



Reference preliminary

Technical Guidance Document

(reference p-TGD)

Chapter 3, Human health hazard assessment

Part of Preliminary TGD

3 HUMAN HEALTH HAZARD ASSESSMENT

In introductory sections of this chapter the contents and rationale for the various sections is described.

3.1 Objective and key issues

3.2 Collection, generation and evaluation of hazard information

This paragraph should include a short section explaining the importance of human data (both for effects and exposure) for risk assessment.

E.g:

Hazard data are usually obtained from animal experiments. However, by their very nature data obtained in human must be considered more relevant for risk assessment and should be used when available. For hazard assessment human data comprise case reports, human volunteer studies, case-control studies, retro- and prospective cohort studies, descriptive studies (morbidity and mortality studies) and health surveillance data. For human exposure data, biomonitoring data are highly relevant in particular for the assessment from human exposure through the environment where biomonitoring data will in most cases be the only (reliable) data available. [Suggested txt PB 31/8]

3.3 Classification & Labelling Human Health

[General considerations, if necessary and not already addressed elsewhere.]

3.4 Derivation of DNEL(s) and other measures for dose-response

[General considerations; details in sections 3.6-3.9]

3.4.1 Introduction

Under REACH manufacturers, importers and downstream users should ensure that they manufacture / place on the market / use substances that do not adversely affect human health. REACH Annex I sets out how manufacturers and importers are to assess and document that the risks arising from the substance they manufacture or import are adequately controlled during manufacture and their own use(s) and that others further down the supply chain can adequately control the risks. REACH (Annex I, 1.0.1) defines the Derived No-Effect Level (DNEL), i.e. the level of exposure above which humans should not be exposed. In the risk characterisation, the exposure of each human population known to be or likely to be exposed is compared with the appropriate DNEL. The risk to humans can be considered to be adequately controlled if the exposure levels estimated do not exceed the appropriate DNEL. [Suggested txt TS 22/8]

DNEL(s) should be derived for all substances subject to registration that are manufactured/imported/used in quantities of 10 tonnes or more per year, as part of the chemical safety assessment (CSA). DNEL(s) should be documented in the chemical safety report (CSR). In

case the substance meets the criteria for classification as dangerous or is assessed to be a PBT or vPvB, the DNEL is subsequently to be used:

- a. in the risk characterisation part of the chemical safety assessment, and
- b. for hazard communication, via extended SDS.

With respect to the derivation of DNEL(s), REACH (Annex I, 1.4.1) specifies that:

“(a) DNEL(s) shall be established for the substance, reflecting the likely route(s), duration and frequency of exposure. For some endpoints, especially mutagenicity and carcinogenicity, the available information may not enable a threshold, and therefore a DNEL, to be established. If justified by the exposure scenario(s), a single DNEL may be sufficient. However, taking into account the available information and the exposure scenario(s) in Section 9 of the Chemical Safety Report it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans liable to exposure indirectly via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure. A full justification shall be given specifying, *inter alia*, the choice of the information used, the route of exposure (oral, dermal, inhalation) and the duration and frequency of exposure to the substance for which the DNEL is valid. If more than one route of exposure is likely to occur, then a DNEL shall be established for each route of exposure and for the exposure from all routes combined. When establishing the DNEL, the following factors shall, *inter alia*, be taken into account:

- (a) the uncertainty arising, among other factors, from the variability in the experimental data and from intra- and inter-species variation;
- (b) the nature and severity of the effect;
- (c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies.”

From this it follows that, based on an integration of all available and relevant human health hazard data, the DNEL can be considered as an ‘overall’ No-Observed-(Adverse-) Effect-Level (NO(A)EL) for a given exposure (route, duration, frequency), accounting for uncertainties/variability in these data and the human population exposed. Whereas the current legislation on new and existing substances requires a comprehensive risk assessment and a risk characterisation (RC) for all relevant toxicological effects, REACH requires a RC for the leading health effect (i.e., the toxicological effect that results in the most critical DNEL) for a given exposure pattern (duration, frequency, route and exposed human population) associated with an exposure scenario (ES), resulting from an identified use. It is to be noted that one exposure pattern can fit to more than one ES. The exposure/DNEL comparison (as proposed in REACH Annex I, 6.3) in principle presents a simple tool for RC, especially for downstream users who do not have the hazard data at their disposal. For any exposure scenario the risk to humans can be considered to be adequately controlled if exposure levels do not exceed the appropriate DNEL (REACH Annex I, 6.4).

3.4.2 If no DNEL can be derived

Although under REACH the assessment of adequate control of risk to humans is principally based on the exposure/DNEL comparison, it may not always be possible to derive DNEL(s). This is the case when:

1. a substance exerts its effect by a threshold mode of action, but the available data do not allow to reliably identify the threshold;
2. a substance exerts its effect by a non-threshold mode of action. In that case it is generally assumed, as a default assumption, that even at very low levels of exposure residual risks cannot be excluded. Consequently, a dose without effect cannot be established;
3. test data (for one or more endpoints) are absent because:

- a. relevant human exposure can be excluded for a substance (see Annex XI-3 and column 2 (specific rules for adaptations from column 1) in Annexes VIII-X)
 - b. physico-chemical properties do not allow testing of a substance
 - c. a substance is registered as on-site isolated intermediate
 - d. a substance is registered as transported isolated intermediate.
- ad 1 This might be the case for the endpoints sensitisation, irritation and acute toxicity.
- ad 2 This is especially the case for the endpoints mutagenicity and carcinogenicity, as also remarked in REACH – Annex I, 1.4.1. It is to be noted that, as a consequence of the uncertainties in establishing a safe exposure level for these non-threshold substances, REACH specifically targets at removing or substantially reducing exposures to these substances. For example, the authorisation requirement for substances of very high concern aims to assure that these substances are properly controlled and eventually replaced by suitable alternative substances or technologies where these are economically and technically viable (REACH, article 54). [using input of DB 3/8]
- ad 3a One might argue that where relevant human exposure can be excluded, the derivation of a DNEL is superfluous since the outcome of the risk assessment will in any case be negligible risk.
- ad 3b Substances that cannot be tested due to extreme physico-chemical properties, e.g. extremely flammable substances, are not likely to pose a risk other than coming from these physicochemical properties. One could argue that e.g. systemic effects resulting from exposure because of the use of a substance will not be significant.
- ad 3c In REACH, article 17 describes the information requirements for on-site isolated intermediates. Any available existing information on e.g. human health properties shall be submitted, without any additional testing. So, if no data or no adequate data are available, it may not be possible to derive a DNEL. However, for on-site isolated intermediates a strict control is required. There will be no or only very limited exposure possible, and only on the manufacturing site. For these compounds, communication to downstream users is not an issue.
- ad 3d Article 18 of REACH describes the information requirements for transported isolated intermediates. Any available existing information on e.g. human health properties shall be submitted, together with the information specified in Annex VII for transported isolated intermediates in quantities of more than 1,000 tonnes per year. So, if no data or no adequate data are available, it may not be possible to derive a DNEL. However, for transported isolated intermediates exposure of the general population is not an issue. Given that a strict control is required, only very limited exposure may be expected for specific workers.

If it is not possible to identify a DNEL, then REACH (Annex I, 1.4.2) requires that this shall be clearly stated and fully justified. REACH (Annex I, 6.5) requires further that for those human effects for which no DNEL could be derived, a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out in the risk characterisation part of the CSA. [deletion requested by DB 3/8]

In the qualitative approach there is no estimation of specific levels of risk for a given exposure pattern and emphasis is placed on assessing the adequacy of control of exposure in the human population of interest (e.g. workers, consumers, or humans exposed indirectly via the environment). The qualitative approach directly proceeds to the level of consequences without special consideration of the risk characterisation and evaluation part of the risk assessment process. This approach is similar to the ALARA-principle (*as-low-as-reasonably-achievable*) originally used in the area of radiation protection.

REACH only refers to a qualitative approach for human effects for which no DNEL(s) can be derived, in the case of e.g. non-threshold carcinogens. However, it can be very useful to include in this qualitative assessment an additional quantitative element in order to assess the likelihood that effects are avoided (as required in Annex I, 6.5). This quantitative element aims to describe the magnitude of the risk at particular exposures and assists the risk manager to focus on the areas of greatest concern in relation to the potency of the substance and the relative risks. It allows for non-threshold substances to differentiate exposure scenarios for which existing control measures already result in very low human health risks from those for which existing control measures are less effective.

The assumption in both the qualitative and quantitative approach is that there is no level of exposure that is without excess risk. Whereas for threshold substances the NOAEL is the typical dose descriptor in the DNEL approach, for non-threshold substances a NOAEL cannot be derived and thus another descriptor of the dose-response has to be used. It is proposed to derive a reference risk level which is considered to be of very low concern for a certain exposure scenario, i.e. a DMEL (derived minimal effect level or level of very low concern)¹, while addressing methodological uncertainties. Contrary to the risk assessment for threshold effects, by definition for non-threshold carcinogens a dose without cancer risk cannot be derived. Therefore the establishment of a reference risk level clearly is of societal concern and needs policy guidance. There might be a common understanding that a reference risk level considered to be of very low concern can be described by a pragmatic range of a certain lifetime cancer risk (e.g. of 10⁻⁴, 10⁻⁵ or 10⁻⁶). These risk values are calculated from a predetermined, moderate cancer risk (e.g. a T25 value derived from a rodent long-term cancer bioassay or reliable human cancer data from epidemiological studies, via linear extrapolation), or the dose obtained by applying an additional assessment factor for high-to-low-dose extrapolation to e.g. the T25 value. The reference risk level of very low concern as well as the magnitude of this additional assessment factor would have to be harmonised and accepted at the policy level.

For threshold substances, a DNEL is used as a decision point which should not be exceeded, indicating a safe exposure. For non-threshold substances, a DMEL is a tool to describe the dose-response in relation to the potency of the substance.

[changes based on input by DB 3/8]

3.4.3 Overview of aspects to be considered in derivation of DNEL(s) (DMEL(s))

Based on the specification given in REACH (Annex I, 1.4.1), several aspects need to be considered in deriving DNEL(s). These are addressed below. It is to be noted that most aspects (in particular on uncertainty/variability, populations, and routes) also apply to the derivation of DMEL(s).

Data requirements

The derivation of DNELs is required for the Chemical Safety Assessment (CSA) of substances manufactured/imported/used in quantities from 10 tpa onwards. For each tonnage level standard data requirements have been specified in REACH (Annex VII-X, in conjunction with annex XI), but REACH also requires that any other relevant hazard information that is available (i.e. on other endpoints and/or from other test and non-test methods) is taken into account. Even at the lower tonnage levels the data requirements include several studies that should allow the derivation of a quantitative estimate of the dose without adverse effects, i.e. a NOAEL (e.g. 28/90 repeated dose

¹ proper abbreviation has to be agreed on in the group

toxicity study, screening reproductive/developmental toxicity study) and thus the derivation of a DNEL. As further toxicological information is requested at each higher tonnage level or might become available in literature, this might influence the DNELs. As a consequence, DNEL(s) should be reconsidered at each higher tonnage level.

For derivation of DNELs, all available hazard information (in accordance with Annexes VII-XI) needs to be evaluated (see 3.2) and, where possible, N(L)OAELs need to be established (see 2.4). It is to be noted that under REACH the data may originate from epidemiological studies, studies with experimental animals, in vitro studies and non-testing sources ((Q)SAR), read across or chemical categories).

Uncertainty/variability

REACH requires differences between effect assessment data and the real human exposure situation to be addressed, taking into account variability and uncertainty within and between species. [suggested by FC 3/8]

In order to address these differences, assessment factors (AF) should be applied. The applied AF only correct for uncertainties/variability in the effect data, not for exposure uncertainties.

Populations

DNELs may have to be derived for workers, consumers, and/or man via the environment (MvE). For very specific exposures it might even be necessary to derive DNELs for certain vulnerable subpopulations within these populations (e.g. for children, due to their distinct behaviour and in case of indications/suspicions of higher sensitivity).

It is not always necessary to derive DNELs for all mentioned populations. Depending on the exposure pattern, only DNELs for the relevant populations will have to be derived.

Routes

In view of the anticipated exposure routes for the various populations, DNELs may have to be derived for oral exposure (consumers/MvE), inhalation and dermal exposure (workers/consumers/MvE), and/or combined exposure.

It is not always necessary to derive DNELs for all mentioned routes. Depending on the exposure pattern, only DNELs for the relevant routes of exposure will have to be derived.

Duration of exposure

In practice, the different populations will be exposed for different periods of time to a chemical substance. Since the duration of exposure will often have an impact on the effect(s) that may arise, different DNELs for various exposure durations should be discriminated.

In general, two types of exposure duration can be differentiated: long-term exposure and short-term/peak exposure. Thus, reflecting the exposure pattern, DNELs for long-term exposure and/or DNELs for short-term/peak exposure will have to be derived.

Systemic and local effects

Depending on the substance, DNELs may have to be derived for systemic effects, for local effects or for both.

A DNEL should preferably cover both systemic and local effects. DNELs for systemic effects can in principle be based on all types of studies, unless low dose local effects prevent appropriately high systemic exposure to occur. For DNELs adequately covering local inhalation and local dermal effects, however, route-specific data need to be available.

Units

[\[below txt suggestion based on comment by PB 31/8\]](#)

DNELs can either be expressed as internal values or as external values. For systemic effects, in principle, internal values are more valuable since systemic adverse health effect of substances are related to the concentration of the substance or its active metabolite(s) in the receptor compartment. However, in practice only for a limited number of substances internal values, i.e. biomonitoring data, are available. On the other hand, for substances with inhalation as the single or major route of exposure, external values may be preferred. Also, these values are much easier handled in compliance check in case of other use conditions than in the communicated ES by downstream users when mostly only external exposure estimates available.

For local effects, which cannot be expressed in internal levels, external values should be used.

In general, the most appropriate and/or reliable monitoring method (external monitoring, biomonitoring) should drive the expression of the DNEL. In practice, however, external values will be commonly used.

Relevant, external dose units for the DNEL are mg/person/day or, alternatively, mg/kg bw/day for oral and dermal exposure. The relevant dose unit of the DNEL for inhalation is mg/m³, both for systemic and local effects. In case of local dermal effects the relevant unit is mg/cm² or ppm

Note: in principle, molar units should be preferred over mass units. [\[comment by PB\]](#)

3.4.4 How to derive DNEL(s)/DMEL(s)

A DNEL/DMEL can be derived as follows:

- Step 1: Derivation of typical dose descriptors (e.g. NOAELs, BMD, LD50, T25, OR, RR....) from all available studies on the different endpoints (see also 2.4);
- Step 2: When necessary, modification of the dose descriptor to the correct starting point;
- Step 3: Application of assessment factors to the correct starting point to obtain endpoint-specific DNEL(s)/DMEL(s) for the relevant/potential exposure pattern (duration, frequency, route and exposed human population);
- Step 4: Selection of the leading health effect and the corresponding DNEL(s)/DMEL(s).

Before going into the details of steps 1-4 in sections 3.6-3.9, first the endpoint-specific assessments will be described in section 3.5 because there guidance can be found on how to deal with some aspects of steps 1 to 3 for the different endpoints.

3.5 Endpoint-specific assessments

3.5.1 Toxicokinetics, metabolism and distribution

To be filled-in by special WG

3.5.2 Acute effects: acute toxicity

To be filled-in by EWG

3.5.3 Acute effects: irritation and corrosivity

To be filled-in by EWG

3.5.4 Sensitization

To be filled-in by EWG

3.5.5 Repeated dose toxicity

To be filled-in by EWG

3.5.6 Mutagenicity

To be filled-in by EWG

3.5.7 Carcinogenicity

To be filled-in by EWG

3.5.8 Reproduction toxicity

To be filled-in by EWG

The general structure of these chapters is given in the box below

3.5.x Human health endpoint x

Introduction

This should be a commentary on the relevance/importance of the endpoint to human health; mention should be made of other endpoints that are related to the endpoint of interest.

Definition

Should define the meaning of the endpoint and the main terms used to describe it

Objective

Should explain what information on this endpoint will contribute to the overall goal of understanding the potential effects on (human) health.

Information requirements

Include the relevant general text for all endpoints on REACH information requirements and possibilities for adaptation (text available in the human health endpoint sections in the Reference p TGD).

Detail the minimum requirements for information on the endpoint that are prescribed by Annexes IV to IX of the REACH regulation; generic factors that particularly apply to the endpoint should also be listed. Care should be taken to maintain consistency with the terminology and criteria used in the regulatory documentation so as to avoid inconsistencies in interpretation.

Information and its sources

Give an overview of all the types of data and their sources that may be used to provide information on the endpoint of interest. Data that are 'prerequisites' for the endpoint e.g. physicochemical data, should also be highlighted as well as data from other endpoints that can provide information on the endpoint of interest e.g. repeat dose toxicity data for the reproductive toxicity endpoint.

Note:

Guidance on generic (i.e. not endpoint-specific) aspects of all the types of data, sources of information and exposure considerations listed below is being developed by other PMG-appointed working groups. As soon as it becomes available this guidance will be made available by the PMG to all the EWGs.

NB: EWGs should only identify endpoint-specific sources of information, since for the most part existing databases will cover multiple endpoints and therefore identified as part of Task 1 of the overall project.

Non-human data

Non-testing data

Describe the non-test methods that can provide information on the endpoint of interest, e.g. SAR, QSAR, chemical categories, read across etc.

For the application of (Q)SARs to the endpoint of interest, provide an overview of those models that are able to generate estimates for the endpoint under consideration. If possible, include information on (or reference/links to) the compliance with OECD principles for the given model and endpoint.

Testing data

Describe the tests with biological systems that can provide information on the endpoint of interest.

In vitro data

Provide an inventory of the officially adopted EU- OECD test guidelines and their applicability domain. Provide an overview of other methods under development and/or (pre)validation for the endpoint of interest, giving an indication of the applicability domain of each method and an overview of (or reference to) its validation status.

Animal data

Provide an inventory of the officially adopted animal test guidelines, referencing the relevant EU-/OECD guidelines, which can provide information on this endpoint. List also all studies

that may not be compliant with current guidelines but which, nevertheless, can provide useful information on this endpoint.

Human data

Describe the type of studies that can provide information on the endpoint of interest, e.g. case studies, epidemiological studies and even controlled studies where these are ethical and available.

Exposure considerations

Provide guidance on aspects of exposure that are of specific significance to the endpoint.

Evaluation of available information for a given substance

Provide guidance (structured where possible e.g. in tabular or road map format) on the process of judging and ranking the available data for a given substance in terms of its adequacy (reliability and relevance) completeness and remaining uncertainty.

Note:

Guidance on generic (i.e. not endpoint-specific) aspects of all the characteristics (i.e. adequacy [reliability and relevance], completeness and remaining uncertainty) of all types of data, sources of information and exposure considerations listed below is being developed by other PMG-appointed working groups. As soon as it becomes available this guidance will be made available by the PMG to all the EWGs.

Non-human data

Non-testing data

Describe how to evaluate the data for a given substance generated by non-testing approaches, e.g. SAR, QSAR, chemical categories read across etc.

Propose formats (QSAR Reporting Formats) and give examples to illustrate how to assess the relevance and reliability of a model prediction for a given substance. This includes information on the model (e.g. compliance with OECD principles) and information on the model prediction (e.g. whether the substance falls within the applicability domain of the model, reliability of the prediction).

NB Reporting formats for categories and read-across (including SARs) will be proposed by the Task 3 Drafting Group

Testing data

Describe how to evaluate the data for a given substance generated by studies in biological systems.

In vitro data

Provide guidance and formats on how to judge the applicability and validity of the outcome of various study methods for a given substance. Provide guidance on how to assess the quality of the conduct of a study. This should include how to establish whether the substance falls within the applicability domain of the method and the validation status for the given domain. Indicate what questions need to be answered concerning such aspects as vehicle, number of duplicates, exposure/incubation time, GLP-compliance or comparable quality

description.

Give an assessment of the relevance of the parameters assessed by the test in relation to the endpoint under consideration.

Animal data

Provide guidance on how to evaluate the data for each type of study, highlighting particular points to be taken into account and key considerations for judging and ranking quality of the data for a given substance. Provide an overview of critical parameters to be taken into account in judging the relevance and reliability of such data.

Human data

Provide guidance on how to evaluate the human observational data that relate to this endpoint, indicating the criteria to be applied for establishing the quality and reliability of the data and their applicability in the overall assessment. Information/guidance should be given on how to assess the relevance and reliability of human data. For controlled studies, if any, guidance should be given on the conduct of these studies for the endpoint under consideration.

Exposure considerations

Highlight any endpoint-specific aspects to be taken into account in application of the exposure data to the evaluation of the available information.

Remaining uncertainty

Provide an indication of the adequacy and reliability of the data that may be used as a basis for assessment of human hazard for this particular endpoint.

Conclusions on “the Endpoint”

Provide guidance on how the available data should be applied in order to reach a conclusion on its adequacy for informing decisions on classification and labelling and its use in assessment of risk (dose-response). Where appropriate, guidance should be given on the development of a weight of evidence (WoE) approach for the endpoint that can be used to establish the adequacy of the available data vs. the tonnage-triggered information requirements of Annexes V-VIII REACH.

Note:

Generic guidance on a WoE approach will be developed by a PMG-appointed working group; as soon as it becomes available this guidance will be made available by the PMG to all the EWGs.

Concluding on suitability for Classification and Labelling

Guidance should be provided on how a WoE approach, comparing available adequate information with the tonnage-triggered information requirements by REACH, may result in concluding on meeting the requirements of the current Classification & Labelling Annex VI of the Dangerous Substances Directive 67/548/EEC. The likely changes to be introduced under the evolving GHS should also be taken into account where these are known.

Concluding on suitability for Chemical Safety Assessment

Guidance should be provided how a WoE approach, comparing available adequate information

with the tonnage-triggered information requirements by REACH, may result in concluding on dose response assessment and identification of dose descriptors.

Information not adequate

A WoE approach, comparing available adequate information with the tonnage-triggered information requirements by REACH, may result in the conclusion that the requirements are not fulfilled. In order to proceed in further information gathering the following testing strategy can be adopted:

Intelligent Testing Strategy (ITS) for “the Endpoint”

Fundamentally based on a WoE approach, the ITSs should be developed with the aim of generating sufficient data for a chemical to support its classification or exclusion from classification, its risk assessment and its PBT (vPvB) assessment.

Objective / General principles

Ensure that the objective is this testing strategy is to give guidance on a stepwise approach to hazard identification with regard to the endpoint; a key principle of the strategy is that the results of one study are evaluated before another is initiated. The strategy should seek to ensure that the data requirements are met in the most efficient and humane manner so that animal usage and costs are minimised.

Preliminary considerations

The guidance given in sections 1.2 – 1.4 above will have enabled the identification of the data gaps that need to be filled in to meet the requirements of REACH as defined in Annexes IV to IX. Careful consideration of existing toxicological data, exposure characteristics and current risk management procedures is recommended to ascertain whether the fundamental objectives of the ITS (see above) have already been met. Give guidance on other factors that might mitigate data requirements for the endpoint of interest e.g. possession of other toxic properties, characteristics that make testing technically not possible.

Testing strategy

Develop a testing strategy for the endpoint that takes account of existing data on toxicity, exposure characteristics as well as the specific rules for adaptation from standard information requirements, as described in column 2 of Annexes V-VIII, together with some general rules for adaptation from standard information requirements in Annex IX

Examples and Case studies

Include one or more examples and/or case studies here to illustrate the guidance given, particularly in relation to the ITS.

3.6 Step 1: Derivation of typical dose descriptors (e.g. NOAELs, BMD, LD50, T25....) from all available studies on the different endpoints

In the preceding section, as well as in 2.4, guidance is given on how the typical dose descriptors should be determined for the various individual human health endpoints. Next step is to collect in a table all available dose descriptors from the available data for the different endpoints, thereby making a distinction between endpoints relevant for short-term exposure and endpoints relevant for long-term exposure, and between local and systemic effects where applicable.

Table X Most relevant dose-descriptor per endpoint for a certain substance as a result of its hazard assessment.

Endpoint	Most relevant quantitative dose descriptor ¹ (appropriate unit) or qualitative assessment		Associated critical effect ²	Remarks on study ³
	Local effect ⁴	Systemic effect ⁵		
Acute toxicity ⁶ - oral - dermal - inhalation				
Irritation/Corrosivity - skin - eye - resp. tract		NA ⁷ NA NA		
Sensitisation - skin - resp. tract		NA NA		
Repeated dose ⁸ sub-acute/ semi-chronic/ chronic - oral - dermal - inhalation				
Mutagenicity - in vitro - in vivo				
Carcinogenicity - oral - dermal - inhalation				
Reproductive toxicity ⁸ fertility impairment - oral - dermal - inhalation developmental tox - oral - dermal - inhalation				

¹ NOAEL (NOAEC), LOAEL, T25, BMD10 etc or any other dose descriptor; indicate whether this concerns a no or lowest observed effect level etc;

² In this column the critical effect for which the dose descriptor is determined is provided.

³ This column is for indicating whether data were available, whether the substance is classified for this endpoint, for shortly describing specifics of the study (e.g. 28-d gavage rat, 5 d/wk or 2-gen diet rat, 7 d/wk), and for indicating (additional) uncertainty in available data;

⁴ Units are mg/m³ for inhalation, and mg/cm² for dermal exposure;

⁵ Units are mg/m³ for inhalation, and mg/kg bw/day for oral and dermal exposure;

⁶ In general, sublethal toxicity is a more rational starting point for acute toxicity than mortality data; information on acute toxicity may also be derived from e.g. repeated dose toxicity studies or reproductive toxicity studies.

⁷ Not applicable.

⁸ Note these repeated exposure studies may also show relevant acute effects of the test substance.

3.7 Step 2: When necessary, modification of the dose descriptor to the correct starting point

In a few situations, the effects assessment is not directly comparable to the exposure assessment in terms of exposure route, units and/or dimensions. In these situations, it is necessary to convert the dose descriptors for the threshold and non-threshold effects (N(L)OAEL, T25 etc.) into a correct starting point (corrected N(L)OAEL, T25 etc.). This applies to the following situations:

- If for a given human exposure route there is an effect parameter for the same route in experimental animals but for that particular exposure route there is a difference in bioavailability between experimental animals and humans at the relevant level of exposure.

Note: How would you know that there is a difference without data ? [\[Comment by PB\]](#)

- If for a given human exposure route there is not an effect parameter for the same route (in experimental animals or humans).
- Differences in respiratory volumes between experimental animals and humans.

Additionally for non-threshold effects:

- If the duration of exposure and/or observation in a cancer study in experimental animals differs from the standard lifespan of these animals.
- Differences between occupational and lifetime conditions of exposure.

If human exposure is evaluated by biomonitoring, the calculation of DNEL values is straightforward if studies in animals or humans are available which relate (1) the effect directly to the biomonitoring parameter or (2) the biomonitoring data directly to another dose descriptor [\[suggested by PB\]](#)

Differences in route of exposure and guidance on bioavailability issues

If no adequate experimental effect data are available on the relevant route of exposure for the population under consideration, route-to-route extrapolation might be an alternative. Route-to-route extrapolation is only considered appropriate in case of systemic effects. In these situations corrections should be made for differences in kinetics and metabolism. Since in general it is difficult to quantify differences in metabolism, excretion and distribution and include them (as an assessment factor) in an overall AF, in practice only differences in bioavailability between the different routes, as determined by the percentages of absorption, can be accounted for. It is to be noted that route-to-route extrapolation is associated with a high degree of uncertainty and should be conducted with caution relying on expert judgement. Additional, relevant testing should also be considered.

Default absorption values have been proposed (see e.g. section 3.5.1(?) for dermal absorption defaults), but substance-specific data on absorption via the different routes are to be preferred. In the absence of these data for both the starting route and the end route (the route to which the extrapolation is being made), worst case assumptions have to be made. Worst case in this context therefore means assuming a limited absorption for the starting route, leading to a lower internal N(L)OAEL, and, a maximum absorption for the end route, leading to the lowest external N(L)OAEL.

It is proposed, in the absence of route-specific information on the starting route, to include a default factor of 2 (i.e. the absorption percentage for the starting route is half that of the end route) in the case of oral-to-inhalation extrapolation. The inclusion of this factor 2 means for example that 50% (instead of 100%) absorption is assumed for oral absorption, and 100% for inhalation. Note that if data on the starting route (oral) are available these should be used, but for the end route (inhalation), the worst case inhalation absorption should still be assumed (i.e. 100%). No default factor should be introduced (i.e. factor 1) in case of inhalation-to-oral extrapolation, because a two times higher oral compared to inhalation absorption is not considered likely. On the assumption that, in general, dermal absorption will not be higher than oral absorption, no default factor (i.e. factor 1) should be introduced when performing oral-to-dermal extrapolation. The other possible, but less usual, situations of route-to-route extrapolation should be handled on a case-by-case basis. Guidance on route-to-route extrapolation of toxicity data when assessing health risks of chemicals has for example been produced by IGHRC (2006). [To be inserted in reference list: The Interdepartmental Group on Health Risks from Chemicals (IGHRC). Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals. <http://www.silsoe.cranfield.ac.uk/ieh/ighrc/ighrc.html>]

Differences in respiratory volumes between experimental animals and humans

In case the inhalation route is involved one should also keep the principle of allometric scaling in mind when using inhalation volumes for animals and humans. This implies that standard respiratory volumes (in l/min/kg bw) for rats and humans differ by a factor of 4 (see also Section 3.8, Table 3-2, and Appendix I, part 1). The physiological default values with respect to allometric scaling are given in Table 3-1. For certain situations deviations from these assumptions might be necessary, e.g. during 8 hours light activity at work the respiratory rate becomes higher than standard. These differences need to be corrected for, in order to obtain the correct starting point. It is to be noted that within one endpoint, these corrections result in a corrected starting point that is not the same for workers as for the general population.

Table 3-1 Default physiological parameters under the allometric scaling principle

	Rat	Human
Body weight	250 g	70 kg
Respiratory volume (standard; sRV)	0.2 l/min/rat = allometric scaling ^a 0.8 l/min/kg bw	0.2 l/min/kg bw
↓ for relevant duration:	↓	↓
6 h exposure	0.29 m ³ /kg bw	5 m ³ /person
8 h exposure	0.38 m ³ /kg bw	6.7 m ³ /person
24 h exposure	1.15 m ³ /kg bw	20 m ³ /person
Respiratory volume light activity for worker (wRV)		
8 h exposure		10 m ³ /person

a Difference between metabolic rate scaling and body weight scaling for rats and humans: 4 (see also Table 3-2)

How to derive a correct starting point

In Figure 3-1 it is illustrated how the modification of the starting point works out for one of the most common situations, i.e. an oral N(L)OAEL from a rat study (in mg/kg bw/day) that is to be used to assess inhalatory exposure of humans (in mg/m³).

Detailed guidance on modification of the starting point for this and other situations is given in Appendix I, part 2.

In this detailed guidance it is also indicated whether allometric scaling should be included in step 3 of the DNEL/DMEL derivation or whether this is already implicitly done at this point in step 2.

Figure 3-1 Modification of the starting point: conversion of an oral rat N(L)OAEL into a corrected inhalatory N(L)OAEC to assess human inhalatory exposure.

$$\begin{aligned} \text{corrected inhalatory N(L)OAEC} &= \text{oral N(L)OAEL} * \frac{1}{\text{sRV}_{\text{rat}}} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{inh-rat}}} * \frac{\text{ABS}_{\text{inh-rat}}}{\text{ABS}_{\text{inh-human}}} \\ &= \text{oral N(L)OAEL} * \frac{1}{\text{sRV}_{\text{rat}}} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{inh-human}}} \end{aligned}$$

For workers (8 hours per day) :

$$\begin{aligned} \text{corrected inhalatory N(L)OAEC} &= \text{oral N(L)OAEL} * \frac{1}{\text{sRV}_{\text{rat}}} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{inh-human}}} * \frac{\text{sRV}_{\text{human}}}{\text{wRV}} \\ &= \text{oral N(L)OAEL} * \frac{1}{0.38 \text{ m}^3/\text{kg}/\text{d}} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{inh-human}}} * \frac{6.7 \text{ m}^3(8\text{h})}{10 \text{ m}^3(8\text{h})} \end{aligned}$$

ABS: Absorption; sRV: standard Respiratory Volume; wRV: worker Respiratory Volume.

Additional correction factors for non-threshold effects:

Below two correction factors specifically for non-thresholded carcinogenic effects are described, that are not applied for thresholded effects. The reason for their introduction is that these non-thresholded carcinogenic effects are assumed to be directly proportional to the accumulative lifetime dose received, i.e. irrespective of the height of the dose, whereas for threshold effects a response is assumed to be basically independent of the accumulated lifetime dose received, but only depends on whether a daily dose exceeds this threshold or not.

Differences in duration of exposure and/or observation in a cancer study and the standard lifespan

For non-threshold carcinogens, for a cancer study that does not have full compliance to the testing requirements of an actual testing guideline the minor differences in dosing (regimen or treatment duration) should be corrected. If an experiment is terminated before the standard lifespan, the number of tumours found is assumed to be an underestimate of the number that would have been present after lifetime administration. If, for example, dosing is terminated at w weeks (w<104 weeks) before the standard lifespan of 104 weeks and the animals are observed until termination of the experiment at 104 weeks, the lifetime daily dose d giving the observed tumour incidence is

corrected by $w/104$. If dosing is terminated at $w1$ and observation is until $w2$ weeks, the lifetime daily dose giving the observed tumour incidence is corrected by $(w1/104)$ ($w2/104$). Thus an experiment lasting for 22 months in rats with the standard lifespan of 24 months will then be corrected by $(22/24)2 \times d$. Along the same line of argument: if animals are dosed 5 days per week, the daily dose giving the observed tumour incidence will be simply corrected by $(5/7) \times d$.

Differences between occupational and lifetime conditions of exposure

For non-threshold carcinogens, lifetime risks for consumers and for humans exposed indirectly via the environment is associated with daily exposure of 24 hours (7 days a week) for 75 years. This exposure duration is considered equivalent to the life-time exposure in experimental studies of 1.5 to 2 years, dependent on species and strain used (see Appendix I, part 3). For workers, however, the exposure time is 8 hours per day, 5 days per week, 48 weeks per year for 40 years. This implies that for workers, a correction factor should be applied to the dose descriptor based on animal life-time exposure data. As a default, a value of 2.8 ($7/5 \times 52/48 \times 75/40$) is proposed for this correction factor.

After modification of all available dose descriptors (where necessary), all corrected starting points should be collected in a table, one per exposed population.

Table XX Corrected dose descriptors for the relevant exposure pattern for workers/consumers/man via the environment¹

Endpoint	Lowest relevant dose descriptor ² (appropriate unit)		Corrected dose descriptor (appropriate unit)	
	Local ³	Systemic ⁴	Local ³	Systemic ⁴
Acute toxicity - oral - dermal - inhalation				
Irritation/Corrosivity - skin - eye - resp. tract		NA ⁵ NA NA		
Sensitisation - skin - resp. tract		NA NA		
Repeated dose sub-acute/ semi-chronic/ chronic - oral - dermal - inhalation				
Mutagenicity - in vitro				

- in vivo				
Carcinogenicity				
- oral				
- dermal				
- inhalation				
Reproductive toxicity				
fertility impairment				
- oral				
- dermal				
- inhalation				
developmental tox				
- oral				
- dermal				
- inhalation				

¹ Select the relevant population;

² NOAEL (NOAEC), LOAEL, T25, BMD10 etc or any other dose descriptor; indicate whether this concerns a no or lowest observed effect level etc;

³ Units are mg/m³ for inhalation, and mg/cm² for dermal exposure;

⁴ Units are mg/m³ for inhalation, and mg/kg bw/day for oral and dermal exposure;

⁵ Not applicable.

3.8 Step 3: Application of assessment factors to the correct starting point to obtain endpoint-specific DNEL(s)/DMEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population)

The next step in the calculation of a DNEL is to derive and apply a so-called ‘overall assessment factor’). The overall AF is a factor addressing differences between experimental effect assessment data (usually from animal studies) and the real human exposure situation, taking into account variability and uncertainty. Overall AF is derived by combining a number of individual assessment factors dealing with several issues related to the available dataset. Preferably, the value for each individual assessment factor is based on substance-specific information. However, although sound in principle, in practice the approach has limitations (data are often scarce, especially toxicodynamic data, and human data) and therefore default assessment factors most often need to be used. Each step in the process, including any choice for an assessment factor, whether substance-specific or default should be explained as transparently as possible, with a qualitative narrative in the chemical safety report (CSR).

The following sections give guidance on the main issues to include in derivation of the overall AF applied in the general assessment procedure for threshold endpoints and, if dealt with quantitatively, non-threshold endpoints. The individual factors contributing to the overall AF are described separately and by the end of the section, guidance is given on how to combine these into an ‘overall assessment factor’.

At the same time, the descriptions point to many issues to be considered in qualitative discussions of the applicability and reliability of the effects assessment database.

Assessment factors

Assessment factors are numerical values. They are used to address the differences between the experimental data and the human situation, taking into account the uncertainties in the extrapolation procedure and in the available data set. In principle, all data on a specific substance need to be reviewed thoroughly in order to use, as far as possible, substance-specific information for the

establishment of appropriate values for the various assessment factors. When substance-specific information is not available, data on analogues, which act with the same mode of action as the chemical under consideration, should be taken into account. However, when the available data do not allow the derivation of substance-specific or analogue-specific assessment factors, default assessment factors should be applied. It should be emphasised that default assessment factors represent a fall back position rather than the starting point.

Several publications exist on the use and/or quantification of assessment factors in human health risk assessment. For illustration, a short overview of defaults proposed in some of these publications is given in Appendix II. For more background information and further reading, the reader is referred to the original publications.

Defaults typically proposed for human health risk assessment are point estimates. Additionally, default distributions have been proposed for assessment factors, acknowledging that lognormal distributions best describe variability and uncertainty in these factors. Some of these distributions are based on NOAEL-ratios derived from comprehensive toxicological databases. Some risk assessors, however, doubt the thoroughness and validity of such derived distributions.

It is noted that there is uncertainty on which overall protection level is reached when different factors are combined into an overall assessment factor in one way or the other, including whether the individual factors are dependent or independent of each other. Which value is chosen and which procedure for combining individual assessment factors into an overall assessment factor depends *inter alia* on the specific view of the risk assessor.

Annex II reflects this situation by illustrating the wide variation in approaches. It is obvious, that a harmonised consensus becomes difficult. This was also proven during the development of this guidance document where different stakeholders have been consulted. Interestingly, however, there are quite some similarities in individual and overall assessment factors obtained via the different approaches (see the table in Appendix II). This, combined with the desire to recommend a harmonised set of default factors to be used in risk assessments and thereby securing transparency, led to the default factors recommended in this guidance document.

It is to be stressed that any choice for an assessment factor, whether substance-specific or default, should be explained as transparently as possible in the risk assessment report. The concept of substance-specific data to replace part or all of default assessment factors for inter- and intra-species differences is elaborated upon in a recent draft guidance document from IPCS (WHO/IPCS, 2001), nicely exemplified with case studies illustrating the types of data most valuable and how they can be used.

Assessment factors relating to the extrapolation procedure

Several aspects are involved in the extrapolation of experimental data to the human situation, *inter alia*:

- interspecies differences;
- intraspecies differences;
- differences in duration of exposure;
- high to low dose extrapolation;
- use of alternative data;
- quality of whole database.

Interspecies differences

Data from animal studies are the typical starting points for risk characterisations and thus differences in sensitivity between experimental animals and humans need to be addressed, with the default assumption that humans are more sensitive than experimental animals. Where human data are used as the starting point for the risk characterisation, no extrapolation and no assessment factor is necessary for interspecies differences in sensitivity.

Interspecies differences result from variation in the sensitivity of species due to differences in toxicokinetics and toxicodynamics. Some of the toxicokinetic differences can be explained by differences in body size (and related differences in basal metabolic rate).

If no substance-specific data are available, the standard procedure for threshold effects would be, as a default, to correct for differences in metabolic rate (allometric scaling) and to apply an additional factor of 2.5 for other interspecies differences.

Allometric scaling extrapolates doses according to an overall assumption that equitoxic doses (when expressed in mg/kg bw/day) scale with body weight to the power of 0.75. This results in different default allometric scaling factors for the different animal species when compared with humans (see Table 3-2).

Table 3-2 Allometric scaling factors for different species as compared to humans

Species	Body weight (kg)	AS factor
Rat	0.250	4
Mouse	0.03	7
Hamster	0.11	5
Guinea pig	0.8	3
Rabbit	2	2.4
Monkey	4	2
Dog	18	1.4

a) assuming human body weight is 70kg

The factors are derived according to the formula:

$$\frac{bw_{\text{human}}/bw_{\text{animal}}}{(bw_{\text{human}}/bw_{\text{animal}})^{0.75}} = (bw_{\text{human}}/bw_{\text{animal}})^{0.25}$$

[all txt suggestions below by SB]

Allometric scaling is based on the assumption which was originally predicted mathematically and subsequently substantiated by empirical investigations (Schneider et al., 2004) [Schneider K, Oltmanns J and Hassauer M (2004) Allometric principles for interspecies extrapolation in toxicological risk assessment – empirical investigations. *Regulatory Tox and Pharm*, 39(3), 334-347.] that the effects of toxicological relevance are driven by the basal metabolic rate as it affects physiological processes such as cardiac output, blood flow and perfusion of liver and kidneys which, in turn, affect the elimination/clearance of most chemicals. Allometric scaling is an empirical approach for interspecies extrapolation of a significant number of kinetic processes related to toxicity which is generally applicable to substances that are essentially renally excreted, but not to compounds that are highly extracted by the liver and excreted in the bile. It appears that species differences in biliary excretion and glucuronidation are independent of caloric demand (Walton et al., 2001). [Walton K, Dorne JL,

and Renwick AG (2001) Uncertainty factors for chemical risk assessment: interspecies differences in glucuronidation. *Food Chem Toxicol* 39, 1175-1190.] Allometric scaling according to caloric demand would apply most appropriately to those substances for which the unmetabolised parent or a stable metabolite is the relevant toxic species and clearance is according to first-order processes. Conversely, the applicability of allometric scaling when toxicity is a consequence of exposure to a very reactive parent compound (or metabolite) that is not removed from the site of formation, is less well supported (USEPA, 1992). [USEPA 1992. Draft Report: A cross-species scaling factor for carcinogen risk assessment based on equivalence of mg/kg^{3/4}/day; Notice. Federal Register 57(109):24152-2424173.] It is to be noted that allometric scaling should not be applied if the effects are not dependent on metabolic rate or systemic absorption, e.g. in the case of local effects. Allometric scaling should also not be applied in cases where doses are expressed as concentrations (in mg/m³ or in mg/kg food) as these are assumed to be already scaled according to the allometric principle, since ventilation rate and food intake directly depend on the basal metabolic rate. Allometric scaling is also not appropriate for acute lethal effects as these effects, which are accomplished by an immediate and intolerable level of damage to some critical homeostatic processes, may be independent of caloric demand and related physiological processes which affect toxicity (UESPA, 2006). [USEPA 2006. External Review Draft: Harmonisation in interspecies extrapolation – use of BW^{3/4} as default method in derivation of the oral RfD. Risk Assessment Forum Technical Panel. EPA/630/R-06/001.] Special care should be taken when route-to-route extrapolation has been performed. See detailed guidance on this in Annex I – part 2, and a short summary thereof in Table 3-3.

For non-threshold effects, the standard procedure would be, as a default, to correct only for differences in metabolic rate (allometric scaling). Because the linear model used for non-threshold effects for extrapolation from high to low dose (i.e. over about four orders of magnitude) is considered sufficiently conservative, it also accounts for remaining interspecies differences, as well as for differences in intraspecies sensitivity. Thus, if applicable, for non-threshold effects only a correction for allometric scaling is necessary.

Local effects

For local effects, i.e. effects at the portal of entry (on the skin, the respiratory tract or the gastrointestinal tract), different factors should be taken into account when assessing interspecies differences. In this respect, consideration of the mechanism of toxicity is crucial, e.g. if the effect is a simple destruction of membranes due to the phys-chem properties (e.g. pH) of the chemical concerned as opposed to a mechanism involving local metabolism.

In terms of kinetics, where the mechanism of effect is direct chemical/pH reactivity, no further kinetic considerations apply (interspecies kinetic factor of 1). In contrast, where tissue metabolism is a factor, the same kinetic considerations should apply (i.e. a chemical-specific interspecies kinetic factor or the default value), as would be the case for e.g. kidney or liver damage arising from systemic metabolism. In relation to the dynamic factor, if considerations of the mechanism indicate that the effect seen is a simple destruction of membranes due to the phys-chem properties (e.g. pH) of the chemical concerned, one might assume that animals and humans will respond in the same way (interspecies dynamic factor of 1) unless there is clear evidence for a significant quantitative difference in protective mechanisms. Where a local metabolic process is involved, which could apply to either or both activation or deactivation of the original substance, then the same dynamic considerations (i.e. a chemical-specific interspecies dynamic factor or the default value) should apply, as would be the case for e.g. kidney or liver damage arising from systemic metabolism. If tissue metabolism is involved, which could lead to the formation of different metabolites at different rates in different species, interspecies dynamic differences on how these metabolites interact with specific targets (which will determine the ultimate toxic response) cannot be completely ruled out.

In case substance-specific information shows specific susceptibility differences between species, which are not related to differences in basal metabolic rate, the additional factor of 2.5 should be modified accordingly.

Table 3-3 When to apply allometric scaling (AS) factor in step 3

Human exposure route (unit)	Experimental animal effect parameter (unit)	Apply AS factor?
Oral (mg/kg bw/day)	Oral (mg/kg bw/day)	Yes, see Appendix 1, part 2 examples A1/B2
	Dermal (mg/kg bw/day)	Yes, see Appendix 1, part 2 example B6
	Inhalatory (mg/m ³)	Yes, see Appendix 1, part 2 example B4
Dermal (mg/kg bw/day)	Oral (mg/kg bw/day)	Yes, see Appendix 1, part 2 example B5
	Dermal (mg/kg bw/day)	Yes, see Appendix 1, part 2 examples A1/B2
	Inhalatory (mg/m ³)	Yes, see Appendix 1, part 2 example B4
Inhalation (mg/m ³)	Oral (mg/kg bw/day)	No, see Appendix 1, part 2 example B3
	Dermal (mg/kg bw/day)	No, see Appendix 1, part 2 example B3
	Inhalatory (mg/m ³)	No, see Appendix 1, part 2 examples A2/B1

Intraspecies differences

Humans differ in sensitivity to toxic insult due to a multitude of biological factors such as genetic polymorphism affecting e.g. toxicokinetics/metabolism, age, gender, health status and nutritional status. These differences can be the result of genetic and/or environmental influences. This intraspecies variation is greater in humans than in the more inbred experimental animal population.

If the N(L)OAEL has been derived from an animal study, animal intraspecies variation/differences has already to some extent been accounted for in that N(L)OAEL. Ideally therefore, the intraspecies factor should reflect the *additional* interspecies variability, i.e. the difference between variability in the human population and variability in the animal population. The variability within the experimental animals is however assumed to be small and in addition, difficult to quantify. Therefore the intraspecies assessment factors suggested below are not corrected for animal variation.

It is recognised that in order to always cover the most sensitive person exposed to any chemical would require a very large default assessment factor. That is of course not workable and it is usually assumed that a default assessment factor of 10 is sufficient to protect the larger part of the population, including e.g. children and the elderly. For threshold effects, this factor of 10 is also the standard procedure, as a default, when assessing exposure to the general population. It is recognised that there are differences between children and adults in toxicokinetics (especially babies in their first months) and toxicodynamics (especially at different stages of development). These differences may render

children more or less susceptible to the toxic effects of a substance. A higher intraspecies extrapolation factor for children from 10 to 100 should be considered when:

- There are indications or suspicions, obtained from, for example, experiments in adult animals, epidemiological studies, *in vitro* experiments and/or SARs (Structure Activity Relationships), of effects on organ systems and functions that are especially vulnerable under development and maturation in early life (in particular the nervous, reproductive, endocrine and immune systems and also the metabolic pathways), and
- There are deficiencies in the database on such effects in young animals.

For workers, as standard procedure for threshold effects a default assessment factor of 5 is to be used, based on the fact that this sub population does not cover the very young, the very old, and the very ill.

Because the linear model used for non-threshold effects for extrapolation from high to low dose (i.e. over about four orders of magnitude) is considered sufficiently conservative, it also accounts for differences in intraspecies sensitivity. Thus, in contrast to threshold effects, for non-threshold effects no assessment factor is to be applied for this extrapolation step.

As for interspecies assessment factors, relevant substance-specific information on intraspecies variations should always be used to adjust or substitute the default factors (see e.g. WHO/IPCS, 2001).

Local effects

Intraspecies differences result from variation in the sensitivity of individuals due to differences in toxicokinetics and toxicodynamics. It should be noted that for local effects, if the mechanism of toxicity is direct chemical/pH reactivity, no further kinetic considerations apply (intraspecies kinetic factor of 1). In contrast, where tissue metabolism is a factor, the same kinetic considerations should apply to the metabolism issue, as would be the case for e.g. kidney damage arising from systemic metabolism (see text under ‘Interspecies differences’).

Differences in duration of exposure

A factor allowing for differences in the experimental exposure duration and the duration of exposure for the population and scenario under consideration needs to be considered taking into account that a) in general the experimental NOAEL will decrease with increasing exposure times and b) other and more serious adverse effects may appear with increasing exposure times.

The following default assessment factors are to be applied, as a standard procedure:

- semi/sub chronic to chronic: 2
- subacute to chronic: 6
- subacute to semi/sub chronic: 3

‘semi/sub-chronic’ usually refers to a 90 day study

‘sub-acute’ usually refers to a 28 day study

‘chronic’ usually refers to a 1.5 - 2 year study (for rodents).

These default assessment factors are generally to be applied for systemic effects and, in case of toxicity testing by inhalation, for local tissue damage in the respiratory tract.[\[suggested by NR 8/8\]](#)

Note: these default factors do not apply to cancer studies, as differences in duration of exposure and/or observation are already addressed in step 2 (see 3.7).

As always, substance-specific information should overrule the default values. A higher factor may be considered in cases where e.g. *in vitro* or QSAR evidence suggests that the substance may cause severe chronic effects, which cannot possibly be detected in a short term study.

Also bioaccumulating substances may in some situations call for a higher assessment factor. If, for example, there are indications of potential accumulation (for instance triggered by lipophilicity of the substance), the database needs to contain information on the rate of elimination to further explore the accumulation potential. If accumulation is likely, the toxicity studies need to be of sufficient length to cover the accumulation period (e.g. the time to reach a steady-state concentration). If there is limited information on these aspects, the assessor needs to consider whether the database may be inadequate, and to which extent this lack of information should affect the assessment factor.

A lower factor may be used if there is specific evidence that exposure duration is of no or low importance. This might be e.g. relevant for certain local effects in the respiratory tract for which there is no substantial difference in N(L)OAELs following acute and subacute exposure by inhalation and thus are considered rather concentration- than dose-dependent. [suggested by NR 8/8]

Below text is moved to AF 'Quality of whole database'

High to low dose extrapolation

This aspect only concerns non-threshold carcinogens. Assuming a level of very low concern of 1:100,000, the factor to be applied for high to low dose extrapolation is 25,000. This value is derived from the dose descriptor T25 (lifetime cancer risk of 25:100) and assuming a linear dose response down to the level of very low concern chosen (1:100,000); $25:100/1:100,000$ results in a factor of 25,000. Of course the level of very low concern would have to be harmonised and accepted at the policy level.

Note: in previous meeting Norbert and Dinant offered to make a example-paper comparing threshold and non-threshold approach both through steps 1-4 for an example – and take into this comparison the current EFSA and US EPA approaches. This paper – prepared by Norbert - is separately sent out and not yet included in this guidance text as N & D felt a group-discussion first was needed on this.

Uncertainty factor associated with use of alternative data

Under REACH the use of alternative data, e.g. *in vitro* data, (Q)SAR, read across or chemical categories, is stimulated and preferred above performing additional animal studies, if considered justified. This may, however, introduce some additional uncertainty. If dose descriptors are derived on this basis the additional uncertainty may be addressed by an extra uncertainty factor. Guidance for the value of this extra factor may be found in the endpoint specific sections 3.5.1-3.5.8. Generic issues coming out of this could be described here.

Quality of whole database

There is a separate text proposal by Maria that should cover the below green marked text which now is in the report as a separate assessment factor on 'Dose-response relationship (incl. severity of effect)', and as text originally from page 29 on qualitative assessment elements in Risk Characterisation.

For the dose-response relationship, consideration should be given to the uncertainties in the NOAEL as the surrogate for the true no-adverse-effect-level (NAEL), as well as to the extrapolation of the LOAEL to the NAEL (in cases where only a LOAEL is available or where a LOAEL is considered a more appropriate starting point).

The size of an assessment factor should take into account the dose spacing in the experiment (in recent study designs generally spacing of 2-4 fold), the shape and slope of the dose-response curve, and the extent and severity of the effect seen at the LOAEL.

When the starting point for the DNEL calculation is a LOAEL, it is suggested to use an assessment factor between 3 (as minimum/majority of cases) and 10 (as maximum/exceptional cases). However, the Benchmark dose (BMD) approach is, when possible, preferred over the LOAEL-NAEL extrapolation (see Section 2.4).

A BMD calculated as the lower confidence limit of the dose that produces a response of 5% (BMD5) is on average assumed to be comparable to a NOAEL (WHO, 2000, p. 16). If other BMD indicators are used, e.g. a BMD10, it should be considered on a case-by-case basis whether an additional dose-response assessment factor is needed.

When the starting point for the DNEL calculation is a NOAEL, the default assessment factor, as a standard procedure, is one. However, a larger assessment factor may be applied in specific cases such as the following:

- a shallow dose-response curve giving uncertainty about the statistical derivation of the NOAEL
- exceptional cases of serious effects at dose levels slightly higher than the NOAEL (i.e. at the LOAEL) – this corresponds to a very steep dose-response curve
- poor quality of study from which the NOAEL is derived (e.g. few animals and inconsistent spacing between doses) also give uncertainty about the statistically derived NOAEL
- other concerns related to the identified NOAEL; e.g. for sensitisation (how certain is the NOAEL identified?) and carcinogenicity (is the mode of action for a presumed threshold carcinogen completely understood?)

It is difficult to give exact guidance for the magnitude of an assessment factor for such specific situations. They should be determined on a case-by-case basis. The registrant may also choose to discuss these issues qualitatively.

In some cases neither a NOAEL nor a LOAEL can be identified, which e.g. might be the case when assessing acute toxicity based on a LD50 or LC50. In such situations, an extra assessment factor may have to be applied, see Section 3.5.2.

[Volgens minutes moet deze tekst evt. geïntegreerd worden met die onder 'Quality of whole database'. MW moet eerste aanzet hiervoor geven.]

Also in the quantitative approach the RC, the interpretation of the RCR should always be accompanied with a qualitative discussion, addressing (a.o.) aspects that could not be dealt with in a quantitative way.

(Below text is from qualitative assessment of risk page 29)

Some aspects to consider in the final qualitative discussion are:

- how extensive is the database supporting the risk assessment;
- does the database include human data as well as experimental animal data;
- does the database reflect the relevant route of exposure – especially extrapolation from the oral to the inhalation route is critical;
- does the data base include test data on more than one species;
- if multiple species are tested, do they all respond similarly to the test substance;

- what is the adversity, severity and potency of the effect;
- the quality of the studies e.g. study design, performance and reporting;
- what are the data gaps (see further details in end-point specific sections);
- what are the uncertainties in the exposure assessment;
- is exposure characterised by combined exposure to several closely related substances with the same critical end point;
- what are the scientific uncertainties;
- what is the overall confidence in the database.

(NB: These aspects might partly have been covered by some of the quantitative assessment factors)

Overall assessment factor

The overall assessment factor is obtained by simple multiplication of individual assessment factors discussed in the previous paragraphs.

Table 3-4 presents an overview of the individual default assessment factors, which should be used in the absence of relevant substance-specific information.

Table 3-4 Default assessment factors

Assessment factor		Default value
Interspecies	- correction for differences in metabolic rate per body weight	AS ^{a, b}
	- remaining differences	2.5 ^c
Intraspecies	- worker	5 ^c
	- general population	10 ^{c, d}
Exposure duration	- subacute to sub/semi-chronic	3
	- sub/semi-chronic to chronic	2
	- subacute to chronic	6
High to low dose extrapolation	- high to low dose extrapolation ^f	25,000
Alternative data	- issues related to reliability of the alternative data	1 ^g
Quality of whole database	- issues related to completeness and quality of the available data	2-5
	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1 ^e
	- ?	

a AS = factor for allometric scaling (see Table 3-2)

b Caution should be taken when the starting point is an inhalation or diet study

c Not to be applied for non-threshold carcinogens

d Not always covering risk characterisation of very young children

e See text for deviations from default

f Only for non-threshold carcinogens
 g to be provided by EWGs

Deriving endpoint-specific DNEL(s)/DMEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population):

The resulting DNEL value for an endpoint and exposure pattern is derived by directly applying the overall AF to the corrected (according to step 2) dose descriptor:

Thus for a corrected NOAEL:

$$\text{Endpoint-specific DNEL} = \frac{\text{NOAEL}_{\text{corr}}}{\text{AF}_1 \times \text{AF}_2 \times \dots \times \text{AF}_n} = \frac{\text{NOAEL}_{\text{corr}}}{\text{Overall AF}}$$

Likewise, the resulting DMEL value for an endpoint and exposure pattern is derived by directly applying the overall AF to the corrected (according to step 2) dose descriptor:

Thus for a corrected T25:

$$\text{Endpoint-specific DMEL} = \frac{\text{T25}_{\text{corr}}}{\text{AF}_1 \times \text{AF}_2 \times \dots \times \text{AF}_n} = \frac{\text{T25}_{\text{corr}}}{\text{Overall AF}}$$

The endpoint-specific DNEL(s)/DMEL(s) should be collected in tables, one per exposed population.

Table XXX Endpoint-specific DNEL(s)/DMEL(s) for the relevant exposure pattern for workers/consumers/man via the environment¹

Endpoint	Corrected dose descriptor (appropriate unit)		Endpoint-specific DNEL/DMEL (appropriate unit)	
	Local ²	Systemic ³	Local ²	Systemic ³
Acute toxicity - oral - dermal - inhalation				
Irritation/Corrosivity - skin - eye - resp. tract		NA ⁴ NA NA		
Sensitisation - skin - resp. tract		NA NA		
Repeated dose sub-acute/ semi-chronic/ chronic - oral - dermal - inhalation				
Mutagenicity - in vitro				

- in vivo				
Carcinogenicity				
- oral				
- dermal				
- inhalation				
Reproductive toxicity				
fertility impairment				
- oral				
- dermal				
- inhalation				
developmental tox				
- oral				
- dermal				
- inhalation				

¹ Select the relevant population;

² Units are mg/m³ for inhalation, and mg/cm² for dermal exposure;

³ Units are mg/m³ for inhalation, and mg/kg bw/day for oral and dermal exposure;

⁴ Not applicable.

3.9 Step 4: Selection of the leading health effect and the corresponding DNEL(s)/DMEL(s)

As introduced in section 3.4.4, a DNEL and/or DMEL can be derived as follows:

- Step 1: Derivation of typical dose descriptors (e.g. NOAELs, BMD, LD50, T25....) from all available studies on the different endpoints (see also 2.4);
- Step 2: When necessary, modification of the dose descriptor to the correct starting point;
- Step 3: Application of assessment factors to the correct starting point to obtain endpoint-specific DNEL(s)/DMEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population);
- Step 4: Selection of the leading health effect and the corresponding DNEL(s)/DMEL(s).

In step 4 of the DNEL/DMEL approach, from all available DNEL(s)/DMEL(s) the lowest DNEL or DMEL value for each relevant exposure pattern, i.e. each relevant population, each relevant exposure route and each relevant exposure duration, are selected, as these represent the leading effect for that particular exposure pattern and will thus drive the (quantitative) risk characterisation.

Table XXXX DNEL / DMEL values for the leading health effect

Exposure pattern	DNEL/DMEL (appropriate unit)	
	Local ¹	Systemic ²
Short-term exposure		
Workers		
- dermal		

- inhalation		
Consumers		
- oral		
- dermal		
- inhalation		
Long-term exposure		
Workers		
- dermal		
- inhalation		
Consumers		
- oral		
- dermal		
- inhalation		
Man via the environment		
- oral		
- inhalation		

¹ Units are mg/m³ for inhalation, and mg/cm² for dermal exposure;

² Units are mg/m³ for inhalation, and mg/kg,bw for oral and dermal exposure;

For discussion:

The DN(M)EL derivation ends at step 4. However, at this point there may also be endpoints for which no DNEL could be derived, and for which also no other alternative quantitative approach (DMEL) was applicable. Hence, in order to decide what to take forward to the RC and what to communicate via SDS, a next step would be necessary to weigh the DN(M)ELs from step 4 against the endpoints dealt with in a qualitative way. How to deal with this weighing?]

3.10 Conclusions on classification and labelling of the compound

As indicated in the introductory chapter one objective of the human health hazard assessment is the classification and labelling of a substance performed in accordance with Directive 67/548.

From the above described assessments per human health endpoint it can be concluded whether the substance should not be classified at all, is dangerous, or is very dangerous and will have to be subjected to authorisation.

In case the substance is classified, a risk characterisation is needed, i.e. the calculated DNEL(s) and/or DMEL(s) should be compared to the estimated exposure values associated with all actual scenarios of production (if applicable), use and handling of the substance.

3.11 Conclusion for risk characterisation purposes

Under REACH, the human health risk characterisation principally consists of a comparison of the exposure of each human population known to be or likely to be exposed with the appropriate DNEL (REACH Annex I, 6.3). This exposure/DNEL comparison results in a risk characterisation ratio (RCR). For any exposure scenario the risk to humans can be considered to be adequately controlled if exposure levels do not exceed the appropriate DNEL (REACH Annex I, 6.4).

Thus, the quantitative RC approach is as follows:

$$\text{RCR} = \frac{\text{Exposure}}{\text{DNEL}}$$

If Exposure < DNEL → Risk is adequately controlled

If Exposure > DNEL → Risk is NOT adequately controlled

REACH also requires that for those human effects for which no DNEL could be derived, a qualitative assessment of the likelihood that effects are avoided when implementing the exposure scenario shall be carried out in the risk characterisation part of the CSA. As pointed out in chapter 3.4.2, also for non-threshold substances it is proposed to give a quantitative description of the expected exposure. Therefore the DMEL (derived minimal effect level or level of very low concern) has been introduced. This value can be used as an additional element for risk characterisation purposes.

$$\text{RCR} = \frac{\text{Exposure}}{\text{DMEL}}$$

If Exposure < DMEL → Risk is of very low concern

If Exposure > DMEL → Risk is of concern.

This approach for non-threshold substances offers additional guidance to risk managers in differentiating exposure scenarios for which existing control measures already result in very low human health risks from those for which existing control measures are less effective.

It is to be noted that for threshold substances, a DNEL is used as a decision point which should not be exceeded, indicating a safe exposure. For non-threshold substances, a DMEL is a tool to describe the dose-response in relation to the potency of the substance.

[above changes proposed by DB 3/8]

Risk characterisation in case of combined exposure

All human populations (workers, consumers, humans indirectly exposed via the environment) may be concurrently exposed to a specific substance via different routes of exposure. Route-specific exposure may specifically contribute to the total internal body burden via route-specific absorption of the substance. Thus, concurrent exposure via different routes of exposure needs to be accounted for when characterising overall systemic health risks.

Both exposure levels and DNELs can either be expressed as external values or as internal values. Transformation of external values into internal values is routinely performed by using default or experimental absorption data. In some cases, it might be alternatively possible to estimate the relative systemic availability of a substance for different routes of exposure by comparing toxicity

data for the different routes of exposure. In any case, care should be taken that the absorption data used for the transformation of external to internal values are not contradictory to route-specific toxicity data. *This provided*, risk characterisation can be consistently performed either with external or internal dose units.

When using internal values as dose units for exposure and for the DNEL (internal body burden in mg/kg/d, internal DNEL in mg/kg/d) the risk-relevant consequence of concurrent route-specific exposure is directly expressed as total internal body burden. Comparison of the total internal body burden with the internal NOAEL directly results in the RCR for combined exposure.

For good reasons exposure levels for the different routes of concurrent exposures (oral intake, dermal contact, exposure by inhalation) and the corresponding DNELs might be expressed as external values. Based on external values, route-specific risk characterisation ratios are calculated. In order to account for combined exposure and thus for combined risk characterisation, the route-specific RCRs need to be combined/integrated. Assuming an identical qualitative toxicity profile for the different routes of exposure combined risk characterisation may be based on a simple combination of the route-specific risk characterisation ratios:

$$\text{RCR (combined exposure)} = \text{RCR (oral)} + \text{RCR (dermal)} + \text{RCR (inhalation)}$$

Whenever there is an exposure scenario with a second or third concurrent route of exposure, a RCR of less than 1 for a single route of exposure need not necessarily result in a “safe” exposure scenario.

The risk to humans can only be considered adequately controlled for an exposure scenario with concurrent/parallel routes of exposure if the risk characterisation ratio for combined exposure (the sum of the route-specific risk characterisation ratios) is less than the reference value of 1.

[above text suggested by NR 8/8]

APPENDIX I**Bioavailability, route-to-route extrapolation and allometric scaling****Examples to illustrate how to obtain consistent results**

When transferring study results from animals to humans, care has to be taken to use a meaningful physiological parameter as a reference value for scaling issues. This Appendix illustrates in part 1 some issues related to this. Part 2 gives specific guidance on how to deal with differences in bioavailability and how to conduct route-to-route extrapolation in the situations identified in Section 3.7. In Part 3 default parameters for lifetime cancer studies are summarised which are relevant to derive consistent dose descriptors.

Part 1 - Scaling issues

Where inhalative data are concerned, air concentrations for animal and human exposure are generally compared directly. Using this approach implies standardisation of inhalative data with reference to the respiratory rates. Since respiratory rates depend directly on caloric demand this means, that inhalative study results are (implicitly) extrapolated to humans on the basis of metabolic rate scaling (also termed allometric scaling).

Oral data usually are expressed in dose per kg bodyweight. Comparing oral data directly would mean, to use body weight as a reference for scaling purposes. If, however, allometric scaling shall be used for standardisation, it has to be taken into account that metabolic rate does not correlate directly with body weight but with the body weight modified by the exponent 0.75 (metabolic rate \approx body weight^{0.75}). On that background data from different species expressed as dose per kg bodyweight need to be adjusted to caloric demand before they can be compared based on metabolic rate. According to the different average bodyweights of the animal species, when comparing oral and dermal data with humans, specific allometric scaling factors are needed for each specie (see **Table 3-2** in Section 3.8).

If oral data are used to evaluate inhalative exposure situations and the oral data are scaled on the basis of body weight, risk assessors need to be aware of the aspect outlined above. Usually respiratory rates for animals and humans are used for dose adjustment. For consistent results care has to be taken that the respiratory rates used in combination with the respective bodyweights match the allometric equation. In addition a special situation occurs for workers. Compared to a standardised situation with basal caloric demand, workers usually are in a status of elevated activity with higher respiratory rates. This has to be compensated for as well.

The following examples shall outline the procedure. The physiological values used in these examples are taken from **Table 3-1** in Section 3.7.

In examples I and II, oral data from the rat are used to decide on a corresponding air concentration for humans. For simplicity 100% absorption for the oral and the inhalative route for animals and humans is assumed. The air concentration is calculated in two different ways.

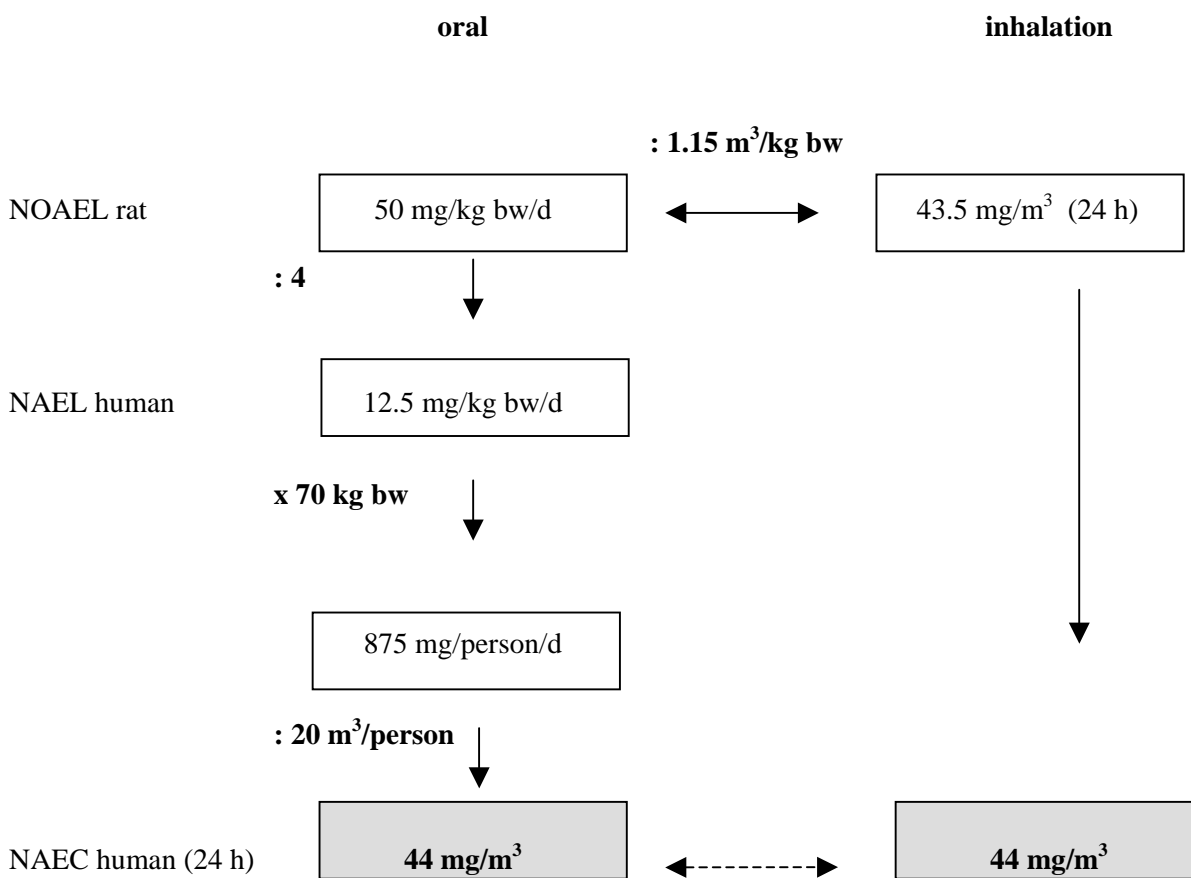
On the left side of the examples, the oral NOAEL for the rat in a first step is transferred to humans with a factor of 4 for allometric scaling. With help of a standard human body weight (70 kg) and a default human breathing volume referring to the specific conditions of the respective population (20 m³ for general public in 24 h hours and basal caloric demand, 10 m³ for workers in 8h and light activity), this dose is then translated into an air concentration.

On the right side of the examples, the oral dose for the rat is converted to the corresponding air concentration using a standard breathing volume for the rat ($1.15 \text{ m}^3/\text{kg}$ for 24 hours exposure of general public, $0.38 \text{ m}^3/\text{kg}$ for 8 hours exposure of workers, see **Table 3-1**). For workers the resulting air concentration needs to be additionally corrected for the difference between basal caloric demand and caloric demand under light activity. This correction factor derives from the inhalative volumes in 8 hours under the respective conditions (6.7 m^3 for base level, 10 m^3 for light activity).

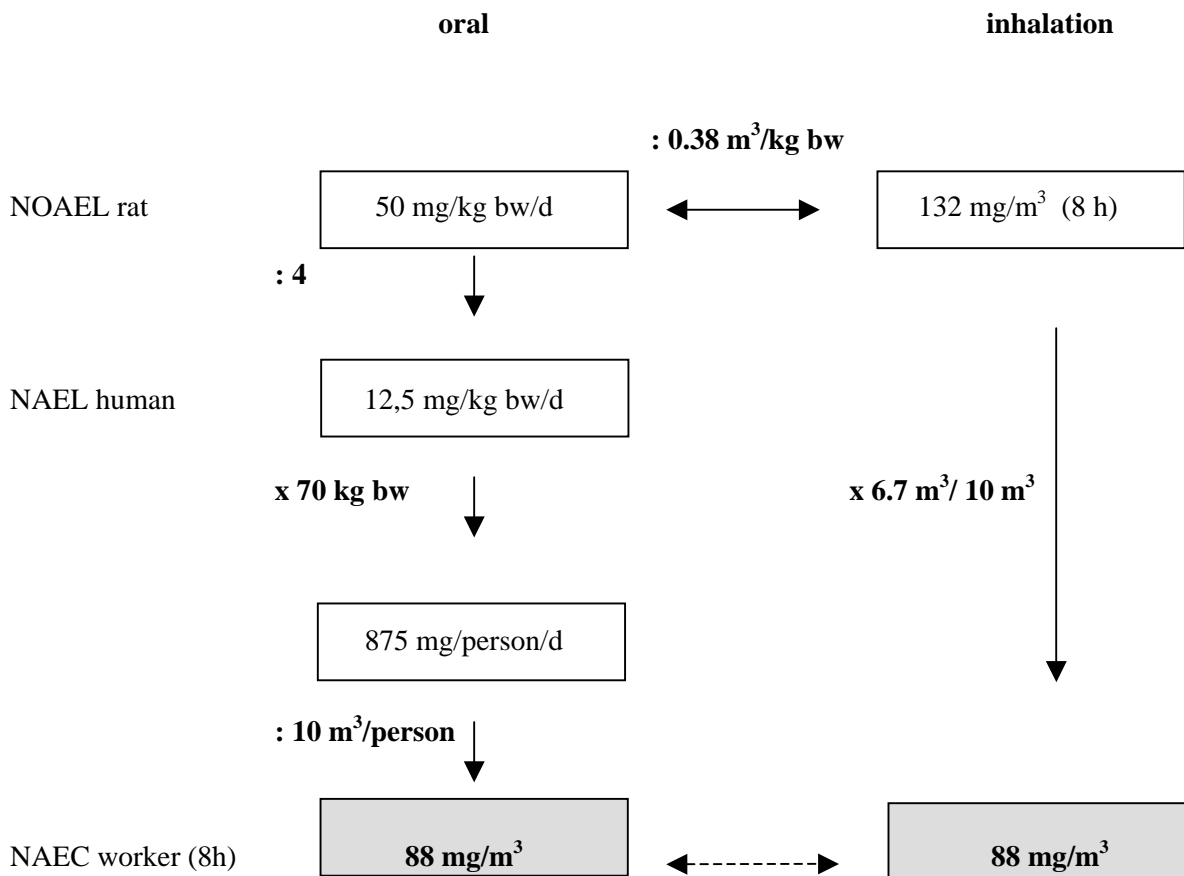
As can be seen from the results, the two different ways of calculation lead to the same results.

Examples (assuming 100 % bioavailability for both routes in both species)

I. General public



II. Workers



Part 2 – Guidance on modification of starting point

This part specifically outlines the procedure taking into account bioavailability issues. The examples especially concern the conversion of the N(L)OAEL/C into an adequate starting point for DNEL derivation, but also apply to other dose descriptors for e.g. non-threshold effects, and thereby relates directly to Section 3.7 of the main text. The examples presented also indicate whether allometric scaling should be included in step 3 of the DNEL/DMEL derivation or whether this is already implicitly done at this point. In most cases substance-specific information relating to differences in bioavailability will not be available. Section 3.7 suggests default factors for some of these situations.

A. If for a given human exposure route there is an effect parameter for the same route (in experimental animals or humans) and for that particular exposure route there is no difference in bioavailability between experimental animals and humans at the relevant level of exposure, then in principle no modification of starting point is necessary [example A.1]. However, if the exposure route is via inhalation, then for workers a correction is necessary for the differences in respiratory rates under standard conditions and under conditions of light activity [example A.2].

A.1. Oral[#] exposure; oral absorption rat = oral absorption human

For step 2: no modification necessary

For step 3: as to interspecies differences, apply factor for allometric scaling (4 for rat).

[#]similar situation for the dermal route

A.2. Inhalatory exposure; inhalation absorption rat = inhalation absorption human

For step 2: For workers, the inhalatory N(L)OAEC rat needs to be corrected for the difference between respiratory rates under standard conditions and under conditions of light activity (sRV_{human} versus wRV; see **Table 3-1** in Section 3.7):

For workers:

$$\begin{aligned} \text{corrected N(L)OAEC} &= \text{inhalatory N(L)OAEC} * \frac{\text{sRV}_{\text{human}}}{\text{wRV}} \\ &= \text{inhalatory N(L)OAEC} * \frac{6,7 \text{ m}^3}{10 \text{ m}^3} \end{aligned}$$

For step 3: as to interspecies differences, do not apply factor for allometric scaling.

B. Modification of starting point is necessary

- If for a given human exposure route there is an effect parameter for the same route (in experimental animals or humans) but for that particular exposure route there is a difference in bioavailability between experimental animals and humans at the relevant level of exposure [examples B.1 and B.2].
- If for a given human exposure route there is not an effect parameter for the same route (in experimental animals or humans) [examples B.3-B.6].

B.1. Inhalatory exposure; inhalation absorption rat ≠ inhalation absorption human

For step 2: correct inhalatory N(L)OAEC rat (in mg/m³) for differences in inhalation absorption between rats and humans. Additionally, for workers a correction is needed for the difference between respiratory rates under standard conditions and under conditions of light activity (sRV_{human} versus wRV; see **Table 3-1** in Section 3.7).

$$\text{corrected N(L)OAEC} = \text{inhalatory N(L)OAEC} * \frac{\text{ABS}_{\text{inh-rat}}}{\text{ABS}_{\text{inh-human}}}$$

For workers:

$$\text{corrected N(L)OAEC} = \text{inhalatory N(L)OAEC} * \frac{ABS_{inh-rat}}{ABS_{inh-human}} * \frac{sRV_{human}}{wRV}$$

For step 3: as to interspecies differences, do not apply factor for allometric scaling.

B.2. Oral[#] exposure; oral absorption rat ≠ oral absorption human

For step 2: correct oral N(L)OAEL rat (in mg/kg bw/day) for differences in oral absorption between rats and humans as follows:

$$\text{corrected N(L)OAEL} = \text{oral N(L)OAEL} * \frac{ABS_{oral-rat}}{ABS_{oral-human}}$$

For step 3: as to interspecies differences, apply factor for allometric scaling (4 for rat).

[#] similar situation for the dermal route

B.3. Inhalatory exposure; oral[#] N(L)OAEL rat

For step 2: convert oral N(L)OAEL rat (in mg/kg bw/day) into inhalatory N(L)OAEC rat (in mg/m³) by using a default respiratory volume for the rat corresponding to the daily duration of human exposure (sRV_{rat}; see **Table 3-1** in Section 3.7), followed by a correction for differences in absorption between routes (if the case), and a correction for differences in inhalation absorption between rats and humans (if the case). For workers an additional correction is needed for the difference between respiratory rates under standard conditions and under conditions of light activity (sRV_{human} versus wRV; see **Table 3-1** in Section 3.7).

$$\begin{aligned} \text{corrected inhalatory N(L)OAEC} &= \text{oral N(L)OAEL} * \frac{1}{sRV_{rat}} * \frac{ABS_{oral-rat}}{ABS_{inh-rat}} * \frac{ABS_{inh-rat}}{ABS_{inh-human}} \\ &= \text{oral N(L)OAEL} * \frac{1}{sRV_{rat}} * \frac{ABS_{oral-rat}}{ABS_{inh-human}} \end{aligned}$$

For workers:

$$\text{corrected inhalatory N(L)OAEC} = \text{oral N(L)OAEL} * \frac{1}{\text{sRV}_{\text{rat}}} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{inh-human}}} * \frac{\text{sRV}_{\text{human}}}{\text{wRV}}$$

For step 3: as to interspecies differences, do not apply factor for allometric scaling.

similar situation with dermal N(L)OAEL

B.4. Oral[#] exposure; inhalatory N(L)OAEC rat

For step 2: convert inhalatory N(L)OAEC rat (in mg/m³) into oral N(L)OAEL rat (in mg/kg bw/day) by using a default respiratory volume for the rat corresponding to the daily duration of human exposure (sRV_{rat}; see **Table 3-1** in Section 3.7), followed by a correction for differences in absorption between routes (if the case), and a correction for differences in oral absorption between rats and humans (if the case).

$$\begin{aligned} \text{corrected oral N(L)OAEL} &= \text{inhalatory N(L)OAEC} * \text{sRV}_{\text{rat}} * \frac{\text{ABS}_{\text{inh-rat}}}{\text{ABS}_{\text{oral-rat}}} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{oral-human}}} \\ &= \text{inhalatory N(L)OAEC} * \text{sRV}_{\text{rat}} * \frac{\text{ABS}_{\text{inh-rat}}}{\text{ABS}_{\text{oral-human}}} \end{aligned}$$

For step 3: as to interspecies differences, apply factor for allometric scaling (4 for rat).

similar situation with dermal exposure

B.5. Dermal exposure; oral N(L)OAEL rat

For step 2: convert oral N(L)OAEL rat (in mg/kg bw/day) into dermal N(L)OAEL rat (in mg/kg bw/day) by correcting for differences in absorption between routes (if the case) as well as for differences in dermal absorption between rats and humans (if the case):

$$\text{corrected dermal N(L)OAEL} = \text{oral N(L)OAEL} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{derm-rat}}} * \frac{\text{ABS}_{\text{derm-rat}}}{\text{ABS}_{\text{derm-human}}}$$

$$\text{oral N(L)OAEL} = \text{oral N(L)OAEL} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{derm-human}}}$$

For step 3: as to interspecies differences, apply factor for allometric scaling (4 for rat).

B.6. Oral exposure; dermal N(L)OAEL rat

For step 2: convert dermal N(L)OAEL rat (in mg/kg bw/day) into oral N(L)OAEL rat (in mg/kg bw/day) by correcting for differences in absorption between routes (if the case) as well as for differences in oral absorption between rats and humans (if the case):

$$\begin{aligned} \text{corrected oral N(L)OAEL} &= \text{dermal N(L)OAEL} * \frac{\text{ABS}_{\text{derm-rat}}}{\text{ABS}_{\text{oral-rat}}} * \frac{\text{ABS}_{\text{oral-rat}}}{\text{ABS}_{\text{oral-human}}} \\ &= \text{dermal N(L)OAEL} * \frac{\text{ABS}_{\text{derm-rat}}}{\text{ABS}_{\text{oral-human}}} \end{aligned}$$

For step 3: as to interspecies differences, apply factor for allometric scaling (4 for rat).

Part 3 - Dose calculations in lifetime studies

Table 1 Default values for dose calculations, i.e. standard lifespan, body weights, food and water intake and inhalation volume (based on Gold et al., 1984 and Paulussen et al., 1998)

Experimental animal	Sex	Standard lifespan ^a (years)	Body weight ^c (kg)	Food per day ^b (g)	Water per day ^b (ml)	Inhalation volume (l/ hr)
Mouse	Male	1.5 - 2	0.03	3.6 (120)	5 (167)	2.5
	Female	1.5 - 2	0.025	3.25 (130)	5 (200)	2.2
Rat	Male	2	0.5	20 (40)	25 (50)	20.5
	Female	2	0.35	17.5 (50)	20 (57)	15.7
Hamster	Male	2	0.125	11.5 (92)	15 (120)	7.2
	Female	2	0.110	11.5 (105)	15 (136)	7.2

a) Note: for certain strains of mice documented lower lifespan values of minimally 1.5 years are acceptable (OECD TG 451);

- b) In brackets the daily food or water consumption is given in g or ml per kg body weight per day, as appropriate.
- c) These are typical values used for lifetime studies.

Table 2 Standard values for dose calculations for humans exposed in workplaces, as consumers and via the environment (taken from Gold et al., 1984 and ICRP, 1975).

Parameter		DEFAULT Value	
Consumer, Humans-via-the-environment		Worker	
Lifespan (year)	75	Worklife (year)	40
Body weight (kg)	70	Length of workday (hour)	8
Food intake (kg/day)	1.4	Working days/week	5
Water intake (l/day)	2.0	Working weeks/year	48
Inhalation volume (m ³ /24 hours)	20	Body weight, male and female (kg)	70
		Male, inhalation volume (m ³ /8 hours) light work	10

APPENDIX II**Assessment factors suggested from different research groups and regulatory bodies**

In the DNEL/DMEL-approach, effect assessment uncertainties are dealt with by means of assessment factors, which should preferably be substance-specific, otherwise default (see Section 3.8). This appendix presents a short overview (including a summary table, **Table 1**) with defaults suggested for various assessment factors by different research groups and regulatory bodies. The overview is not meant to be exhaustive, and for more background information and further reading, the reader is referred to the original publications.

As can be seen from **Table 1**, defaults typically proposed for human health risk assessment are point estimates. A more recent development is the suggestion for probabilistic distributions as defaults for assessment factors: as lognormal distributions are thought to best describe variability and uncertainty in assessment factors, these distributions have been derived based on NOAEL-ratios from comprehensive toxicological databases. Although promising, up to now these probabilistic distributions have not been widely used in risk assessment, a.o. because it requires decisions on the percentile of the population one wants to protect (e.g. 50th percentile (= geometric mean of distribution) or 90th, 95th or 99th percentile (= P₉₀, P₉₅ or P₉₉ of distribution).

Explanation*Assessment factors for interspecies differences*

Interspecies differences result from variation in the sensitivity of species due to differences in toxicokinetics and toxicodynamics. Where human data are used as the starting point for the risk characterisation, no extrapolation is necessary and hence no assessment factor is normally suggested for interspecies differences in sensitivity.

Where data from animal studies are the typical starting point for risk characterisation, the default assumption in general is that humans are more sensitive than experimental animals. As can be seen from **Table 1**, the traditional default suggested for interspecies extrapolation is 10, which sometimes is subdivided in a default of 4 (10^{0.6}) for toxicokinetic differences and a default of 2.5 (10^{0.4}) for toxicodynamic differences.

Since some of the toxicokinetic differences can be explained by differences in body size (and related differences in basal metabolic rate), others have suggested as a default to, where appropriate, correct for differences in metabolic rate (allometric scaling; see Section 3.8), followed by the application of a default factor for other toxicokinetic and toxicodynamic differences. The size of the latter varies from 1 to 3 (see also footnotes to **Table 1**). Next to these point estimates, also default lognormal distributions have been established for this additional factor.

Assessment factors for intraspecies differences

Humans differ in sensitivity due to a number of biological factors (such as age, gender, genetic composition and nutritional status). The intraspecies variation in humans is greater than in the more homogeneous experimental animal population.

Although other values have been proposed, defaults typically suggested for the general population (representing all age groups, including children and elderly) are a factor of 10, sometimes equally subdivided in defaults of 3.16 (10^{0.5}) for both toxicokinetic and toxicodynamic differences. A lower default factor (e.g. 3) is generally suggested for the worker population, because the very young and very old are not part of this population.

For the intraspecies assessment factor also probabilistic distributions have been proposed. It is to be noted that the ones proposed by Vermeire et al. (1999, 2001) are not database-derived distributions, but theoretical distributions of which the P₉₉-values are consistent with the traditional defaults of 10 and 3.

Assessment factors for differences in duration of exposure

Taking into account that a) in general the experimental NOAEL will decrease with increasing exposure times and b) other and more serious adverse effects may appear with increasing exposure times, a factor allowing for differences in the experimental exposure duration and the duration of exposure for the population and scenario under consideration is normally applied in risk assessment.

As can be seen in **Table 1**, different factors have been suggested for exposure duration extrapolation, depending on the type of extrapolation (subacute to semichronic, semichronic to chronic, subacute to chronic) and the kind of effect (systemic or local). Probabilistic distributions have also been suggested.

Assessment factor for uncertainty in route-to-route extrapolation

Given the uncertain nature of route-to-route extrapolation and the fact that it can only be applied in specific cases, no defaults have been typically proposed for this factor, necessary in case no adequate data are available on the relevant route of exposure for the population and exposure scenario under consideration.

Assessment factor for dose-response relationship

For the dose-response relationship, consideration should be given to the uncertainties in the NOAEL as the surrogate for the true no-adverse-effect-level (NAEL), as well as to the extrapolation of the LOAEL to the NAEL (in cases where only a LOAEL is available or where a LOAEL is considered a more appropriate starting point). Taking into account the dose spacing in the experiment, the shape and slope of the dose-response curve (and in some approaches the extent and severity of the effect seen at the LOAEL), defaults typically suggested for this assessment factor range from 1–10 (see **Table 1**). The Benchmark dose (see Section 2.4) has also been suggested as acceptable alternative to the LOAEL-NAEL extrapolation, or even a probabilistically derived benchmark dose distribution.

Other aspects relating to the dataset

Next to extrapolation, other important aspects of risk characterisation are the adequacy of and confidence in the available dataset and the nature of the effect. Most often these aspects are dealt with in a qualitative way. When dealt with in a quantitative way, default values of 1-10 have been proposed (see **Table 1**), but there is no agreed basis for these values. The US-EPA uses the term modifying factor to cover uncertainties other than the 'extrapolation' assessment factors.

Overall assessment factor

Typically, the overall assessment factor is the product of the individual assessment factors, by assuming independency of the factors. It is to be realised that this multiplication is in general very conservative: when each individual assessment factor by itself is regarded as conservative, multiplication will lead to a piling up of conservatism. Hence, the more extrapolation steps are taken into account, the higher the level of conservatism.

Although not widely used up to now, a more recent development in risk assessment is the use of probability distributions and Monte Carlo simulation to obtain the overall assessment factor. By

acknowledging that each assessment factor is uncertain and is best described by a lognormal distribution, propagation of the uncertainty can be evaluated by Monte Carlo simulation yielding a lognormal overall distribution for the combined assessment factor. This offers the possibility for a quantitative estimate of the probability that an adverse effect will occur in a certain population at the estimated exposure level. Moreover, the distribution of the overall assessment factor can be probabilistically combined with the distribution of the Benchmark dose, as also the effect parameter is uncertain and is best described by a lognormal distribution.

Table 1 Summary of default assessment factors used in human health risk assessment.

Assessment factors	WHO/ IPCS (1987, 1990, 1994, 1999)	US-EPA (1993)	ECETOC (2003)	BAUA (D) (TRGS, 1998)	Danish EPA 2001	Kalberlah & Schneider (1998); Kalberlah et al. (1999)	Schneider et al. (2005)		TNO/RIVM (NL) (Vermeire et al., 1999, 2001)	
							Probabilistic ^m	determi- nistic	Probabilistic ^m	
Interspecies	10	10	AS ^a		10	AS ^{e,f}	AS ^e x (GM 0.97; GSD 3.24) [4.35 (P ₉₀); 6.67 (P ₉₅); 14.9 (P ₉₉)]	10	AS ⁱ x (GM 1; GSD 4.5) [7 (P ₉₀); 12 (P ₉₅); 33 (P ₉₉)]	
Non-occupational - toxicokinetics - toxicodynamics	4.0 2.5									
Occupational				AS ^e		AS ⁱ x 3				
Intraspecies	10	10			10		for P ₉₀ of individuals: ⁿ GM 1+2.31; GSD 3.57 [12.8 (P ₉₀); 19.8 (P ₉₅); 45.7 (P ₉₉)] for P ₉₅ of individuals: ⁿ GM 1+3.82; GSD 4.34 [26.1 (P ₉₀); 43.8 (P ₉₅); 117 (P ₉₉)] for P ₉₉ of individuals: ⁿ GM 1+8.96; GSD 6.45 [98.7 (P ₉₀); 193 (P ₉₅); 687 (P ₉₉)]	10	GM 1+3; GSD 1.6 [6.6 (P ₉₀); 7.6 (P ₉₅); 10 (P ₉₉)] GM 1+1.4; GSD 1.2 [2.7 (P ₉₀); 2.85 (P ₉₅); 3 (P ₉₉)]	
Non-occupational - toxicokinetics - toxicodynamics	3.16 3.16		5 ^b		25 8 3					
Occupational			3	5 ^g	5 ^g					

Table

1

continued

overleaf

Table 1 continued Summary of default assessment factors used in human health risk assessment

Assessment factors	WHO/ IPCS (1987, 1990, 1994, 1999)	US-EPA (1993)	ECETOC (2003)	BAUA (D) (TRGS, 1998)	Danish EPA 2001	Kalberlah & Schneider (1998); Kalberlah et al. (1999)	Schneider et al. (2005)	TNO/RIVM (NL) (Vermeire et al., 1999, 2001)	
							Probabilistic ^m	determi- nistic	Probabilistic ^m
Duration of exposure <i>System. eff./Local inhal. eff.</i> - semi-chronic to chronic - subacute to semi- chronic - subacute to chronic <i>Local dermal effects</i>		10	2/NN ^c 6/NN ^c NN ^c	2/4 2/4 6/12	1-100 ^p	2-3 (GM) 2-3 (GM) 6-7 (GM)	GM 4.39; GSD 1.82 [9.45 (P ₉₀); 11.8 (P ₉₅); 17.6 (P ₉₉)] GM 3.95; GSD 2.14 [10.5 (P ₉₀); 13.8 (P ₉₅); 23.2 (P ₉₉)] GM 4.14; GSD 2.03 [10.3 (P ₉₀); 13.3 (P ₉₅); 21.6 (P ₉₉)]	10 10 50-100 NN ^j	GM 2; GSD 3.5 [10 (P ₉₀); 16 (P ₉₅); 37 (P ₉₉)] GM 2; GSD 4 [12 (P ₉₀); 20 (P ₉₅); 50 (P ₉₉)] GM 5; GSD 3.5 [25 (P ₉₀); 39 (P ₉₅); 92 (P ₉₉)]
Route-to-route [#] Oral to inhalation Oral to dermal			ND	1 ^h 1 ^h				ND ^k	ND ^k
Type of critical effect	1-10							1	
Dose-response curve Appropriate NOAEL LOAEL to NAEL Alternative	3-10 BMD	10 BMD	NN 3 ^d BMD	3 BMD		10 BMD	BMD distribution	1-10 BMD	BMD (or BMD distribution)
Confidence in database/ database adequacy	1-10							1	
Modifying factor		>0-10							
Overall factor	mult.	mult.	mult.	mult. ^o	mult.	mult.	prob. ^q	mult.	prob. + mult. (for point estimates) ^l

Abbreviations:

AS = allometric scaling ($bw^{0.75}$); BMD = benchmark dose; GM = geometric mean; GSD = geometric standard deviation; mult. = multiplication of the different assessment factors; ND = no default proposed; NN = no (additional) assessment factor needed; P = percentile; prob. = probabilistic combination of distributions for the different assessment factors

Notes:

- # Only for systemic effects (under certain conditions), not for local effects.
- a mouse 7, rat 4, monkey 2, dog 2
- AS not to be applied for inhalation route and for local effects; Although AS does not completely account for interspecies differences, no additional assessment factor for 'residual' interspecies variability because that is largely accounted for in the assessment factor for intraspecies variability.
- b No additional assessment factor for children needed, but attention should be given to effects on developing organ systems, such as reproductive development in pre-puberty.
- c For local effects below the threshold of cytotoxicity.
- d May need to be adjusted depending on dose spacing, shape and slope of dose-response curve and extent and severity of effect seen at LOAEL.
- e mouse 7, rat 4, dog 2, monkey (marmoset) 4, monkey (rhesus) 2 (rounded figures)
- AS only to be applied for systemic effects, with doses in mg/kg bw (not for doses in mg/m^3 or mg/kg feed); not for local effects.
- f Additionally to the AS a factor for possible additional toxicokinetic or toxicodynamic variability is applied, depending on percentile of population one wants to protect: 1 (50th perc.) or 2-3 (95th perc.).
- g After allometric scaling this factor of 5 should be applied as combined assessment factor for intra- and interspecies extrapolation.
- h Similar absorption by all routes is assumed (not necessarily 100%).
- i mouse (25 g) 7, rat (250 g) 4, guinea pig (750 g) 3, rabbit (2 kg) 2.4, monkey (5 kg) 2, dog (15 kg) 1.4
- AS only to be applied for systemic effects following oral and dermal route of administration (with doses in mg/kg bw), not for inhalation route and for local effects.
- j For local skin effects it is assumed that exposure duration can influence the severity of the effects but will not influence the height of the NOAEL.
- k Depends on substance-specific data on absorption for starting route and end route. In case no substance-specific data are available for both routes, a default factor of 2 is used, i.e. as a worst case assumption the absorption percentage for the starting route is half that of the end route.
- l Based on the individual distributions that have been established for some assessment factors, Vermeire et al. (2001) have proposed default distributions of the overall assessment factors for the general population (including consumers) and for workers. If additionally point estimates are involved (e.g. for allometric scaling) these overall distributions have been multiplied accordingly. Vermeire et al. (2001) also give guidance on how to apply the probabilistic default distributions in human health risk assessment and on how to quantitatively interpret the results. For e.g. inter x intra x semi-chronic/chronic extrapolation (based on semi-chronic rat study) this works out as follows:

	Default distribution of combined AFs (inter x intra x semi-chronic/chronic)				AS (rat)	Default distribution of overall AF			
	GM	GSD	P90	P95		GM	P90	P95	P (of default)
General population	8	7.5	101	206	4	32	404	824	99 (10x10x10)
Workers	4.8	7.1	60	121	4	19	240	484	93 (3x4x3x10)

In this table the confidence limits (GM and P-values) are indicative of the percentile of the population that one wants to protect (e.g. GM: 50%, P95: 95%).

- m Lognormal distributions with parameters geometric mean (GM); geometric standard deviation (GSD) and shift, if not zero.
- n The three distributions cover the difference between the median sensitive and the sensitive individual at the workplace. Sensitive individuals are defined as being equal or more sensitive than 90%, 95%, or 99% of the working population (P₉₀, P₉₅, P₉₉-percentile of the interindividual distribution for a specific substance), respectively, for distributions 1, 2, and 3. Distributions (lognormal with shift 1) describe variation over substances and case studies evaluated in regard to inter-individual sensitivity
- o By estimating the different parameters as typical values with central tendency, the product of these parameters reveals a central tendency estimate of the combined assessment factors. For evaluation of existing chemicals this approach is modified as follows: an additional factor is used to account for the uncertainty of the assessment and the confidence in the database. By multiplication with this factor the initial estimate is modified in terms of precaution. The resulting value represents the overall assessment factor.
- p An overall assessment factor concerning “quality and relevance” of the data covering uncertainties in relation to e.g. LOAEL to NOAEL extrapolation; duration of exposure; route-to-route extrapolation; severity of effects; lack of data etc.
- q The individual distributions that have been established, including the BMD distribution, are combined by probabilistic modelling. As result a target distribution is obtained which represents a substance-specific probabilistic estimate of the health-based reference value and its uncertainty for a certain quantile of the human population (e.g. P95 of individuals). If another quantile is of interest, a new calculation using the according distribution for intraspecies differences (e.g. P99 of individuals) is performed.