



EUROPEAN COMMISSION  
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL  
Directorate C - Public Health and Risk Assessment  
**C7 - Risk assessment**

**SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS**  
**SCHER**

**Opinion on**

**The revised chapter for “Human Health Risk  
Characterisation” of the Technical Guidance Document  
on Risk Assessment in support of Directive 93/67/EEC  
on new notified substances and Regulation 1488/94 on  
existing substances of new and existing substances”**

**(Draft of November 2005)**

Adopted by the SCHER  
during the 13<sup>th</sup> plenary of 19 September 2006

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## **1. BACKGROUND**

The human health risk characterisation guidance chapter has been developed for application to new and existing substances. The revised chapter is the result of work done by a sub-group of the Technical Committee on New and Existing Substances with participants from Member States, Industry and the Commission. The chapter represents a number of changes as compared to the previous TGD version, including the recommendation to use default assessment factors for assessing threshold effects and, where appropriate, approaches to quantitative assessment of non-threshold effects.

## **2. TERMS OF REFERENCE**

DG Environment has requested the opinion from the SCHER on the revised chapter for “Human Health Risk Characterisation” of the Technical Guidance Document on Risk Assessment in support of Directive 93/67/EEC on new notified substances and Regulation 1488/94 on existing substances of new and existing substances” (TGD) (Draft of November 2005).

The SCHER is requested to examine the following questions:

- (1) Does the SCHER find the methods for human health risk characterisation generally appropriate?
- (2) An important new development in this guidance is the consensus reached on the assignment of default assessment factors for threshold effects, that may where relevant and justified be deviated from or modified on the basis of substance-specific information. Can SCHER consider the merits of this approach?
- (3) Another development is that this guidance allows risk assessors to use a quantitative approach for assessment of non-threshold effects, depending on the robustness of the underlying information basis. Can SCHER consider the merits of this approach?
- (4) If the SCHER finds certain approaches or methods for human health risk characterisation not appropriate, the SCHER is invited to suggest possible alternative approaches or methods meeting the same objectives.

## **3. OPINION**

### **3.1. Overall considerations**

The SCHER acknowledges the efforts that have been undertaken to revise and update the human health risk characterisation chapter of the TGD. Basically, the TGD describes all necessary tools and procedures for the risk assessment of chemical substances. Moreover, the TGD specifically addresses the risk assessment of chemicals with limited or insufficient data. Although the majority of chemicals may indeed have a limited database, focussing on this situation in the TGD bears the risk, that even substances with sufficient information will be evaluated by a formalistic procedure rather than on a case-by-case approach. Consequently, it is the SCHER’s major recommendation that the TGD clearly indicates, that each substance is a specific case with a specific database and

that any risk assessment of a substance has to consider the specific data that is available. This also implies that a limited data base may be sufficient for a First Tier approach and for a preliminary screening to identify chemicals of low concern.

It should be highlighted that a scientifically defensible risk assessment depends on the availability of a base set of reliable data which in itself is determined by the nature and extent of human exposure to the chemical. Otherwise, the risk assessment is subject to assumptions associated with uncertainties. Consequently, an expert evaluation of the available database should be performed first, i.e., BEFORE any default assessment factors are used. If this analysis shows that the available data is sufficient and reliable for a sound risk assessment, then the use of default assessment factors is not necessary. Remaining uncertainty can be addressed by establishing an acceptable Margin of Safety (MoS), if the available data is poor, this should either result in a request for more information or studies, or in the application of default assessment factors. In the latter case, the need and extent of these factors should be evaluated and modified according to the available data. Moreover, the restrictions and uncertainties associated with the use of assessment factors must clearly be described. It is recommended to include some guidance in the TGD on the conditions under which the second option, i.e., the use of default assessment factors, is applicable.

SCHER is also concerned, that the TGD does not provide a general guidance on how toxicity information from the hazard identification and dose-response analysis (= hazard characterisation) is integrated with the human exposure estimates. A chapter “general aspects” (as in the previous version of the TGD) should be introduced which summarises the key components of risk characterisation.

SCHER also notes that the proposed methodologies are neither complete, nor entirely consistent throughout the TGD nor fully transparent, and that, therefore, a high probability exists for inconsistencies and unrealistic outcomes in the resulting risk characterisation process.

Finally, the SCHER indicates that in view of the new EU chemicals policy (REACH) a large number of risk characterisations and risk assessments will be performed. In this process, the TGD will play an important role to improve the quality and consistency of the assessments. Therefore, the document should be adjusted once the guidance for REACH has been developed. Furthermore, it is important to make the document as clear, reasonable and concise as possible and it is the recommendation of SCHER that the document is scrutinised for consistency and repetitions. Also, more attention needs to be given to the importance of expert judgement in the risk characterisation process; at present, the proposal focuses too much on rather formalistic procedures and insufficiently draws on the importance of expert judgement for a case-by-case evaluation.

### **3.2. Question 1**

*Does the SCHER find the methods for human health risk characterisation generally appropriate?*

Risk characterisation describes the nature and magnitude of risk, including strengths and weaknesses of the exposure and effects analysis, potential sources of risk, and any subpopulations that are at increased risk. It should include information on the confidence in the results and describe the assumptions used and the uncertainties in the analysis.

The proposed methodology in the revised risk characterisation chapter of the TGD, however, addresses only a few of these elements, and, in particular, neglects the aspects associated with the integration of human exposure information. Guidance needs therefore to be added on how to integrate the hazard identification, dose-response assessment (= hazard characterisation) and exposure assessment results; furthermore, guidance should be included on how to assess the overall strengths and weaknesses of the exposure and effects database, and the resulting level of confidence in this database.

Only little practical guidance is provided on the issue of uncertainty (in section 4.1, 4.7.4 and 4.14.), but there is, for instance, no guidance on which representations of uncertainty should be used, how uncertainties should be quantified and when uncertainties might need to be reduced. On the other hand, much space in the document is allocated to dose (concentration) – response (effect) assessment, a step that is part of the hazard characterisation process which is dealt with in chapter 3.4 of the TGD.

Where information relating to issues addressed in other chapters of the TGD is requested, a cross-reference to these chapters might be helpful and should be inserted.

The revised chapter on risk characterisation proposes a traditional methodology, primarily based on deterministic principles. Probabilistic approaches are not considered workable, although they have been recognised by the scientific community as an appropriate approach. The SCHER is therefore of the opinion that probabilistic calculations for exposure assessment should be given preference when appropriate data are available. This helps to avoid an over-conservative approach which is prone to lead to unrealistic outcomes.

The guidance also fails to propose a commonly accepted set of principles defining how mechanistic or mode of action information can be used in the risk characterisations, particularly as it relates to extrapolation issues across and within species, across time, and from high-to-low doses.

Biological markers (biomarkers) that provide direct human dose-response data that will reduce the assumptions and uncertainties that arise from interspecies and high-dose to low-dose extrapolations are only briefly mentioned in the document, but would certainly deserve a specifically dedicated paragraph.

The SCHER acknowledges, though, that it is very difficult to develop general guidance on this issue as biomarkers are very diverse and will often require a case-by-case approach. Overall, the guidance should be kept flexible and open, so that upcoming issues could be integrated, such as, for instance, the risk characterisation for nanoparticles or particularly vulnerable groups.

Sections 4.1 to 4.7, in particular, are not clearly structured, and lack guidance on how toxicity information from the hazard identification and dose-response analysis (= hazard characterisation) is integrated with the human exposure estimates.

As mentioned before, a chapter “general aspects” (as in the previous version of the TGD) should be re-introduced which summarises the key components of risk characterisation, such as information on the nature, reliability, and consistency of the data used; the reason for selection of the key studies and the critical effects and their relevance for humans; the limitations of the available data; the assumptions used, and their implications; the level of scientific confidence in the database; the areas of uncertainty; data needs and the potential impact of new research.

The importance to consider the uncertainties in the exposure assessment is described in general terms in section 4.3. This has rarely been included in the assessments so far, and more practical guidance than given here is needed. There is also a need for guidance how to communicate the uncertainties to the risk managers. Both WHO and EFSA are working on guidance documents in this field, and those may be useful for an extension of this section in the new version of the TGD. It is also important to point at the exposure uncertainties in the tests used to determine the effects.

A clear definition of the terms combined, aggregated and cumulative exposure is needed as those are being used more and more frequently. In the WHO document “Risk Assessment Terminology” (WHO, 2004) the working group did not manage to give those definitions, but it has to be done to avoid further confusion. The SCHER suggest the following:

- Cumulative exposure is the total exposure to one stressor from several sources and/or via several pathways
- Aggregate exposure is total exposure to one stressor from several sources and/or via several pathways over time
- Combined exposure describing the exposure to several stressors giving similar effects.

SCHER fully agrees with the proposition that combined exposures should be given specific attention in the risk characterisation step (section 4.3.3). However, there is only limited and somewhat confusing guidance provided on how to address this issue under the referred sections (4.3.3, 4.4.2 with Appendix VIII, and 4.6).

Furthermore, there is no clear distinction made between combined, cumulative and aggregated exposures; in this context SCHER also notes that the wording “concomitant exposure” (in sections 4.3.3 and 4.4.2) should be replaced by “combined exposure”.

SCHER also supports that the risk characterisation should take into consideration cumulative exposure to very closely related and similar acting chemical substances (e.g. salts of metal or closely related derivatives of organic substances) (section 4.3.3.). Aspects of cumulative exposure should, however, clearly be separated from the aspect of combined exposure to a single chemical from different exposure routes and exposure scenarios. Overall, more transparent guidance on when and how to perform combined and/or cumulative risk characterisation is necessary.

Section 4.8 (Acute Toxicity): most of the proposed text addresses elements of hazard characterisation and not of risk characterisation, and should therefore be modified.

Furthermore, it would be more important to focus on information on systemic effects at sub-lethal doses rather than on information relating to local irritation, which actually is the topic of the next section (4.9 Irritation). The statement that “the severity of local effects should be proportional to the dose level” is not correct, because the severity of local effects is generally more a function of the local concentration than of the dose level. Useful guidance on the selection of endpoints and uncertainty factors for acute exposure situations can be found in the Standing Operating Procedures for the Acute Exposure Guideline Committee (NRC, 2001).

Section 4.9 (Irritation), 4.9.1./General issues: It needs to be explained why “it may be necessary to estimate exposure levels for comparison with the N(L)OAEL value for an

analogous substance if possible” when “it is thought that respiratory irritation may be caused by inhalation of the substance”.

Section 4.9 (Irritation), 4.9.2./Skin and eye irritation: It is mentioned that rats are known to be less sensitive than rabbits in skin tests. However, it is also known that the skin of rabbits is generally much more sensitive to irritation than human skin. Hence, the merit of the statement relating to the different sensitivity for the overall risk characterisation of human exposure is not clear.

Section 4.9 (Irritation), 4.9.3./Respiratory irritation: The guidance itself casts doubt on the appropriateness of the general default assessment factor of 2.5 for the interspecies difference between rat and man, as the sensitivity of rat may indeed be much higher than that of humans in some cases, whilst in others the reverse may be true. The SCHER would recommend a case-by-case evaluation based on the available human and experimental evidence. A scientific basis for interspecies extrapolation of nasal olfactory irritants from rodents to humans has been provided by Frederick et al. (1998).

Section 4.10 (Corrosivity): It should be mentioned that also physico-chemical properties ( $\text{pH} \leq 2$  or  $> 11.5$ ; buffering capacity) have to be considered.

Section 4.11 (Sensitisation): The justification on why only the dermal and respiratory exposure routes are considered in the document (“...as these routes are the most relevant ... to industrial chemicals ....”) is not supported by SCHER as risk characterisation needs to include also consumer (including children’s) exposure which may indeed be through the oral route as the most relevant route (e.g. mouthing behaviour of toddlers). The SCHER recommends that the wording of the justification is modified and that sensitisation after the oral route of exposure, if relevant, is to be evaluated on a case-by-case basis by expert judgement.

Although data on sensitisation and elicitation thresholds is momentarily scarce, more knowledge will be available in the long-term. Modern testing protocols, e.g. the mouse local lymph node assay already produce dose-response information, and the TGD should therefore more clearly recommend the use of a threshold approach if the available data allows for it.

Unlike in other chapters, assessment factors are also proposed for the vehicle used (if different from the human exposure situation), skin integrity, exposed part of the body etc. Other chapters, in particular those on skin irritation, acute and repeated dose toxicity, would need to be adapted for consistency.

Sensitising skin area doses are very similar between mice and humans, and a reduced interspecies extrapolation factor of  $10^{0.5}$  (rounded to 3) has been proposed by Griem et al. (2003), if data from the mouse local lymph node assay is used. It is recommended to include this aspect in the guidance document.

The justification of a smaller intraspecies factor for sensitisation based on the age aspect appears to be not very well founded and should be re-considered. The respective sections should be modified to point out, that all available information needs to be evaluated to justify or modify the uncertainty or default factor applied.

The definitions of the sensitisation and elicitation thresholds should be revised to be in line with the commonly used language, i.e. the elicitation threshold (or minimum elicitation threshold, MET) is the level of exposure below which no sensitisation reaction is expected. The concept behind the MET is that there is an “elicitation threshold” below which also no sensitisation reaction is expected.

Section 4.11.2 (Respiratory sensitisation): Here, in contrast to other sections, assessment factors are suggested that also consider the potential seriousness of the condition. Other sections would need to be adapted for consistency.

Section 4.12 (Repeated Dose Toxicity): Provided that the database is sufficient, the benchmark dose approach should be allowed as stand-alone alternative and not just “in addition”. The SCHER is aware that according to the EU legal text, a NOAEL should be used if available, and also notes that currently available datasets are often not entirely suitable for applying a benchmark dose model. Nevertheless the benchmark approach is the scientifically more appropriate method, and therefore recommended as the preferred method.

SCHER notes that the lack of relevance for humans of certain adverse effects in animals is not addressed in this section (e.g. alpha<sub>2u</sub>-globulin-induced nephropathy). With regard to these effects, a cross-reference to TGD chapter 2, section 3 could be added.

Section 4.13 (Mutagenicity): For non-threshold mutagens, the risk characterisation should be performed either qualitatively or quantitatively with the same methodology as proposed under the carcinogenicity section. With regard to the quantitative approach, SCHER has the same comments as outlined under the carcinogenicity section and under question 3 of this document.

It should be mentioned, that, in addition to cytotoxicity, also the relevance of the mechanism of genotoxicity to anticipated *in vivo* exposure should be considered, e.g. if positive responses are elicited *in vitro* under non-physiologic exposure conditions such as high osmolarity or low pH.

Section 4.14 (Carcinogenicity): this section has plenty of information in it which actually would better fit in the “general issues” section, such as the sections on “uncertainties in data and methodology”, “assessment factors”, and on “modifying elements”, as they are not specific to this section. The SCHER notes that the lack of relevance for human risk of certain mode-of-actions is not addressed (e.g. alpha<sub>2u</sub>-globulin-induced renal toxicity or liver tumours induced by peroxisome proliferator-activated receptor alpha agonists; cf. also IPCS, 2005). With regard to these effects, a cross-reference to TGD chapter 2, section 3 should be added.

Comments with regard to the quantitative assessment of non-threshold carcinogens are provided below (cf question 3). Some consideration should also be given to more recent carcinogenicity study protocols, e.g. with transgenic mouse strains, especially to caution their relevance beyond hazard identification, because - at this stage – the interpretation of the results and their use for a quantitative risk assessment are difficult (EMEA, 2004).

It is generally recognised that human data from epidemiological studies, if available and of sufficient quality, are preferred as the starting point for quantitative risk analysis of carcinogens above the use of data from experimental animal studies. Besides the advantages that epidemiological data do not require species-species extrapolation, exposure conditions of the study are usually much more comparable to those in the target population than those applied in an animal experiment.

SCHER agrees, that in situation of limited availability of epidemiological data (especially on new substances), risk assessment needs to be based on experimental animal data. However, epidemiological data should be strongly considered in case such data are available (existing substances). TGD should propose a clear protocol for judging the epidemiological evidence for hazard identification and for cancer risk

characterisation. Approaches to quantitative risk assessment based on epidemiological data have been described by WHO (2000) and recently by Goldbohm et al. (2006). The steps include selection and evaluation of epidemiological data, derivations of relative risk as a function of exposure from the selected epidemiological data and calculation of excess lifetime risk for an exposed target population. SCHER also proposes to evaluate the MOE for carcinogens.

In case of observational studies, where persons have not been randomly assigned to exposed versus unexposed groups, data may be affected by bias and confounding, which distorts the exposure-disease association. The TGD should emphasise the need to use good epidemiological practise to minimise major sources of bias and confounding. Cross-reference to TGD chapter 2, sections 3.11.2., 3.11.3, and 3.12.3. (Reprotox) on the use of epidemiological data should be included.

Section 4.15 (Reproductive Toxicity): this section is very short, and lacks much critical detail. For instance, the risk characterisation with regard to the male reproductive system is not addressed.

### **3.3. Question 2**

*An important new development in this guidance is the consensus reached on the assignment of default assessment factors for threshold effects, that may where relevant and justified be deviated from or modified on the basis of substance-specific information. Can SCHER consider the merits of this approach?*

The risk characterisation process should address uncertainties in the assessment of exposure and effects data, including, for instance, the extrapolation of animal data to man, the extrapolation of differences in exposure duration, the route-to-route extrapolation and in the lack of confidence in the available data base. Different organisations, regulatory bodies and individuals have therefore developed default uncertainty factors (assessment factors) to compensate for the lack of respective knowledge and to describe a risk with as little uncertainty as possible. The revised TGD chapter on risk characterisation now lists some of these efforts in a tabular overview. In parallel, the revised guidance suggests that default assessment factors should be applied and that these may be modified on basis of substance-specific information, where relevant and justified.

SCHER re-iterates here some points already made in the “general considerations” section of this document, namely, that the extent and nature of human exposure determines the scope of data that is necessary for a reliable risk characterisation and risk assessment. If sufficiently robust data is available, then there is no need to apply default assessment factors and expert judgment is recommended to describe the risk with as little uncertainty as possible.

Only if the expert evaluation of the available database has shown that the data is too poor for a sound risk characterisation, then the application of default (or modified) assessment factors would be an option. In that case, the uncertainties associated with the use of these factors must clearly be pointed out in the risk assessment report. The SCHER recommends that this step-wise approach is laid out in the TGD.

The SCHER also recommends that more emphasis is given to the scientific expertise as compared to the rather formalistic approach that is presently proposed in the TGD, because experience has shown that the uncritical application of assessment factors may

lead to unrealistic outcomes. This is mostly ascribed to the scientifically debatable justifications, from which the default assessment factors are derived and to the consequences when combining the uncertainties. The use of default values for assessment factors therefore needs caution.

Whilst the revised TGD very much stresses the benefit of transparency, for most of the proposed default factors no scientific justification was provided, and the SCHER therefore cannot generally approve these factors. In the following, comments are provided which are specific to certain assessment factors proposed in the draft TGD chapter.

For the difference in sensitivity between species, an allometric scaling factor is proposed based on the assumption that the differences in sensitivity would only be due to differences in body size and related differences in the basal metabolic rate. This is scientifically justified. However, the proposal to apply an additional factor of 2.5 for “other interspecies differences” cannot be accepted, unless this is referring to potential toxicodynamic differences as described in the document by WHO (2005) on interspecies differences. This should be clarified in the guidance.

In case of species differences relating to toxicokinetics and toxicodynamics, it would be appropriate to use the method that has been proposed by the WHO (2005).

The “traditional” default assessment factor of 10 is proposed (except for workers) to account for intrahuman variability, including children and the elderly. If experimental data relating to effects on vulnerable organ system and functions are not available from young animals (which may almost always be the case), a higher assessment factor (up to 100) should be considered for children (no further guidance or justification is provided). The SCHER, again, is of the opinion that the WHO method and its justification is more appropriate (WHO, 2005). The SCHER does also not support the proposed assessment factor of “5” for workers. This contradicts the guidelines of the Scientific Committee for Occupational Exposure Limits (SCOEL) which state that “Ufs (Uncertainty Factors) must be established on a case-by-case basis and cannot be forecasted or established in advance.” (SCOEL, 1999).

No scientific justification is provided for the proposed default assessment factors relating to the duration of the exposure; efforts should be made to include such justification in order to increase the acceptability of these factors.

For uncertainties in the dose-response relationship assessment, a default assessment factor between 3 and 10 is suggested, if the point of departure for the MOS calculation is a LOAEL. There is no information on how the defaults have been derived, and, for instance, it also remains unclear how slope of the dose-response curve is taken into account. Overall, no justification for the proposed default values (nor references where such could be found) was provided.

The suggestion to use an “additional assessment factor” that is “considered to be sufficiently large to cover the significant inherent uncertainties” in the case where only an LD(LC)<sub>50</sub> value is available, is rather vague and does not help the risk assessor. Rather than proposing an “additional assessment factor”, the uncertainty should be described and a final evaluation be based on expert judgement on a case-by-case basis.

SCHER is also concerned that the proposed use of different assessment factors is not consistent throughout the document, e.g. assessment factors for vehicles are recommended in some chapters (skin sensitisation), but not in others for which they

might be as appropriate (e.g. acute toxicity, irritation) (see also remarks under question 1).

The SCHER also notes that the World Health Organisation has established guidance on the use of mechanistic data to replace default assessment factors for interspecies extrapolation and intraspecies variability (WHO, 2005; cited as WHO/IPCS (2001) draft in Section 4.7.1 of the proposed guidance).

This approach, which appears to be complementary to the proposed TGD method, first subdivides the uncertainty factors for interspecies differences and human variability into toxicokinetic (TK) and toxicodynamic (TD) components. The data relevant for each subcomponent is then evaluated to determine whether chemical-specific data can be used in place of one or more of the default values. In the absence of chemical-specific data, default values of 2.5 ( $= 10^{0.4}$ ) and 4.0 ( $= 10^{0.6}$ ) were established for the TD and TK component of interspecies differences, while the default values for the TD and TK components of interindividual differences respectively, were each established at 3.16 ( $= 10^{0.5}$ ).

The SCHER recommends that the updated reference to the WHO method (2005) is added to the proposed TGD, because it includes the need to adjust the default values when appropriate data are available.

### 3.4. Question 3

*Another development is that this guidance allows risk assessors to use a quantitative approach for assessment of non-threshold effects, depending on the robustness of the underlying information basis. Can SCHER consider the merits of this approach?*

The use of quantitative methods for the assessment of non-threshold effects represents a novel approach compared to the previous guidance. In the absence of mechanistic or mode-of-action data to suggest a threshold, risk estimates must rely on the extrapolation of the dose response obtained from epidemiology or animal studies to give estimates of risk for human exposure. The difficulty lies in choosing the right dose-response model when extrapolating from the high doses normally used in animal studies to low environmental levels of exposure and to give an acceptable estimate of risk.

For non-threshold carcinogens, the revised TGD now recommends two methods for a quantitative approach to estimate the risk: 1) The method based on the lifetime cancer risk and 2) the cancer risk based on a Margin of Exposure (MoE). For both methods the use of the so-called T25 dose is recommended as “dose descriptor” with the possibility to use a BMD05 in addition if “data are adequate for modelling purposes”. Essentially, the T25 dose (i.e. the dose giving a 25% increase of cancer in animals, usually based on the most sensitive tumours) is converted to an equivalent Human T25 (HT25) by the use of scaling factors and linear extrapolation to low dose levels. The BMD05 is defined as the benchmark dose representing a 5% response.

The SCHER misses the statement that that the risk characterisation of non-threshold effects should be based on expert judgment that considers all available data, i.e., all dose-response curves, mechanistic / mode-of-action data and their relevance for humans. The best basis for a risk assessment is the dose response of an epidemiological study. Equivalent to this is the dose response of a valid carcinogenicity study in animals and detailed knowledge about interspecies differences that allow extrapolation of the animal data to man. If the available data is not suitable for the calculation of a benchmark dose, then SCHER agrees with the proposed use of the T25 dose descriptor as “starting point”

and with the default use of linear extrapolation to low dose levels. The use of the T25 dose descriptor should, however, not generally be recommended, as this approach only takes into account one point of the dose response curve, whereas calculation of a benchmark dose includes all data and by this the slope of the dose response. With the suggestion to use the BMD05 where it will make a difference to the outcome, the proposed guidance indeed acknowledges that there might be relevant differences in the outcome depending on the method used.

The SCHER would therefore like to see a clear recommendation for the use of the benchmark approach (if the data allow for it) over the T25 method.

SCHER concurs with the EFSA (EFSA, 2005) in that the BMDL10 is the most appropriate “starting point” and that the T25 should only be used in cases where the data are inadequate for deriving an estimate of the BMDL10. The BMDL10 is an estimate of the lowest dose that is 95% certain to cause not more than 10% cancer incidence above control and which is derived from animal or human data by best-fit modeling within the range of experimental data considering all available information on the dose-response curve. The BMDL10 is hence associated with much less uncertainty than a deterministic starting point (“point-estimate”) as recommended in the current draft of the TGD. The MoE is calculated by dividing the BMDL10 by the estimated human exposure; it is therefore possible, to calculate scenario-specific MoE.

In cases where very low exposures can reliably be demonstrated, e.g. for genotoxic impurities, the concept of “Threshold of Toxicological Concern (TTC)” should be considered. This approach attempts to develop a minimum risk value for any chemical, including those of unknown toxicity, taking chemical structure into consideration (ILSI, 2005). It has therefore to be evaluated whether this concept is applicable to the class of compound in question. SCHER agrees that this concept should currently not be used as a generic approach, because its limitations in particular with regard to certain classes of compounds, are not yet well understood, but that it should be given a careful consideration. The guidance document should therefore be amended to reflect the current limitations of the method (mainly, that reliable exposure data must be available, and that the applicability for the structural class must be demonstrated), but it should also be clearly stated that this concept merits careful consideration on a case-by-case basis. The typo with regard to the reference (Kroes et al., 2000) should be corrected.

The guidance should also mention that, if no valid information is available at all, any exposure to genotoxic carcinogens should be as low as is reasonably practicable (ALARP).

In this context, SCHER recommends, that also “biomarkers of effect” should be given more consideration in the guidance to aid in the extrapolation of low doses and exposure.

### **3.5. Question 4**

*If the SCHER finds certain approaches or methods for human health risk characterisation not appropriate, the SCHER is invited to suggest possible alternative approaches or methods meeting the same objectives.*

SCHER acknowledges the efforts that have been undertaken to revise and update the risk characterisation chapter of the TGD. However, the proposed guidance is clearly biased towards effect assessment (hazard identification) of compounds with a poor data-base. As a consequence there is the impression, that instead of a case-by-case evaluation any risk assessment is a rather formalistic exercise that by the use of default assessment

factors overcomes all uncertainties and does not require specific case-by-case evaluation. SCHER recommends therefore to clearly indicate, that each risk assessment requires a case-by-case evaluation and to provide guidance on how to consider and overcome insufficient data. To emphasize this step by step approach the chapter “Human Health and Risk Characterisation” should be structured as follows:

- General requirements for a science based risk assessment
- Evaluation of the available database including strengths and weaknesses of the **exposure and effects** analysis, potential sources of risk, and any subpopulations that may be at increased risk. It should include information on the confidence in the results and describe the assumptions used and the uncertainties in the analysis. (A cross-reference to TGD Chapter 2, Section 3 on effects assessment could be included.)
- Guidance how and to what extent specific data gaps can be narrowed by toxicokinetic, toxicodynamic, mechanistic and mode-of-action information
- Guidance to use and adapt specific default-assumptions considering additional information

SCHER is specifically concerned about the preferred and general use of uncertainty assessment factors and their combination. Instead, it needs to be pointed out, that, in case default-factors are applied, the extent of their use needs to be adapted according to the available information. This requires consideration of mechanistic and toxicokinetic data to estimate actual interspecies differences and interindividual variability in the toxicokinetic behaviour of a substance and its target organ effects, i.e. its toxicodynamics.

Guidance on the use of this information would encourage the risk assessor to search for such information and would enable a rational application of adequate default factors. Also, simple biologically based models or more complex physiologically based pharmacokinetic (PBPK) and biologically based dose-response (BBDR) models are a way forward in evaluating all data, and these methods need to be specifically addressed.

Exposure assessment is an integral part in the risk assessment process. Since section 4.3 on exposure assessment considerations and uncertainties is rather short, SCHER recommends including cross-references to relevant chapters in the TGD dealing with exposure information and its assessment.

In addition, it has to be specifically pointed out, that potential variation in exposure should be accounted for by using exposure data collected with a strategy that recognises exposure variability, or by using worst-case assumptions and estimation techniques to evaluate the highest reasonably foreseeable exposure levels. The use of uncertainty factors may also be necessary to account for uneven distribution of exposure levels. Although it is rightly pointed out that “...exposure assessment uncertainties need to be considered alongside the uncertainties related to the interpretation of the effects data in the risk characterisation process”, no practical guidance is provided in this respect.

When revising the chapter “Human Health and Risk Characterisation” SCHER also recommends a better description with regard to the following points:

Whilst SCHER is basically in agreement with the proposed approach to quantitative risk assessments for non-threshold carcinogens and mutagens, the committee is concerned because the methodology is based on a deterministic point-estimate and a linear extrapolation model. While this is certainly an easy to perform approach, the

uncertainties with regard to the actual dose-response curve caution against its general use. For the risk assessment of genotoxic carcinogens, an approach using the BMDL10 as dose descriptor, based on all available dose-response and mechanistic information, is therefore recommended by the SCHER (for details see answer to question 3, above).

Based on scientific arguments, the SCHER would also like to see a clear recommendation for the use of the benchmark dose, if the available database allows for it.

The SCHER is aware that according to the EU legal text, a NOAEL should be used if available, and also notes that currently available datasets are often not entirely suitable for applying a benchmark dose model. Nevertheless, the benchmark approach permits the use of all available dose-response information in deriving a N(L)OAEL, whilst if a N(L)OAEL is determined by the traditional method (as suggested in the TGD), i.e. by using data from the single dose (T25), the data from the entire dose response curve are not considered.

The SCHER also notes that the MOS approach will be replaced by Derived No Effect Levels (DNELs) in REACH. The MOS approach and the DNEL approach use the same input (exposure estimate, NOAEL/NOAEC, assessment factors), i.e. using the MOS and the DNEL approach on the same data set will give the same conclusion, however, the way of presenting the outcome is different. An advantage of the DNEL approach is that the DNEL is directly comparable to exposure estimates and measurements, and any new exposures can therefore easily be compared with the available DNEL. It would also allow for an easier priority setting with regard to necessary measures for certain exposure scenarios. It should therefore be considered whether the DNEL approach should in future form part of the revised TGD.

#### **4. CONCLUSION**

The SCHER recognises the efforts that have been spent in updating the risk characterisation chapter of the TGD.

Nevertheless, the SCHER recommends some substantial changes to the document before its adoption, including:

- The inclusion of an introductory chapter on what “risk characterisation” is (similarly to the respective section in the risk characterisation chapter of the previous TGD version).
- The avoidance of a formalistic approach with regard to the proposed default assessment factors. Instead, emphasis should be given to case-by-case decisions based on expert judgement and scientific justification. In some cases, however, default assessment factors may still be required.
- Guidance on how to integrate exposure information into the risk characterisation process.
- A framework structure for the presentation and evaluation of mode-of-action and/or mechanistic data for the risk characterisation step, including the analysis of relevance to humans and the analysis of combined exposures. Because of the importance of this information, such a framework should be considered even if

there appeared to be a lack of opportunity to apply such frameworks on the basis of the available datasets in the past.

- Guidance on the use of biomarkers of effects to aid in the extrapolation of low doses and exposure.
- Further to the use of the IPCS Cancer Framework for Mode of Action and the BMD05 approach, the consideration of mechanistic data and non-deterministic parameters, such as the BMDL10 as “starting point” for the quantitative risk assessment of non-threshold carcinogens and mutagens.
- An expansion of the “Threshold of No Toxicological Concern” section.
- A clear transparent protocol for judging the epidemiological evidence on the stage of hazard identification and calculation of cancer risk (hazard characterisation).
- Emphasis to use good epidemiological practise to minimise major sources of bias and confounding.

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## **6. ACKNOWLEDGEMENTS**

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are:

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