TNsG on Annex I Inclusion

Revision of Chapter 4.1: Quantitative Human Health Risk Characterisation

These Technical Notes for Guidance were adopted during the 34th meeting of representatives of Members States Competent Authorities for the implementation of Directive 98/8/EC concerning the placing of biocidal products on the market (16-17 September 2009)

TNsG on Annex I Inclusion

Revision of Chapter 4.1: Quantitative Human Health Risk Characterisation

based on the outcome of the

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and

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and

the Biocides Technical Meetings: TM III07, TMV07, TMI08 and TMIII08

and

comments made in the public consultation in 2009

4.1 Introduction

The TNsG on Annex I Inclusion are issued at Community level identifying criteria for unacceptable effects and conditions for inclusion of active substances in Annex I, IA or IB of Directive 98/8/EC and provide recommendations for human health risk characterisation to assist both Applicants and authorities.

Where a critical effect is **threshold-based** and exposure data are reliable, quantitative risk assessment should be carried out for each exposed population, product-type, and method of application relevant for the respective biocidal products as indicated by the exposure assessment. The risk characterisation method should follow the general principles of both the MOE concept applied for industrial chemicals and the AOEL approach in the risk assessment of Plant Protection Products (PPP). The derivation of acute, medium-term and long-term Acceptable Exposure Levels (AELs) as general health-based reference values are proposed. The term AEL resembles the AOEL (Acceptable Operator Exposure Level). The omission of the term operator underlines that the AEL is the reference value for the human population as a whole.

For **non-threshold effects** the basic evaluation principles are described under *4.3 Evaluation of each human health endpoint* of the TNsG on Annex I inclusion.

Non-threshold carcinogens are strong candidates for comparative assessment to verify whether there are safer alternative substances to replace them. Consideration should be given to whether there are socio-economic and/or public health reasons to support the use of the substance, although final conclusions on these can normally not be made at this stage. Risk characterisation for non-threshold carcinogens should be conducted following a qualitative approach for cancer effects. When enough data are available, a semi-quantitative assessment can be performed to provide more information for risk management. The relevance of the mode of action for humans should also be considered **[1]**. The REACH guidance **[2]** provides the DMEL concept (Derived Minimal Effect Level) with two methodologies for semi-quantitative risk assessment for carcinogenic substances with a non-threshold mode of action: the 'linearised' approach referring to the lifetime cancer risk and the 'Large Assessment Factor' approach as originally proposed by EFSA **[3]**. Guidance for the evaluation of carcinogenic substances with a genotoxic mode of action is also available from U.S EPA **[4]**.

A **tiered approach** for human health risk characterisation of biocides has to be followed. In general, in the **first tier** systemic AELs and MOEs should be derived for acute, medium-term, and long-term exposure via all routes applicable, based on the systemic toxicity of the active substance using appropriate Assessment Factors (AFs). In the absence of chemical-specific data, a default 100-fold assessment factor is applied. Local effects at the port of entry should be dealt with separately. If an unacceptable level of risk is identified for any of the scenarios in the first tier a refinement of the exposure assessment and/or the assessment factors might be performed in the **second tier** giving special attention to route-specific contributions and protection measures. If the active substance can enter the food chain, an Acceptable Daily Intake (ADI) and, if necessary, an Acute Reference Dose (ARfD) should be derived analogously to the procedures for Plant Protection Products (PPPs).

For Annex I inclusion, the combined exposures to the active substance from all representative uses should be considered. Guidance on risk characterisation for combined exposures (aggregate and cumulative) is described in **Chapter 4.4.**

4.1.1 Hazard Identification

Detailed guidance on how to evaluate the available data for all relevant toxicological end-points and for toxicokinetics is provided in the *Technical Guidance Document on Risk Assessment for New and Existing Substances and Biocides* **[5]**. Further useful information for identification of relevant NOAELs for AEL derivation for different exposure duration is provided in REACH guidance **[2],** in guidance documents by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for deriving ARfD **[6] [7]** and ADI **[8],** and by the European Commission for AOEL values for PPPs **[9]**.

4.1.2 Relevant NOAELs for AEL[1] and MOE Derivation

The quantitative extrapolation of hazard from the animal experiment to exposed humans is based on the most relevant endpoints. In most cases, these endpoints should correspond to relevant NOAELs, but LOAELs or benchmark dose levels are also used. Generally, a whole set of relevant NOAELs is established with respect to different exposure time-frames and exposure routes. Relevant NOAELs for AEL and MOE derivation should be identified for all relevant exposure scenarios characterised by duration, frequency as well as route of exposure, and by the exposure profile for the target (sub-) population exposed. It should not be concluded from the absence of a particular exposure scenario for a given product that a relevant NOAEL is not needed, because different exposure scenarios might become relevant with subsequent product authorisations on Member State level. As specified in Article 14 of the Directive 98/8/EC the holder of an authorisation for a biocidal product shall notify the Competent Authority of information concerning an active substance or a biocidal product containing it, which may affect continuing authorisation. If new or additional data on the active substance (a.s) are submitted for the national product authorisation, a re-evaluation of toxicological data already submitted for Annex I Inclusion might be necessary at Member State level.

- **Identification of Critical Effects**

In the first step of hazard assessment, the whole data package should be evaluated for assessment of the most relevant critical effects considering the biological plausibility of the dose-effect relationship, its consistency over the whole data package, its severity and reversibility as well as the mode of action if known and its relevance for humans. For the latter IPCS/WHO has developed a framework for analysing the relevance of a non-cancer **[10]** or cancer mode of action for humans **[1]**. Likewise, appropriate studies should then be identified from which the relevant NOAELs for each of the relevant exposure time frames can be used to establish AEL and MOE values.

Furthermore, the data package should be evaluated with respect to local effects at the port of entry, e.g. lesions in the airways in inhalation studies or on the skin in dermal studies for which the derivation of a local threshold needs to be considered. Also indications for route-specific sensitivity and dose-response relationship shall be taken into account when considering the relevant NOAELs, if the data package allows and external values can be derived.

- **General Approach**

[1] Alternatively: Starting point for AEL derivation

The study in the most sensitive and relevant species resulting in the most relevant lowest LOAELs will be selected for establishing the relevant NOAELs for AEL and MOE derivation. Often, several studies addressing a certain endpoint are available for one species. Different dose spacing in these studies results in different NOAELs and LOAELs. If study design and endpoints addressed are comparable, it might be appropriate to consider these studies together. When the studies are are comparable, regarding study design (endpoints investigated, duration of exposure, route of exposure) and species/strain of animal, the 'overall NOAEL' should be the highest value identified in the available studies that provides a reasonable margin (≥ 2) over the lowest LOAEL, provided that due consideration is given to the shape of the dose–response curve **[11]**.

As a general rule, if several relevant NOAELs are available the one that would result in the lowest Acceptable Exposure Level (AEL) for a given time-frame should be chosen.

- **Relevant Time-Frames**

A comparison of relevant NOAELs for AEL derivation for different time-frames provides useful information on the influence of exposure duration on the severity and spectrum of toxicity. Therefore, an assessment of the entire data package is of high scientific value, as it helps in elucidating time-dependency of toxicity. This information is helpful to adjust human health risk assessment to varying time-frames for professional as well as consumer exposure.

The ILSI Health and Environmental Sciences Institute Task Force for Systemic Toxicity Assessment has also proposed the use of different time-frames for human exposure for which risk assessment might be required for PPPs (Table 1) **[12]**.

The proposed time-frames are considered useful for the quantitative risk assessment of biocidal active substances for inclusion in Annex I of Directive 98/8/EC especially with respect to non-professional users and the general public. For professional users, evaluation often focuses on acute and long-term exposure. If intermittent exposure needs to be evaluated, relevant NOAELs for AEL and MOE derivation obtained from studies with daily administration of the test compound might in some cases be considered a conservative approach erring on the safe side. In this context, all available information on the time-dependency of toxicity should be taken into consideration.

Preferably, **acute** relevant NOAELs for AEL and MOE derivation should be derived based on acute studies with single exposure, which are designed to establish a dose-response relationship including NOAELs. The appropriateness of using doses and end-points from sub-acute, sub-chronic and chronic studies to establish acute relevant NOAELs needs to be carefully considered. Particular weight should be given to observations and investigations at the beginning of repeated-dose studies. However, in the absence of such initial information, all toxic effects seen in repeated-dose studies should be evaluated for their relevance in establishing acute relevant NOAEL for AEL and MOE derivation.

Table 1: Relationship between duration of human exposure and the studies required for hazard identification and establishment of relevant NOAELs for AEL/MOE derivation

Estimated duration of human exposure	Basic toxicity studies	Relevant NOAELs for AEL/MOE derivation
≤ 24 h	Single dose studies designed to determine NOAEL* or repeated dose studies demonstrating relevant acute effects, e.g. - acute neurotoxicity - 28-d/90-d repeated-dose studies, acute effects - developmental toxicity, acute effects	Toxic effects relevant for acute exposure
>24 h – 3 months (max. 6 months)	Repeated-dose studies designed to determine NOAEL, e.g. - 28-d/90-d repeated-dose studies - 90-d neurotoxicity - 12-m dog, depending on nature of effects - developmental toxicity - 2-generation study	Toxic effects relevant for medium-term exposure
> 6 months (min. 3 months)	Chronic studies or repeated dose studies designed to determine NOAEL and demonstrating relevant chronic effects, e.g. - 18-m/24 m chronic/carcinogenicity - 2-generation study, chronic effects - developmental toxicity - 12-m dog , depending on nature of effects	Toxic effects relevant for long-term exposure

* Data from LD_{50} studies can be considered supportive if appropriate acute effects were investigated

In principle, the following four situations could arise:

(1) A relevant acute NOAEL for AEL/MOE derivation is not allocated, since no acute toxic effects have been identified

(2) A relevant acute NOAEL for AEL/MOE derivation is based on an appropriately designed single-dose study

(3) A relevant acute NOAEL for AEL/MOE derivation is based on a repeated-dose study (including developmental/embryotoxicity studies), since the critical effect is also considered relevant for a single exposure

(4) A conservative relevant acute NOAEL for AEL/MOE derivation is based on a repeated-dose study if the critical effect was not adequately evaluated in a single dose study.

Most often, the **medium-term** relevant NOAEL for AEL and MOE derivation will be based on a repeated dose toxicity study (28-day or 90-day) or studies investigating specific end-points, e.g. reproductive toxicity, developmental toxicity or sub-acute neurotoxicity. If there are indications that effects only become evident in chronic toxicity studies but might be initiated by sub-acute or sub-chronic exposures, the NOAEL for these effects in the long-term studies should be considered in selecting medium-term relevant NOAELs for AEL/MOE derivation. For the medium-term time frame the estimated duration of human exposure can be from >24 h to 3 (max. 6) months. The decision on whether the estimated duration of human exposure for this time frame should be 3, 4, 5 or 6 months, will be a case by case decision. The toxicokinetic properties of the active substance, such as slow elimination, potentially leading to prolonged internal exposure even after cessation of external contact with the

biocidal product or the reversibility of the repeated-dose and chronic effects have to be considered.

In most cases, the relevant **long-term** NOAEL for AEL and MOE derivation will be based on a long-term toxicity study, generally a lifetime study in rats or mice, or studies investigating specific end-points such as reproductive toxicity or hormonal effects. Depending on the nature of effects the NOAEL from studies of shorter duration (e.g.: one-year dog study or developmental toxicity study) can be used for the derivation of the long-term AEL if the NOAEL is lower than the one based on a chronic toxicity study. In principle the one-year dog study is more relevant for the derivation of the medium-term AEL.

4.1.3 Selection of Assessment Factors

Risk characterisation requires the choice of Assessment Factors (AFs), which account for extrapolation from animal toxicity data to the exposed human population.

At present, with the exception of genotoxic carcinogens and non-threshold mutagens, hazard assessment for different toxicological end-points is based on the assumption of a threshold.

The setting of the overall AF is a critical step, which considers inter-species variation and intra-species variation.

In the absence of sufficient chemical-specific data a default 100-fold AF is applied to the relevant NOAEL for AEL derivation in the first tier of risk characterisation (see Figure 1A). The basis for this approach is a 10-fold factor for inter-species variation and a 10-fold factor for intra-species variation. Variability is governed by toxicokinetic as well as toxicodynamics factors.[2]

Chemical-specific AFs as proposed by the WHO International Programme on Chemical Safety (WHO/IPCS) **[13]** can be introduced to replace a default AF if specific information is available on:

(1) Inter-species differences in toxicokinetics

(2) Inter-species differences in toxicodynamics

(3) Human variability in toxicokinetics

(4) Human variability in toxicodynamics

The use of scientifically valid human data reduces the level of uncertainty in comparison to extrapolation from animal models and is seen as a valuable contribution to science-based decision making. Biomonitoring studies, epidemiological data and medical poisoning records can be some of the sources of human data. Human volunteer studies should not be performed for the purposes of the BPD. However, human monitoring data can be requested for products already authorised for use under the BPD. As a prerequisite for the consideration of the use of human volunteer studies that have been performed for the purpose of regulatory frameworks other than the BPD, studies in humans should include clear statements that they were performed in accordance with internationally accepted ethical standards **[14]**, e.g. the Declaration of Helsinki **[15]**. In some cases, the use of human data in regulatory safety assessment might lead to more stringent exposure limits for some biocides than those that

[2] The default value of 100 was included in the TNsG on Annex I inclusion (April 2002) and thus applied in previous evaluations of biocidal active substances. It is also included in the AOEL guidance document in the context of risk assessment of plant protection products under Directive 91/414 as well as in FAO/WHO (JEFCA, JMPR) and U.S EPA evaluations.

would have been derived on the basis of animal data only. If human data are used for AEL derivation, the 10fold inter-species AF is omitted and the 10-fold AF for intra-species variation is regarded adequate.

In addition to uncertainties in inter-species differences and intra-species variability, additional AFs for the following elements should be considered:

1. the nature and severity of the effect
2. the human (sub-)population exposed
3. deviations between the exposure in the study providing the NOAEL and the estimated human exposure as regards frequency or pattern
4. duration extrapolation [2]: AFs for duration extrapolation should be handled on a case by case basis, to use the best available data in risk characterisation. It is specifically noted that the possibility for duration extrapolation does not change the data requirements for the dossier, and duration extrapolation can not be used in justifying study waiving.
    - subchronic to chronic: AF of 2
    - subacute to subchronic: AF of 3
    - subacute to chronic: such an extrapolation should normally not be necessary. In exceptional cases, e.g. if the chronic data is considered to be of insufficient quality for risk characterisation, but it can nevertheless be concluded that chronic exposure does not result in more severe effects, an AF of 6 can be used.
5. Dose-response relationship
    - extrapolation from LOAEL to NOAEL
    - the slope of the dose-response curve
6. the overall quality of the toxicity data package

If the severity of the critical effect at the LOAEL was judged to be of particular significance an additional AF might be considered necessary. So far, this AF has been from 3 to 10. Quantification should be determined on a case-by-case basis taking into account the dose-response data.

If the derivation of the AEL was based on a LOAEL and not a NOAEL, an additional AF has to be considered. This factor will vary depending on the slope of the dose-response curve and the magnitude of the effect at the LOAEL. This extrapolation step should be based on expert judgement. The benchmark dose (BMD) concept can also be used when data allows and it is deemed appropriate. Guidance for using the BMD approach can be found in **[2]** (chapters R.8.2, R.8.4). The use of LOAELs to set AELs should be a last resort; however, where the effects at the LOAEL are of moderate magnitude and not severe, the use of a LOAEL and an appropriate assessment factor reduces the need for additional animal studies.

For local effect at the port of entry (skin, eye, G.I. tract) it is sometimes justified to assume that either toxicokinetics or –dynamics (or both) do not contribute significantly to interspecies differences (as for example in the case of direct/pH-driven chemical action on tissue/cell membranes). In such cases, based on sound scientific reasoning, the 10-fold default factor might be reduced dependent on the mode of action. With regard to local effects on the respiratory tract, guidance is available e.g. from the EU project ACUTEX **[16]**, which

proposes to apply reduced interspecies AFs when extrapolating data obtained in rats to humans. Given that there could be significant quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms between humans and animals and when there is no data to inform on this uncertainty, it is prudent to assume that humans would be more sensitive than animals to effects on the respiratory tract. In such a situation the default factor of 2.5 to address remaining uncertainties should be applied.

For other risk evaluation programmes in the EU (DNEL methodology in the context of REACH) slightly different default approaches concerning inter- and intra-species variability are applied. As a main difference, both the MOS approach for new and existing substances and the DNEL methodology in the context of REACH extrapolate inter-species differences according to the allometric scaling principle (species differences in caloric demand) in combination with an additional default factor of 2.5 to account for remaining uncertainties. For the rat, given the usual average body mass, the overall inter-species default factor is 10 and thus similar to the approach outlined above ($4 \times 2.5 = 10$). For the dog, the default value is lower ($1.4 \times 2.5 = 3.5$); for the mouse higher ($7 \times 2.5 = 17.5$). Allometric scaling can be used for biocides, generally as a refinement step in the risk characterisation. REACH guidance should be used **[2]** (Chapter R.8.4.3.1). Allometric scaling can be used when the toxic effect is essentially determined by the area under the (plasma) concentration curve over time, as opposed, for example, to the peak plasma concentration or another pharmacokinetic variable. Allometric scaling should not be applied (or should be adjusted) if there are indications of significant inter-species differences in the bioavailability of the substance, if its clearance is known not to scale approximately with the body weight to the power of 0.75, if the kinetics cannot be assumed as dose-proportional over the dose-range considered, or if the animal species can be considered especially susceptible or unsusceptible to the effects in question. Whenever substance specific data is available, it should be used instead of the default values and approaches.

In addition, when available, data from the use of PBPK modelling shall be used for the purpose of refining the assessment factors. PBPK models will not remove all of the uncertainty from the risk assessment process. The rationale for using PBPK models in risk assessment is that they provide a documentable, scientifically defensible means of bridging the gap between animal bioassays and human risk estimates. Guidance on the use of PBPK modelling is currently under preparation within the WHO/IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, and should be followed when available **[17].**

The rationale for the choice of the AFs should be explained in detail in the dossier or report.

4.1.4 Acceptable Exposure Levels (AELs[3])

Depending on use patterns of biocidal products, humans will be exposed either as professional or non-professional users or due to secondary exposure, e.g. after application of biocidal products for domestic use. Risk assessment has to consider specific effects on sensitive sub-populations where appropriate such as infants, children, the elderly or women of childbearing age.

[3] The term AEL resembles the AOEL (Acceptable Operator Exposure Level) used for the purposes of the PPPD. The omission of the term operator underlines that the AEL is an overall reference value for the human population as a whole.

Systemic AELs are established as general health-based reference values for the human population as a whole including sensitive sub-populations taking into account use patterns and exposure scenarios. In principle, these AELs should be derived independently of the route of exposure. Such AELs represent the internal (absorbed) dose available for systemic distribution from any route of exposure and are expressed as internal levels (mg/kg b.w/day).

AELs for biocidal active substances can be determined as a threshold estimation of a daily or interrupted exposure of the general human population or a specific sub-population likely to be without an appreciable risk of adverse effects during a specified period of time. AELs should be established for all relevant time-frames of exposure (acute, medium-term, and long-term) based on the full toxicological data package available.

The derivation of AELs should follow the same common scientific principles as the derivation of the AOEL proposed by the European Commission Health and Consumer Protection Directorate-General (DG SANCO) **[9]**, which are applied also in other regulatory frameworks, e.g. for PPPs.

4.1.5 Systemic Acceptable Exposure Levels

The majority of studies submitted for inclusion of active substances into Annex I of Directive 98/8/EC are oral studies. However, risk assessment mainly focuses on the dermal and the inhalation exposure routes.

To avoid additional experimental testing of other relevant routes of human exposure, systemic AELs will usually be set on the basis of oral studies, i.e. the external NOAEL is converted to an internal NOAEL with help of the oral absorption provided that the critical endpoints of the substance (including reproductive/developmental toxicity, neurotoxicity and non-genotoxic carcinogenicity) are covered and an adequate assessment factor for irreversible effects is given.

By use of dermal and inhalative route-specific absorption rates the external NOAELs might also be converted to systemic reference values. On that background, any additional information from route-specific studies is of high value for risk characterisation because it reduces the uncertainties associated with route-to-route extrapolation.

In case local effects at the port of entry are to be expected, or there are indications of route-specific differences in toxicity, which are not reflected by absorption data, then additional considerations on appropriate reference values for risk characterisation are necessary (see chapter 4.1.6 below).

For the purpose of human health risk assessment for Annex I inclusion, the AEL should generally be derived for acute, medium-term, and long-term exposure and should be included in the list of end-points (Doc I, Appendix 1 of the CA-Report). Thus, a harmonised base will be provided for later applications for Annex I Inclusion, e.g. of the same active substance in a different biocidal product type, or for the authorisation of biocidal products at Member State level.

Even in cases where the complete toxicological data package does not indicate any acute hazard, setting an acute AEL would be required for the risk characterisation of acute scenarios for certain product types. In this case, the acute AEL may be the same as the medium-term AEL value. On the other hand, if setting a long-term AEL is not supported by the data package, e.g. due to waiving of long term studies based on exposure considerations, this

should also be clearly indicated in the report and in any restrictions related to the Annex I inclusion.

Data waiving arguments are quite common in biocide dossiers. Therefore, it is clearly stated in the TNsG on Data Requirements that the exposure pattern for a particular biocide may lead to the conclusion that a certain type of data are not needed and can be waived. Thus, there might be a lack of data for a certain type of study, route of exposure, or exposure duration. In these cases, caution should be taken, e.g. establishing a long-term reference value based on a NOAEL from a short-term study or a medium-term study (see chapter 4.1.3. above).

4.1.6 External Reference Values for Route-Specific Effects

During handling and/or use of active substances and biocidal products there is the probability of exposure of the skin or by inhalation. Active substances or biocidal products may produce local effects on the skin or the respiratory tract independently of systemic toxicity (e.g. irritation or corrosion). For this type of effects the derivation of a (systemic) AEL might be inappropriate as the actual (external) exposure towards the active substance and not the systemic dose is the determinant of the response. Instead, an external reference value (AEC), derived as local concentration in mg/m^3 air or mg/cm^2 skin should be derived for the quantitative evaluation of actual exposure data in those cases where it would be lower than the systemic AEL converted to an external concentration (considering the route-specific absorption). If this is not deducible a qualitative risk assessment has to be performed.

A route-specific reference value is also needed if data are available showing that toxicity at a specific route (e.g. inhalation) is critically different from what is expected by absorption data in combination with oral studies. Most probably the best choice in this case would be to derive an external reference value for the route in question. For inhalation at the workplace this would typically reflect an Occupational Exposure Limit (OEL) **[18]**.

Regarding sensitisation via skin or inhalative exposure, further research is required to develop and evaluate methods for quantitative risk assessment (skin) or even qualitative risk assessment (respiratory sensitisation). For skin sensitisation semi-quantitative risk assessment can be performed when there is sufficient data available (LLNA test) as outlined in Chapter 4.3 of the TNsG for Annex I inclusion. In the case of substances where effects like skin or respiratory sensitisation are observed and no reference values can be determined (no threshold), the risk characterisation should be driven by these effects for the relevant routes of exposure to ensure adequate protection. Additional guidance on skin and respiratory sensitisation will be available in the context of REACH [2] as well as by IPCS/WHO **[19]**.

4.1.7 The MOE approach

The Margin Of Exposure (MOE) represents a direct comparison of exposure and toxicity. The MOE approach is not intended to provide a health-based limit-value but serves primarily as an instrument for risk characterisation. The MOE is calculated as:

$$\mathbf{MOE} = \frac{\mathbf{NOAEL\ (mg/kg\ b.w/day)}}{\mathbf{Exposure\ (mg/kg\ b.w/day)}} \quad \mathbf{or} = \frac{\mathbf{NOAEC\ (mg/m^3)}}{\mathbf{Exposure\ (mg/m^3)}}$$

The MOE approach is identical to that used in the U.S.A. and the Margin Of Safety (MOS) approach used in the EU TGD or the Toxicity Exposure Ratio (TER) approach used in some other countries.

The MOE should be calculated using the most relevant toxicity endpoint derived from the most relevant study, considering explicitly the exposure scenario under evaluation. From this it follows that acute exposure is compared to NOAELs (or LOAELs) for relevant effects in (sub) acute studies whereas chronic exposure is compared to N(L)OAELs from long term studies. If relevant good quality epidemiology data are available these data prevail over animal studies in certain cases (see section 4.1.3 regarding suitable human data). The selection of endpoints and studies involves expert judgement on a case-by-case basis. According to the TGD for new and existing substances the risk characterisation, based on the MOE approach, is performed for each toxicological endpoint separately. In addition, if more than one study is available with an exposure duration relevant to the exposure scenario under evaluation, it is possible to calculate more than one MOE based on the NOAELs from the different studies to provide more insight in the range of the possible risk.

Based on a calculated MOE, the risk assessor needs to conclude whether the involved exposure to the substance is of concern or not. If the MOE is higher than the overall assessment factor, then the risk under the circumstances specified for the risk characterisation is acceptable. If the MOE is lower than the overall assessment factor the possibility of refining the pattern of use to reduce exposure can be considered by the Applicant. Subsequent revision of the risk characterisation will then indicate whether the risk has become acceptable. This process should be exceptional since the Applicant should have resolved these situations while conducting the risk assessment with their dossier.

4.1.8 Non-threshold carcinogenic substances

As required by the Carcinogens Directive (2004/37/EC), workplace exposure to carcinogenic substances must be avoided or minimised as far as technically feasible. As a general rule, a risk for the general public from secondary exposure to a non-threshold carcinogenic biocidal substance is also unacceptable.

A qualitative risk assessment is always performed, and this should lead to identification of strict risk mitigation measures to be used. If the data on the substance is considered of sufficient quality, a semi-quantitative risk assessment can be performed. This will provide quantitative information on the residual exposure (that will occur regardless of the risk mitigation measures) to be used in risk management.

The semi-quantitative risk assessment for a non-threshold carcinogenic biocidal substance should be performed according to the methodologies described in *Guidance on information requirements and chemical safety assessment (Guidance for the implementation of REACH)* [2] (detailed description in chapter R.8; a concise overview in Part B). Two methodologies can be used, the ‘linearised’ approach referring to the lifetime cancer risk and the ‘Large Assessment Factor’ approach as originally proposed by EFSA [3]. The relevance of the mode of action for humans should always be considered [1].

- **The ‘linearised’ approach** is based on the assumption of a linear dose response for the carcinogenic effect, with the possibility of assuming a supra- or sublinear dose response when appropriate. A relevant dose-descriptor is selected and, if necessary, modified to

adjust for the differences in human and animal exposure routes, conditions etc. The DMEL is derived for a specified cancer risk level, and for each relevant exposure pattern, by a linear high to low dose extrapolation and using further assessment factors if necessary. Extrapolation factors for specified cancer risk levels are given in the REACH guidance. The risk level of very low concern has to be decided on a policy level: based on experience in applying cancer risk values within and outside the EU, levels of 10^{-5} and 10^{-6} have been considered as indicative tolerable lifetime cancer risk levels when deriving reference values for workers and the general population, respectively [2]. Using the 'Linearised' approach, different DMEL values can be calculated, representing different risk levels, e.g., an increase of lifetime cancer risk in 1 per 100.000 exposed individuals (10^{-5}) or 1 per 1.000.000 exposed individuals (10^{-6}).

- **The 'Large Assessment Factor' approach** is formally similar to the assessment of threshold effects in the REACH guidance. As in the 'linearised approach', the dose-descriptor is selected and modified to adjust for the differences in human and animal exposure routes, conditions etc. Starting from this modified dose descriptor, a set of assessment factors (AF) is applied to derive a DMEL for each relevant exposure pattern. The AFs include the ones used for threshold effect assessments, and additional AFs for the nature of the carcinogenic process and to account for the reference point not being a NOAEL. The intraspecies AF is always 10 instead of 5 that is used for workers in REACH. The resulting overall assessment factor is generally much higher than overall assessment factors for threshold effects.

Both approaches result in derivation of a DMEL which in most cases is similar regardless of the choice of methodology used to derive it. The risk-related reference values thereby obtained can be used in judging the significance of any exposure that would remain after introducing the strict risk management measures. It can thus provide information to be used in further targeting the risk management measures. Exposure levels below the DMEL are considered to represent a risk level where the likelihood of effects (cancer) is appropriately low and the risk may be considered to be of very low concern.

Narrative description of the overall quality of the data has to be provided. Special attention should be given to judging whether the exposure assessment is reliable and representative of the actual exposure situations.

The REACH guidance cited above should be applied only to the assessment of the non-threshold carcinogenic effect. It should be done on a case-by-case basis, considering all biocide-specific guidance as well. Conclusions on the cancer risk should be indicated in a clear, explicit and transparent manner, and special consideration has to be given to risk mitigation measures. Expert judgment will play a considerable role in the assessment.

4.1.9 External Reference Values for Exposure via Food

For certain product types and use patterns, especially if the active substance can enter the food chain, an Acceptable Daily Intake (ADI) and if necessary, an Acute Reference Dose (ARfD) should be derived. Intake estimations might be needed to calculate the Theoretical Maximum Daily Intake (TMDI) and to recommend the need for setting specific Maximum Residue Levels (MRLs) for the active substance and metabolites.

If residues in food and feeding stuffs are expected to arise from the use of biocidal products, toxicological reference values should be set according to the principles of ADI and ARfD derivation for PPPs. The ADI is usually based on NOAELs from long-term or sub-chronic

studies divided by an appropriate AF whereas the ARfD is appropriate for assessing risk posed by short-term exposure to acutely toxic residues. ADI and ARfD are usually based on the same NOAEL as the $AEL_{chronic}$ and AEL_{acute} respectively. They are external reference doses and expressed as mg/kg b.w.

For risk assessment of biocidal active substances, ADI and ARfD values for the inclusion of active substances in Annex I of Directive 91/414/EC (PPPs) or Regulation (EEC) No 2377/90 (VMP) should be taken into consideration when necessary.

So far, quantitative risk characterisation for biocides does not take into consideration additional residues in food and feeding stuffs, e.g. from the use of PPP and VMP. To conduct an overall risk assessment, it would be necessary to cover the total amount of residues from all sources.

Internationally harmonised ARfD and ADI values for pesticides and food additives are recommended by the WHO/FAO JMPR or the WHO/FAO Joint Expert Committee on Food Additives and Contaminants (JECFA). Similarly, toxicological reference values are proposed in the EU for the inclusion of active substances in Annex I of Directive 91/414/EC. For biocides assessment, these toxicological reference values should be applied where relevant.

4.1.10 Towards a Tiered Approach for Risk Characterisation of Active Substances

In the dossier and CA-report, the complete toxicological data package and the derivation of NOAEL values should preferably be addressed in a way that a refinement of reference values would only rarely be necessary.

Risk characterisation under the BPD is a challenging task, amongst others because of the amount of data to be evaluated and the variety of exposure situations to be considered and the increasing degree of differentiation if evaluation has to be refined. As an effective way forward it is proposed to perform the risk characterisation as a step-wise procedure, which facilitates an efficient organisation of the workload. If needed, a detailed and demanding analysis of data, in particular those describing actual exposure, will be performed. Concerning the toxicological data package, a comprehensive analysis is requested in any case and should be initiated from the very beginning of dossier evaluation.

The risk characterisation will consist of two tiers. These tiers follow the same principle as the ones used for exposure assessment and described in the TNsG for Human Exposure **[20]**. During risk characterisation both the MOE and the AEL approach need to be followed.

- **Tier 1 (Figure 1A):**

This first tier is based on the NOAELs relevant for AEL and MOE derivation and three different systemic AELs as described in Chapter 4.1.2 shall be derived as agreed reference values for the Annex I inclusion of an active substance. Furthermore, if indicated by the data on the active substance, the derivation of route-specific external reference values shall be considered at this stage as described in chapter 4.1.6. An explanation should be included as to how far the external values correspond to the systemic AELs.

The AEL is compared with the total internal body burden, based on potential exposure without PPE, whereas the MOE is compared with the overall assessment factor used. If the estimated exposure is lower than the reference value, there is no cause for concern and no further refinement for the Annex I inclusion is necessary.

In general a reasonable worst-case estimate of exposure is given not taking into account risk reduction measures such as PPE. However, it might be possible that certain assumptions on exposure reduction e.g. as result of technical specifications, are already included in the assessment at this stage.

In the case of biocidal products that have irritating or sensitising properties the use of PPE would be required and therefore tier 1 should be omitted and the risk characterisation should be performed with the use of tier 2 where the use of PPE is assumed. In addition if actual human exposure data are used in the risk assessment then only a tier 2 risk assessment needs to be performed.

- **Tier 2 (Figure 1B):**

If there is a borderline situation or already clear concern, refinement of the risk characterisation should be performed.

In this second tier a refined exposure estimate is established by introducing risk management tools. This would concentrate primarily for professional users on the input from risk mitigation measures actually used and not yet included in the first tier. Also additional options for exposure reduction, if e.g. addressed by the Applicant, could be taken into account. A refined exposure assessment is obtained then which presumably gives lower values. This estimate is again compared to the relevant toxicological reference values to conclude on concern. The modified scenario will lead to a new risk characterisation for Annex I inclusion.

Exposure data based on surveys or studies with the actual product or with a surrogate may allow further refinement of the exposure assessment as described in the tier 3 of exposure assessment in the TNsG for Human Exposure to Biocidal Products (version 2) **[20]**. When such data is available it should be considered as a further way of refinement if needed at tier 2 of the risk characterisation.

In addition, considerations on the sensitivity of the subpopulation in question will be integrated in this decision. Thus, adjustment of AFs might be applicable, if only specific sub-population will be exposed based, on restrictions combined with the Annex I inclusion. If refinement of assessment factors is required the allometric scaling principle or data available from the use of PBPK modelling can be used.[4]

There is a need to harmonise the outcome of the hazard assessments for industrial chemicals, plant protection products and biocides. It is proposed that in borderline cases the results from other regulatory frameworks are taken into consideration to give support for the decision. This is subject to the second tier of risk characterisation (see Figure 1B).

- **Risk Reduction Measures**

If also in this second tier, concern cannot generally be excluded, one possible result of the evaluation could be to request certain risk mitigation measures as essential for Annex I inclusion. It might also be concluded that certain data would be necessary for product authorisation, e.g. a dermal absorption study with a real product. Finally certain exposure scenarios could be excluded from Annex I inclusion.

The decision to what extent data from the active substance are applicable for the evaluation of risks from use of products, should be made under careful consideration of: (1) route–to–route extrapolation; (2) high dose–low dose extrapolation, as the absorbed percentage generally decreases with increasing concentration; (3) additional substances in the product, e.g. dermal

[4] The Technical Meeting has agreed that the intraspecies factors of 10 for professional users cannot be lowered to 5 and no adjustment is possible.

absorption might change if a biocidal product contains solvents acting as skin penetration enhancers; and (4) differences in physical state between active substance and product, e.g. using granular vs. dissolved a.s. in the biocidal product.

Additionally, in depth characterisation of specific situations might be necessary, e.g. concerning a specific inhalation exposure scenario, including considerations, which do not usually belong to the standard repertoire and include a proposal for exposure mitigation.

A flexible risk characterisation methodology is needed to respond to modifications in input parameters, especially if new exposure scenarios are submitted after the Annex I inclusion in the national authorisation process or to facilitate the evaluation of route-specific protection measures for occupational risk assessment.

For non-professionals, assumptions on the protective effect of risk mitigation measures, which require a minimum level of knowledge, skill and concerted action, e.g. the use of personal protection equipment, cannot be anticipated. Even the use of gloves cannot usually be expected. Risk mitigation measures for non-professionals have to be conceived in a mode, that the biocidal product is provided to the non-professional/consumer in a state, in which the exposure is reduced or excluded without the need of any concerted action by the user (e.g. effective technical measures like bait boxes for rodenticides and insecticides, safety locks on bait stations).

Thus, exposure reduction by risk mitigation measures for non-professional users is limited to specific cases and cannot generally be included in the risk characterisation procedure.

For professional users the situation is different. Professional users come into contact with active substances in the biocidal products as a consequence of their professional life. In most circumstances the professional user is subject to worker protection legislation (Directive 89/391/EC and Council directive 98/24/EC) and has residual risks controlled through control measures. As a general rule, the hierarchy of control principle should be employed (this is the so-called STOP-principle which stands for Substitution, Technical measures, Organisational measures, Personal protection and which ranks these exposure-mitigating measures in order of priority. Priority is given to technical and organisational measures over personal protective equipment). There are also specialised professional users, who will have expert knowledge and skills in handling hazardous biocidal products. It can well be assumed that for these users the variability in exposure for a certain task is comparably low thereby reducing the uncertainty in risk characterisation.

However, some workers will have limited knowledge and skills to handle hazardous biocidal products – particularly if the use of the biocidal product is not routinely required in their workplace. The exposure conditions of these users might be similar to those of non-professional users. In addition, it has to be taken into account that the extent of exposure reduction by a certain measure might critically depend on the exposure route and might be different for different parts of the body.

With respect to the time-frame, risk reduction measures for professionals, as a general rule, are oriented either to mitigate single exposure peaks or to reduce shift average values. Therefore, AELs for acute toxicity and chronic toxicity are mostly fully sufficient for the selection of suitable protection measures. In case a certain intermittent exposure scenario is to be evaluated the time-dependency of toxicity should be considered as additional information for the choice of an appropriate risk management strategy. The medium-term NOAEL relevant for AEL derivation will be helpful evaluating occupational risks, but further support by toxicity data from different time frames might be needed to allow sound extrapolations to the exposure situation in question.

In summary for non-professional users risk reduction by personal protection measures usually cannot be assumed. For professional users the extent of exposure reduction seems to depend on their knowledge, training and skills to handle hazardous substances. Whereas exposure for users with limited knowledge might be similar to those of non-professionals, it can be assumed that for specialised professional users worker protection is effective. It seems essential to consider the degree and reliability of exposure reduction by protection measures case by case before further demanding risk mitigation measures are proposed. The refinement of the exposure assessment therefore resembles an essential element of the second tier in risk characterisation (see figure 1B)

Figure 1(A and B) summarises the proposed tier approach for human health risk characterisation of biocides.

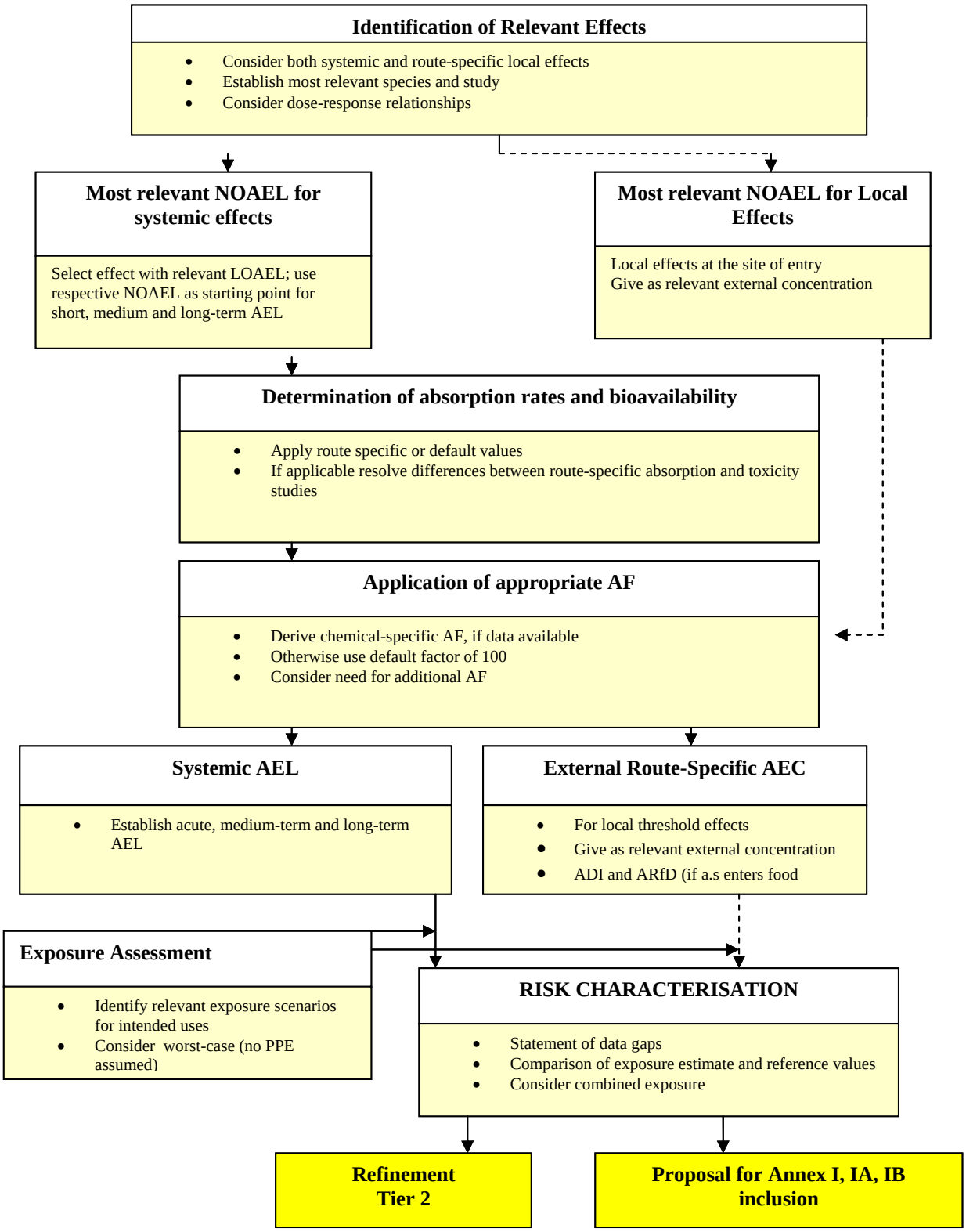

Figure 1A Tier Approach for Risk Characterisation: Tier 1 (basic step)

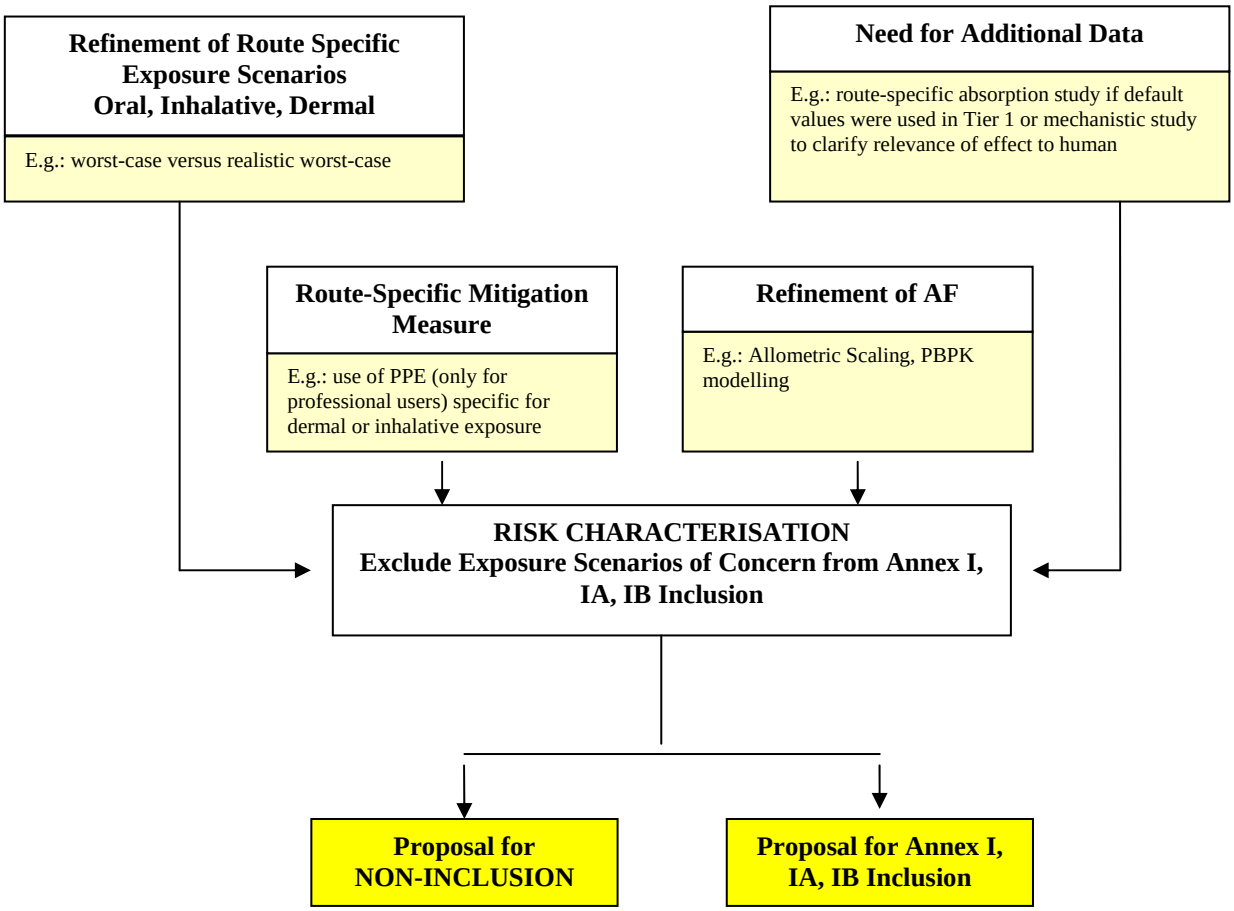

Figure 1B Tier Approach for Risk Characterisation: Tier 2 (Refinement)

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Abbreviations

a.s.	active substance
ADI	Acceptable Daily Intake
AF	Assessment factor
AEL	Acceptable Exposure Level
AEC	Acceptable Exposure Concentration
AOEL	Acceptable Operator Exposure Level
ARfD	Acute Reference Dose
BPD	Biocidal Product Directive (Directive 98/8/EC)
CA	Competent Authority
DNEL	Derived No Effect Level
DMEL	Derived Minimal Effect Level
ECB	European Chemicals Bureau
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization
ILSI	International Life Sciences Institute
IPCS	International Programme on Chemical Safety
JECFA	Joint Expert Committee on Food Additives and Contaminants
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
JRC	Joint Research Centre
LOAEL	Lowest Observed Adverse Effect Level
MOE	Margin of Exposure
MOS	Margin of Safety
MRL	Maximum Residue Level
NGO	Non-Governmental Organisation
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
PBPK	Physiologically Based Pharmacokinetic modelling
PPP	Plant Protection Product

PPPD	Plant Protection Product Directive
PT	Product Type
REACH	EU regulatory framework for the Registration, Evaluation and Authorisation of Chemicals
RMS	Rapporteur Member State
TMDI	Theoretical Maximum Daily Intake
TNsG	Technical Notes for Guidance
VMP	Veterinary Medicinal Product
WHO	World Health Organization

Definitions

AEL Acceptable Exposure Level. General health-based reference value for the human population as a whole, including sensitive sub-populations. The term AEL resembles the AOEL (Acceptable Operator Exposure Level). According to Directive 97/57/EC establishing Annex VI to Directive 91/414/EEC), the AOEL is defined as "... the maximum amount of active substance to which the operator may be exposed without any adverse health effects. The omission of the term Operator, however, underlines that the AEL is an overall reference value for the human population as a whole. As stated in the draft guidance document on the setting of AOELs **[9]**: "*The term "AOEL" under Directive 91/414/EEC implies particular reference to "operators" which are represented by mixers/loaders, applicators and re-entry workers. However, according to Directive 97/57/EC, the AOELs established shall also be used to evaluate the possible exposure of non-occupationally exposed groups (bystanders). Therefore, based on the current Community legislation, the AOELs set for operators and workers should be established in such a way that they are also applicable for bystanders.*" Regarding the use of biocides the terms operator (occupational) and bystander (non-occupational) can be misleading in the way that biocides are often used in non-occupational settings and therefore, the user is not bystander but operator. Thus, the omission of Operator for biocidal risk assessment refers to particularities in the use of biocides as compared to plant protection products

Assessment factor (AF) Assessment factors reflect the degree of uncertainty in extrapolation from experimental test data (e.g. obtained in a limited number of subjects from a limited number of species) to the situation in the human (sub-) population for which the risk characterisation is performed. Sources of uncertainty typically considered by using AFs include inter- and intraspecies variability in terms of toxicodynamics and/or toxicokinetics, differences in route, frequency, or duration of exposure between the experimental data and the scenario considered for risk characterisation, a particular severity of effect, or a poor data base. A non-exhaustive list of expressions which have been used in the past as synonyms or for specific types of AFs would include a.o. the following terms: uncertainty factor, extrapolation factor, modifying factor or safety factor.

DMEL Derived Minimal Effect Level. For non-threshold effects, the underlying assumption is that a no-effect-level cannot be established and a DMEL therefore expresses an exposure level corresponding to a low, possibly theoretical, risk, which should be seen as tolerable risk.

Non-professional user Non-professional users belong to the general population, which primarily is exposed to the biocidal products they are applying, mainly consumer products intended for domestic use. Non-professional users include also employed persons at work places, where the use of a biocidal product is not directly related to the main objective of the business (e.g. use of a domestic fly spray in an office environment, use of disinfectants in the rest room of a kindergarten or a restaurant by regular employees). To distinguish between professionals and non-professionals might be difficult. Therefore, a clear definition of use and user is required.

OEL Occupational Exposure Limit values are set by competent national authorities or other national institutions as limits for concentrations of hazardous compounds in workplace air. Only health effects are taken into account, not other safety issues such as flammable concentrations.

Overall assessment factor In order to obtain a health-based reference value for human risk characterisation (e.g. AEL or AEC), the overall assessment factor is applied to a dose descriptor (in general a NOAEL/LOAEL) observed in an experimental study for the most relevant critical effect. It is calculated by multiplication of all individual assessment factors. [See also definition of Assessment Factor (AF)]

Professional user The professional or industrial user comes into contact with the biocidal product as a consequence of their professional life. In general the professional user is subject to worker protection legislation (e.g. EU Chemical Agents Directive) and has residual risk controlled through control measures, which although a last line of defence, may include the use of Personal Protective Equipment (PPE). However, some workers will have limited knowledge and skills to handle hazardous biocidal products – particularly if the use of biocidal products is not routinely required in their workplace (e.g. incidental use of slimicides, insecticides, irregular disinfection and use of products containing preservatives). The exposure conditions of these users might be similar to those of non-professional users. There are also specialised professional users, who will probably have expert knowledge and skills in handling hazardous biocidal products and their pattern of use will show greater frequency and/or duration of use (e.g. pest control operators).

Reference values This term is used for dose levels which serve as reference for judgment whether a particular exposure scenario can be considered to be without appreciable risk to human health. In general, (toxicological) reference values are established by dividing the dose descriptor (NOAEL/LOAEL) for a critical effect observed in an experimental study by an appropriate overall assessment factor. External reference values are given as concentrations (e. g. in ambient air or of a solution applied to human skin) and refer to both a specific time-frame (short-, medium- or long-term) and route of exposure. In contrast, systemic/internal reference values are given as dose levels on a mg/kg bw basis. They reflect the share of externally applied dose which is systemically available and are thus independent of the rote of application, but are also derived for a specific time-frame. In order to convert systemic/internal reference values into route-specific external ones, the former have to be corrected by the corresponding rate of (dermal, inhalative or oral) absorption, or an estimate thereof.

STOP The STOP principle gives a hierarchy for the selection of risk mitigation measures at the workplace in the order of priority: substitution, technical measures, organisational measures, personal protection