 and 0.2 in male and female mice, respectively. The conversion factors for male and female rats are similar. A similar pattern was also observed by Luijckx et al. (1994), based on four 2-year NTP carcinogenicity studies in F344 rats, where the compound was administered in the drinking water by using a slightly different approach. They observed a twofold increase in drinking water consumption towards the end of the male rat studies, which was attributed to the high incidence of nephropathy in the aging male F344 rat.

In mice, the conversion factors for males tended to be lower than those for females in the first weeks but were higher after about 25 weeks.

From these data, the mean of all weekly means were calculated, representing average conversion factors for chronic (i.e. 104 week) studies. Furthermore, the means for subacute or subchronic (i.e. the first 4 or 13 weeks, respectively) were calculated. The resulting figures are tabulated for rats and mice in Table 5.

Table 5: Mean factors for converting concentrations of substances in drinking water into a daily dose for rats and mice for subacute, subchronic and chronic study duration.

Study type (statistics)	Male rat	Female rat	Male mice	Female mice
Subacute	0.125	0.121	0.174	0.191
Subchronic	0.089	0.093	0.144	0.164
Chronic	0.052	0.057	0.103	0.083

As seen for feed, for rats there are no large differences between males and females in the mean factors for converting concentrations of substances in drinking water into a daily dose. For mice, these differences between males and females are again seemingly larger but the standard deviations are also larger. Therefore it is considered that no sex specific conversion factors are needed and only one single value for each species is selected and the mean values for both sexes used.

Conclusions:

Surprisingly few studies were found where weekly drinking water consumption data were given. Conversion factors for chronic rat and mice studies of 0.05 and 0.09, respectively, could be derived from the data set considered. The Scientific Committee recommends that within EFSA these conversion factors are used as defaults to calculate doses in mg/kg bw per day from concentrations in drinking water in mg/l in the absence of measured actual data. However, as seen with compound concentration conversion factors for feed, it should be noted that the initial dose administered to rats during the first week is 3 times higher than the resulting calculated default dose. The respective ratio for mice can be up to 2.5.

The Scientific Committee also recommends the following conversion factors to be used as defaults for shorter study durations: for subacute studies 0.12 and 0.18 for rats and mice, respectively, and for subchronic studies 0.09 and 0.15 for rats and mice, respectively.

Again, experiments start usually at week 5 to 7. If a subacute or a subchronic study starts at a later age, e.g. after week 25, then the conversion factor for chronic studies should be applied.

5. Using animal data for risk assessment – Uncertainty factors

Uncertainty factors (UFs) (also called assessment factors, safety factors, adjustment factors or extrapolation factors) are used to derive health-based guidance values (HBGV) by extrapolating from experimental animal data to humans (IPCS, 2009).

UFs are intended to cover the uncertainty and variability arising from the inter-species differences, intra-species differences, extrapolation from sub-chronic or subacute to chronic exposure, absence of a No-Observed-Adverse-Effect-Level (NOAEL), quality of the toxicological database, and severity of the effect. Additionally, some considerations will be given about probabilistic approaches and combination of UFs.

5.1. Intra/inter-species extrapolation

The default UF of 100 was introduced in 1954 by Lehman and Fitzhugh, and adopted in 1958 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

This factor was later interpreted as reflecting extrapolation from experimental animal to human (factor 10 for inter-species variability) and extrapolation from an average human NOAEL to a sensitive human NOAEL (factor 10 for human or intra-species variability).

A further division of these inter- and intra-species factors into subfactors based on specific quantitative information on toxicokinetics and toxicodynamics has been proposed by WHO/IPCS (2005). This division permits the use of specific data on a chemical to derive chemical-specific adjustment factors.

(CSAF). Compound specific data for one particular aspect of uncertainty should be used to replace the relevant part of the overall default UF (see table 6).

Table 6: Values for default UFs that can be replaced by CSAFs (WHO/IPCS, 2005)

Source of uncertainty	**Default subfactor**		
	Toxicokinetic	Toxicodynamic	Combined
Inter-species variation	4.0	2.5	10
Human interindividual variation	3.16	3.16	10

EFSA uses body weight as a scale for inter-species extrapolation. Other EU institutions (e.g. European Chemicals Agency (ECHA)) have proposed use of allometric scaling based on caloric demand (metabolic body weight $BW^{0.75}$). The underlying principle is that due to the faster metabolic rate of small animals, humans would less effectively detoxify and/or excrete xenobiotics than laboratory animals. However, many chemicals of concern rely upon specific enzymes or transporters for their toxicity or elimination that do not scale allometrically. Such alternative scaling has not been used so far within EFSA. As no general consensus has been reached yet on alternative scaling, no harmonisation of this approach can be recommended in this opinion.

Conclusions:

If relevant chemical-specific data on kinetics and/or dynamics are available, the default subfactors listed in table 6 should be considered. In the absence of such data, the Scientific Committee recomends using the overall default UF of 100 (10x10).

5.2. Deficiencies in the data available for the assessment.

Significant data deficiencies may warrant an additional factor due to high level of uncertainty. To take into account the quality of the available database, a transparent expert judgement is important on a case-by-case basis. When the standard data package for a regulated chemical is incomplete (e.g. when endpoints which might prove critical were not measured), this might result in a higher critical NOAEL than would be provided by a more complete data package. Therefore, an additional UF may be required (COT, 2007).

In the Guidelines for Drinking Water Quality (WHO, 2008), the application of an additional UF between 1 and 10 is suggested depending on the adequacy of databases.

According to EHC 240, the quality of the total database may affect the choice of UF. Significant data deficiencies may warrant an increased factor due to increased uncertainty. No default values are proposed but rather a case-by-case approach pending on the nature of the deficiencies. Alternatively, when the data were not sufficient to propose a HBGV, JECFA has calculated the ratio between an amount of the substance producing a small but measurable effect in laboratory animals or humans and the estimated human dietary exposure, in order to characterize the risks associated with certain contaminants in food.

In the case of smoke flavours, because they are complex mixtures of variable and incompletely characterised composition, and in view of the limited toxicological data, the EFSA CEF Panel considered it inappropriate to establish an ADI but calculated a margin of safety based on the NOAEL in a 90-day study (EFSA CEF Panel, 2010). The margin of safety was defined as the ratio between the

NOAEL of the critical effect in the animal study on the smoke flavouring and the anticipated dietary exposure of consumers to that smoke flavouring. An additional UF relating to the quality of the toxicological database on which the evaluation is based, can be considered for the interpretation of the margin of safety. In those cases, where the overall evaluation of the genotoxicity studies did not raise cause for concern *in vivo* and where the 90-day studies were of adequate quality by current standards, the CEF Panel considered that, normally, an extra UF of 3-fold in addition to the default UF of 100, should be sufficient to cover the limited duration and statistical power of the pivotal study. Whether a specific margin of safety for a particular smoke flavouring is sufficient is highly dependent on the specific situation (*e.g.* composition, variability and stability, quality of the toxicological data) and default guidance cannot be given.

5.2.1. Extrapolation for duration of exposure

Different approaches followed by international organizations are described in the literature when considering the extrapolation for duration of exposure (see Table 7).

Table 7: Existing UFs used in the extrapolation for the duration of exposure (Falk-Filipsson, 2007)

Organization	Applicability	Extrapolation	Value of UF
US EPA (2002)	Not .defined.	Subchronic to chronic	10
EU (EC, 1996)	Industrial chemicals	Case-by-case based on expert judgement of scientific information	
EMEA/ICH (1997)	Residual solvents in pharmaceuticals	6-month rodents to chronic	2
		3-month rodents to chronic	5
		< 3-month rodents to chronic	10
EC (1967)	Classification and labelling of chemicals for health effects	Subacute to subchronic	3
ECHA, REACH guidance doc (2010)	REACH chemicals	Subacute to subchronic	3
		Subchronic to chronic	2
		Subacute to chronic	6

Subacute: 28-day, subchronic: 90-day, chronic: 1.5 – 2 years.

There have been a number of analyses of data where comparison has been made between NOAELs and/or Lowest-Observed-Adverse-Effect-Levels (LOAELs) from sub-chronic and chronic feeding studies, and ratios between the two developed. Diverging results were obtained from these analyses. However studies used for these analyses have substantial differences in their design, influencing the outcome of the analyses (IGHRC, 2003).

Recently, Zarn et al. (2010) have suggested taking into account the dose decrement related to decreased food intake during chronic feeding studies, when compared to subchronic feeding studies in rats with plant protection products. They concluded that a chronic rat NOAEL can be accurately predicted by dividing the NOAEL from rat subchronic studies by the dose decrement factor of 1.7 between the subchronic and chronic period.

The EFSA Scientific Committee is not in a position to propose default values to extrapolate from subacute to chronic duration. On the basis of a 28-day subacute study, where few parameters are usually investigated (limited study design), an extrapolation for chronic duration should be considered on a case-by-case basis. Therefore it is not recommended to multiply the factors in table 7 (subacute to chronic (6) = subacute to subchronic (3) x subchronic to chronic (2)). However, taking into consideration that the investigations are more extensive in a 90-day study, the extrapolation from subchronic to chronic duration can be performed as proposed by ECHA (UF of 2), supported by Zarn et al. (2010).

588

589 *5.2.2. Accounting for the absence of a NOAEL*

590 In the case where a NOAEL cannot be identified from the critical toxicological study, the evaluation
591 might have to rely on the LOAEL. Several organisations recommend in their guidelines, e.g.
592 Guidelines for drinking water Quality (WHO, 2008), the application of an additional UF of up to 10 to
593 the LOAEL to derive a health-based guidance value.

594 At the same time, as mentioned in EHC 240, the consideration of the shape of the dose-response curve
595 may trigger the need for an additional UF if the curve is very steep, particularly when the NOAEL is
596 close to the LOAEL. In its guidance (2010), ECHA also suggests to take into account the dose spacing
597 in the experiment, the shape and slope of the dose-response curve, and the extent and severity of the
598 effect observed at the LOAEL in order to determine the size of this additional UF.

599 As recommended in a previous opinion of the Scientific Committee, it is preferable to use the
600 benchmark dose (BMD) approach (EFSA, 2009) instead of the NOAEL/LOAEL. An advantage is
601 that, even in the absence of a NOAEL, the BMD approach can still be applied without the need for an
602 additional UF. The use of the BMD approach is also advocated by ECHA in its guidance on
603 Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (ECHA, 2010).

604

605 Conclusions:

606 In case of deficiencies in the data for applications, the EFSA Scientific Committee recommends that,
607 rather than applying an additional UF, the possibility/feasibility of getting additional data improving
608 the quality of the dataset is first considered. Therefore, the lack of data should not directly imply the
609 use of an extra UF.

610 When additional data cannot be obtained or requested, the use of an additional UF to take account of
611 the deficiency of a database should be considered on a case-by-case basis. It is not possible to propose
612 a default value for this UF, as it will be directly dependent on the dataset available.

613

614 Extrapolation from subchronic to chronic duration: the EFSA Scientific Committee recommends the
615 use of an UF of 2, considering the extent of investigations usually performed in 90-day studies.

616 Extrapolation from subacute to chronic duration: the Scientific Committee is not in a position to
617 propose default values, due to differences in the respective study designs.

618

619 Absence of a NOAEL: if the dataset allows for applying the BMD approach, there is no need for
620 applying any additional UF. In cases where the BMD approach cannot be applied, the LOAEL
621 approach will be used and an additional UF will be needed, the size of which should be determined on
622 a case-by-case basis.

623

624 **5.3. Severity and nature of the observed effect**

625 Severity is the degree to which an effect changes and impairs the functional capacity of an organ
626 system. Whilst the application of an additional UF because of the severity of an effect is not routinely
627 used, there are some examples where such a factor was considered necessary.

In EHC 240 (IPCS, 2009), the use of an extra UF for the severity of the effect is recommended for the derivation of the ARfD by JMPR: if a toxicological effect is judged to be irreversible or particularly severe, this should be a trigger to consider the finding in more detail before choosing an appropriate UF.

According to the Guidelines for Drinking water Quality (WHO, 2008), an additional UF might be applied when the end point is a foetal malformation, or when the endpoint determining the NOAEL (or BMDL) is directly related to possible carcinogenicity.

In the field of pesticides, the following principle is described in the legislation, with regard to the establishment of reference values (ADI, ARfD and AOEL): "When the critical effect is judged of particular significance, such as developmental neurotoxic or immunotoxic effects, an increased margin of safety shall be considered, and applied if necessary" (Regulation n°1107/2009). When an additional UF has been considered necessary, a factor of up to 10 was applied.

For genotoxic and carcinogenic compounds which may be found in food, irrespective of their origin, and where no health-based guidance values can be established, the Scientific Committee of EFSA recommends the margin of exposure (MOE) approach (EFSA, 2005). The MOE is the ratio between a reference point on the dose-response curve for the adverse effect and the human intake; as such, it does not make implicit assumptions about a "safe" intake. In this opinion, the Scientific Committee proposed that a MOE of 10,000 or higher, if based on the $BMDL_{10}$[7] from an animal study, and taking into account overall uncertainties in the interpretation, would be of low concern from a public health point of view. However, such a judgement is ultimately a matter for the risk managers. Moreover a MOE of that magnitude should not preclude the application of risk management measures to reduce human exposure. Similarly, under the new European chemicals regulation (REACH), the ECHA guidance (2010) recommends to use a Derived-Minimal-Effect-Level (DMEL) for non-threshold substances, which is a MOE approach.

Conclusions:

The Scientific Committee considers that the need for an extra UF to allow for the severity of an effect is exceptional, and therefore recommends considering its use on a case-by-case basis.

For genotoxic and carcinogenic compounds where no health-based guidance values can be established, the Scientific Committee refers the reader to the margin of exposure approach described in its opinion related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic (EFSA, 2005).

5.4. Probabilistic approaches and combinations of uncertainty factors

One alternative to the use of deterministic uncertainty factors in traditional risk assessment is the use of probabilistic distributions of the UFs. As lognormal distributions are thought to best describe variability and uncertainty in UFs, these distributions have been derived based on NOAEL-ratios from comprehensive toxicological databases. Different methodologies in the literature have provided estimates of UFs for the inter-/intra-species extrapolation, for the exposure duration extrapolation, for the use of a LOAEL, and for the combination of the different UFs.

[7] The $BMDL_{10}$ is the 95th percent lower confidence limit of the BMD of 10% extra risk.

669 In the standard procedure of deterministic risk assessment, the point estimates of various UFs are
670 multiplied to obtain an overall UF. Due to the possible interdependence of several UFs (e.g. time
671 extrapolation and interspecies variability), multiplication of the single UFs may lead to possibly overly
672 conservative estimates. This cumulation of worst case assumptions can be avoided by using
673 probability distributions of the various UFs. Under the assumption that the distributions of the UFs are
674 independent, their combination can be modelled, e.g. using Monte Carlo simulation, yielding a
675 probability distribution of the overall UF. This offers the possibility for a quantitative estimate of the
676 probability that an adverse effect will occur in a certain population at the estimated exposure level.
677 Moreover, the distribution of the overall UF can be probabilistically combined with the distribution of
678 the BMD, as also the effect parameter is uncertain and is best described by a lognormal distribution
679 (ECHA, 2010).

680 Several limitations of these probabilistic approaches for the UFs are highlighted by Vermeire (2001),
681 based on the fact that all distributions proposed are based on analyses of historical data, i.e. NOAEL
682 ratios:

683 1) The criteria used for constructing databases are not always transparent and NOAEL-ratios may have
684 been assessed without knowing the quality of the underlying data.

685 2) The uncertainty in the NOAEL as an estimate of the true No-Adverse-Effect-Level (NAEL) is
686 unknown. If ratios of NAELs would have been used, the distributions would have been less wide (i.e.
687 smaller geometric standard deviation).

688 3) Although the proposed default distributions are considered sufficiently founded to justify their
689 application in human risk assessment, further research on the basis of larger databases is still
690 considered necessary, especially with regard to the intraspecies distribution.

691 4) In the derivation of an interspecies UF from NOAEL-ratios, it is assumed that variability between
692 laboratory animals represents animal-human variability.

693 The advantage of the probabilistic risk assessment is that of more accurate risk estimates consistent
694 with the probabilistic nature of risk, whereas the disadvantages are those of being demanding in terms
695 of data collection/availability, calculation effort and experience of the risk assessor. Other factors
696 limiting the use of probabilistic techniques are the lack of guidance on the approach, including the
697 selection of models. In addition, there are difficulties in interpretation of the computed outcome and
698 the related risk communication. For these reasons, the probabilistic risk assessment is usually
699 undertaken only for substances of high concern and large data availability (ECHA, 2010).

700 The probabilistic approach was used by the EFSA Panel on Contaminants in the Food Chain
701 (CONTAM) when establishing the Tolerable Weekly Intake (TWI) for cadmium (EFSA, 2009). The
702 Panel modelled summary data from the literature relating urinary cadmium concentration to urinary
703 beta-2-microglobulin (B2M), a biomarker of kidney function, in order to derive a reference point from
704 the reported subgroup means. Because the individual data were not available, the CONTAM Panel
705 divided its reference point by a data-derived adjustment factor to allow for individual variability
706 within the dose groups. In contrast, JECFA concluded that it could not be assumed that urinary B2M
707 concentrations would vary as a function of urinary cadmium concentration within a sub-group.
708 Therefore the JECFA modelled the toxicodynamic variability by introducing a log-triangular
709 distribution function with a fixed range of variation by a factor between 1 and 3 below and above a
710 reference point identified from the same data set. Individual values were generated in a Monte-Carlo
711 simulation approach for both increased and reduced individual susceptibility resulting in a distribution
712 around the reference point.

713

Conclusions:

The Scientific Committee recommends that these probabilistic approaches and combination of UFs are further investigated before harmonisation is proposed within EFSA.

6. Rounding of figures when deriving health-based guidance values

Communicating an estimated figure (e.g. an HBGV) with an inadequate number of significant figures may convey a spurious idea of precision, masking therefore the assumptions made and the uncertainty factors that were used to establish the HBGV.

When dealing with a measured value, the degree of precision is determined by the precision of the analytical methodology. When reporting derived values, then the degree of precision should take into account the precision of the components used in the derivation. As a general rule, rounding should happen as late as possible in the assessment process, for example in establishing an ADI.

The Scientific Committee emphasizes that the following rule should be applied for rounding a value: If the digit to the right of the last significant digit is less than 5, that last significant digit is not changed. If the digit to the right of the last significant digit is 5 or greater, that last significant digit is rounded up. A digit is defined as significant if it contributes to the precision of the value, which excludes:

- Leading zeros where they serve merely to indicate the scale of the number (e.g. 0.006 has one significant figure).

- Spurious digits introduced, for example, by calculations carried out to greater accuracy than that of the original data, or measurements reported to a greater precision than the equipment supports (e.g. 2.000).

The practical impact of rounding an health-based guidance value will vary depending on the numerical closeness of the unrounded value to the rounded value, for example the impact of rounding 1.9 to 2 is less than of rounding 1.4 to 1. The latter case could present difficulties for risk managers if, for example, exposure was estimated to be 1.3 mg/kg b.w. per day. One approach to dealing with this would be to round to a single significant figure if the impact of rounding is less than a certain percentage, and to two significant figures if the impact exceeds that percentage.

The measurement of an adverse health effect differs from a chemical analysis in the sense that the precision of the measurement of an effect (or the power to detect an effect) in an animal study is determined by a number of factors, including the numbers of animals per dose group, variability in dose to individual animals throughout the duration of a study (e.g. if the chemical is administered in the diet to animals caged in groups), dose spacing (if a NOAEL approach is used rather than a BMDL), as well as the measurement method used to detect the toxicological endpoint of interest. Consequently, the overall precision is unlikely to be less than 10%. Table 8 illustrates rounding to one or two significant figures such that the rounded figure does not vary by more than 10% from the unrounded figure, and hence is likely to be within the range of experimental error.

752 **Table 8:** Impact of a 10% variation threshold as a rule for rounding

Unrounded figure	Rounded to one significant figure	% change	Proposed rounding	% change
0.098	0.1	2.0	0.1	2.0
0.268	0.3	11.9	0.27	0.7
1.784	2	12.1	1.8	0.9
1.839	2	8.8	2	8.8
5.198	5	-3.8	5	-3.8
14.86	10	-32.7	15	0.9
26.24	30	14.3	26	-0.9
346.3	300	-13.4	350	1.1

753

754 Conclusions:

755 • The degree of precision for measured values is determined by the precision of the analytical
756 methodology

757 • When reporting derived values, then the degree of precision should take into account the
758 precision of the components used in the derivation.

759 • Derived values, such as health-based guidance values, will be rounded to a single significant
760 figure if the impact of rounding is less than 10%, and to two significant figures if the impact
761 of rounding to one significant figure exceeds that percentage.

762

763 CONCLUSIONS AND RECOMMENDATIONS

764 The purpose of this guidance document is harmonisation of default values used by EFSA Scientific
765 Panels and Committee, and not standardisation: it is therefore always possible to deviate from the
766 proposed default values, provided that the rationale for such deviation is described.

767 Following the review of default values used by the EFSA Scientific Panels and Committee, and the
768 EFSA Units, and the most recent national information compiled in the EFSA Comprehensive
769 European Food Consumption Database, the Scientific Committee recommends the following default
770 values to be used in the absence of empirical data:

771 **Body weight (See section 2)**

772 • A body weight of 70 kg should be used as default for European adults.

773 • For dietary exposure assessment, a body weight of 12 kg should be used as default for
774 European infants and children. If deviation from the default value is required for the
775 assessment of specific age groups, the median values identified in table 3 should be used.

776

Total food and liquid intake (see section 3)

- The Scientific Committee was not in a position to propose a harmonised default value for daily total solid food intake for adults. Such values should be considered according to the relevant guidelines and legal requirements. The Scientific Committee however recommends that the EFSA Comprehensive Database is regularly consulted to check the relevance of the default values that are used. The Scientific Committee did not consider possible default values for daily total solid food intake for children, as the EFSA Panels and Units did not report using such default values.

- A 2 L default value for daily total liquid intake is recommended for European adults, including the elderly. For children's total liquid intake, the reader is referred to the NDA opinion on dietary reference values for water where adequate intake levels are provided according to their age.

Factors for converting chemical compound concentrations in feed or drinking water into daily doses in experimental animal studies (see section 4)

Administration of test compounds in feed

- For chronic studies, a default factor of 0.05 for rats and 0.15 for mice, e.g. 1 mg/kg in feed is equivalent to a dose of 0.05 and 0.15 mg/kg bw per day in rats and mice, respectively

- For subacute studies, a default factor of 0.12 for rats and 0.2 for mice

- For subchronic studies, a default factor of 0.09 for rats and 0.2 for mice

- Experiments start usually at week 5 to 7. If a subacute or a subchronic study starts at a later age, e.g. after week 25, then the conversion factor for chronic studies should be applied.

Administration of test compounds in drinking water

- For chronic studies, a default factor of 0.05 for rats and 0.09 for mice, e.g. 1 mg/L in water is equivalent to a dose of 0.05 and 0.09 mg/kg bw per day in rats and mice, respectively

- For subacute studies, a default factor of 0.12 for rats and 0.18 for mice

- For subchronic studies, a default factor of 0.09 for rats and 0.15 for mice

- Experiments start usually at week 5 to 7. If a subacute or a subchronic study starts at a later age, e.g. after week 25, then the conversion factor for chronic studies should be applied.

Uncertainty factors (UFs) used in establishing health-based guidance values (See section 5)

Intra/inter-species extrapolation

- In the absence of chemical-specific data on kinetics and/or dynamics, the Scientific Committee recomends using the overall default uncertainty factor of 100 (10 for inter-species variability x 10 for intra-human variability).

- If available, chemical-specific data on kinetics and/or dynamics should be used. For the remaining components, for which data are not available, the following default sub-factors should be applied:
    - for inter-species variability in toxicokinetics: 4.0
    - for inter-species variability in toxicodynamics: 2.5
    - for intra-human variability in toxicokinetics: 3.16
    - for intra-human variability in toxicodynamics: 3.16

Deficiencies in the data available for the assessment

- In case of deficiencies in the data for applications, the EFSA Scientific Committee recommends that, rather than applying an additional UF, the possibility/feasibility of getting additional data improving the quality of the dataset is first considered. Therefore, the lack of data should not directly imply the use of an extra UF.

- When additional data cannot be obtained or requested, the use of an additional UF to take account of the deficiency of a database should be considered on a case-by-case basis. It is not possible to propose a default value for this UF, as it will be directly dependent on the dataset available.

Extrapolation for duration of exposure

- Extrapolation from subchronic to chronic duration: the EFSA Scientific Committee recommends the use of an UF of 2, considering the extent of investigations usually performed in 90-day studies.

- Extrapolation from subacute to chronic duration: the Scientific Committee is not in a position to propose default values, due to differences in the respective study designs.

Accounting for the absence of a NOAEL

- In its previous opinion, the Scientific Committee recommended using the benchmark dose (BMD) approach rather than the NOAEL or LOAEL for deriving the reference point. When using the BMD approach, there is then no need for an additional UF.

- In cases where the BMD approach cannot be applied and there is no NOAEL for the critical effect, the LOAEL can be used. In this case, an additional UF is needed, the size of which should be determined on a case-by-case basis.

Severity and nature of the observed effect

- The Scientific Committee considers that the need for an extra UF to allow for the severity of an effect is exceptional, and therefore recommends considering its use on a case-by-case basis.

- For genotoxic and carcinogenic compounds where no health-based guidance values can be established, the Scientific Committee refers the reader to the margin of exposure approach.

Probabilistic approaches and combinations of uncertainty factors

The Scientific Committee considered the use of probabilistic distribution of UFs for EFSA's risk assessment, as an alternative for multiplying various UFs for deriving health-based guidance values, which may end up in cumulating worst case assumptions. The Scientific Committee recommends that these probabilistic approaches and combination of UFs are further investigated before harmonisation is proposed within EFSA.

Rounding of figures when deriving health-based guidance values (see section 6)

- The degree of precision for measured values is determined by the precision of the analytical methodology

- When reporting derived values, then the degree of precision should take into account the precision of the components used in the derivation.

- Derived values, such as health-based guidance values, will be rounded to a single significant figure if the impact of rounding is less than 10%, and to two significant figures if the impact of rounding to one significant figure exceeds that percentage.

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941 **APPENDIX**

942 **Default Values proposed for use by EFSA Scientific Panels and Committee, and EFSA Units**

943

Issue for harmonisation	Default value proposed		Remark
Body weight (Kg)	Adults: 70	Infants & children: 12	
Total solid food intake	No default value		
Total liquid intake (L)	Adults: 2	Children: no default values	For children, See http://www.efsa.europa.eu/en/efsajournal/doc/1459.pdf
Converting test compound concentrations in feed (mg/kg), into daily dose (mg/kg b.w. per day)	*Rat* Chronic studies: 0.05 Subacute studies: 0.12 Subchronic studies: 0.09	*Mice* Chronic studies: 0.15 Subacute studies: 0.2 Subchronic studies: 0.2	If a subacute or a subchronic study starts at a later age, then the conversion factor for chronic studies should be applied
Converting test compound concentrations in drinking water (mg/l), into daily dose (mg/kg b.w. per day)	*Rat* Chronic studies: 0.05 Subacute studies: 0.12 Subchronic studies: 0.09	*Mice* Chronic studies: 0.09 Subacute studies: 0.18 Subchronic studies: 0.15	If a subacute or a subchronic study starts at a later age, then the conversion factor for chronic studies should be applied
UF for inter-species extrapolation	No data on kinetics and/or dynamics available: 10	Variability in toxicokinetics: 4.0 Variability in toxicodynamics: 2.5	
UF for intra-human extrapolation	No data on kinetics and/or dynamics available: 10	variability in toxicokinetics: 3.16 variability in toxicodynamics: 3.16	
UF for Deficiencies in the data available for the assessment	No default UF		Consider the possibility/feasability of getting additional data first. If not feasible, use additional UF (value determined on a case-by-case basis).
UF for for duration of exposure extrapolation	Subchronic to chronic: 2	Subacute to chronic: no default UF	
UF to account for the absence of a NOAEL	No default UF		Use the BMD approach. If not possible, consider use of the LOAEL with an additional UF (value determined on a case-by-case basis)
UF to account for the severity and nature of the effect	No default UF	Genotoxic and carcinogenic compounds: Use the Margin of Exposure approach	Usually not needed. If exceptionally considered necessary, UF value determined on a case-by-case basis.

944 UF: Uncertainty Factor

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946 **ABBREVIATIONS**

ADI	Acceptable Daily Intake
ANS	EFSA Panel on Food Additives and Nutrient Sources Added to Food
AOEL	Acceptable Operator Exposure Level
ARfD	Acute Reference Dose
BMD	Benchmark Dose
BMDL	Lower confidence limit of the BMD
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CONTAM	EFSA Panel on Contaminants in the Food Chain
CSAF	Chemical-Specific Adjustment Factors
DCM	EFSA Dietary and Chemical Monitoring Unit (former DATEX Unit)
DMEL	Derived-Minimal-Effect-Level
ECHA	European Chemicals Agency
EHC	Environmental Health Criteria
FAO	Food and Agriculture Organization
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
HBGV	Health-Based Guidance Value
ICRP	International Commission on Radiological Protection
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	Lowest-Observed-Adverse-Effect-Level
MOE	Margin of Exposure
NAEL	No-Adverse-Effect-Level
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NOAEL	No-Observed-Adverse-Effect-Level
NTP	U.S. National Toxicology Program
PPP	Plant Protection Products
PPR	EFSA Panel on Plant Protection Products and their Residues
PRAS	EFSA Pesticides Unit
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
TDI	Tolerable Daily Intake
TTC	Threshold of Toxicological Concern
TWI	Tolerable Weekly Intake
UF	Uncertainty Factor
WHO	World Health Organisation

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