Evaluation Manual for the Authorisation of Biocides

EU part

Biocides

Chapter 4 Human toxicology; risk evaluation human exposure

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Category: biocides

1. GENERAL INTRODUCTION

This chapter (EU exposure part) describes the methodology for estimation of the health risk resulting from primary and secondary exposure for the EU framework. In the EU an Evaluation Manual for Product Authorisation (available at Circa Biocides Public (via the ECB website)) has been developed by The Netherlands and agreed (version 1.0) by all members states in the CA meeting in December 2012.

2. EU FRAMEWORK

The procedure for inclusion of active substances in Annex I of Biocides Directive 98/8/EC [1] is described under EU framework where only the procedure laid down in the EU is described. The NL procedure for evaluation of a substance, described in the NL part, is reverted to where no EU procedure has been laid down.

2.1 Introduction

This chapter describes the manner in which the health risk resulting from primary and secondary exposure is estimated, for which exposure estimation, risk evaluation, and testing for permissibility are considered.
The data requirements and the derivation of toxicological endpoints and limit values that are used when testing for permissibility are discussed in Chapter 4 Human toxicity, EU part.

2.2 Data requirements

To qualify for inclusion in Annex I of 98/8/EC it must be evaluated whether the application of a biocide has no adverse consequences for health when persons get into contact, through primary or secondary exposure, with such a product.
The data requirements are described in Chapter 4 Human toxicity, EU part.

2.3 Risk assessment

Directive 98/8/EC requires a risk assessment of biocides before these can be authorised for the European market. Human risk assessment entails testing of the burdening considered acceptable from a health point of view against the estimated or measured exposure. The burdening considered acceptable from a health point of view is derived from the endpoints as described in Chapter 4 Human toxicity, EU part.

Risks to companion animals (pets) should be considered at the member state level, at the product authorisation stage. The predominant approach should be to use appropriate risk management measures, e.g. labelling instructions.

The underlying assumption is that the hazard assessment, which is performed for humans, will cover the companion animals as well, while the exposure patterns will differ. It would not be sensible to try to perform an exposure assessment and risk characterisation for all companion animal species, especially given that suitable methodology is lacking. Risks to companion animals will therefore be left for the member state authorities to consider at product authorisation (agreement TMIV 2009 see MOTA)

2.3.1 Exposure calculations

The TGD (Technical Guidance Document) on Risk Assessment [2], the TNsG (Technical Notes for Guidance) on Human Exposure 2002 and 2007 [3] as well as the User Guidance [4] elaborate the general principles for drawing up exposure estimates. The procedure for drawing up a human exposure estimate is schematically presented in the User Guidance [4] and the TNsG on human exposure 2007 [3].

Exposure estimation requires mapping of all potential exposure situations and routes in which and through which people can be exposed to biocides. Information on the envisaged use (Statutory Use Instructions / Directions for Use; WG/GA), identification of the exposed population, exposure routes together with personal protection and quantification of the potential chemical intake are required for this purpose.
The User Guidance [4] and the TNsG on human exposure 2007 [3] summarise the information needed about the use to arrive at an exposure estimate.

Initially, exposure is estimated with generic exposure models. More specific models or approaches are also suitable or monitoring data of product/active substance under (representative) conditions of use.
Besides generic exposure models, the TNsG on Human Exposure also describes more specific models or approaches (mathematical). For many uses of different product groups, however, suitable models are lacking or EU agreement about a suitable model has not yet been reached. Pending further research or EU agreement an exposure estimate is drawn up for these uses in the different Member States, based on expert judgement, and where appropriate on the basis of literature data or monitoring data. Suitable (theoretical) models per type of handling (such as different methods of mixing/loading and application) are described in the User Guidance for a number of exposure scenarios for rodenticides and wood preservatives

Humans can be exposed to biocides by use at the place of work or private, and indirectly via the environment. Exposure estimation for the identified possible exposure scenarios is based on information regarding the use, where accidents or misuse are not taken into account. Foreseeable misuse, reasonably expected use not quite in agreement with WG/GA, however, is taken into account

A distinction is made between primary exposure and secondary exposure:

- Primary exposure is the exposure of the professional and non-professional operator/worker (in case MSs do not agree with each other or have different policies (such as different user groups for rodenticides) the notification procedure could be used).
- Secondary exposure is exposure not covered by primary exposure and which relates to exposure of people who are present during a certain activity or are present at a place where a biocide has been applied or where materials are used which have been treated with biocides (including food that possibly contains residues of biocides). An important characteristic of secondary exposure is that such exposure occurs without the exposed person being aware of, or having control over the exposure.

As a general rule, averaging of exposures will not be attempted unless there is sufficient justification (agreement TMIII 2007 see MOTA).

Estimation primary exposure
Initially, exposure is estimated for the unprotected operator/worker in normal working clothes. In a later phase of the evaluation, where necessary, the effect of protective measures is taken into account.
Where, however, for non-professional users wearing personal protection equipment would be the only way to restrict exposure, the product will normally not be authorised (Annex VI Common Principles for evaluation of biocides dossiers, Decision making, Effects on humans 73, Biocides Directive 98/8/EC, see also this chapter § 2.4.2).

Where monitoring date under field conditions are lacking, exposure is first estimated by means of models. Suitable models for a number of exposure scenarios per type of

handling (such as different methods of mixing/loading and application), together with indicative exposure values, are described in the form of a table in the User Guidance (see User Guidance [4] and computer exposure models based on computerised database of exposure data in the TNsG on human exposure [3]).

For many applications of different product groups suitable models are still lacking or EU agreement about a suitable model has not yet been reached (see also §2.5 Developments. The Human Exposure Expert Group (HEEG) was established in TM V 2007. The group consists of experts nominated by MS CAs, and works mainly by e-consultation and e-mail discussions. It discusses issues that arise during discussions of CARs, as well as issues on methodology and needs for update of guidance documents. The expert group does not make decisions, but produces opinions and proposals which are brought to TM for endorsement. So the HEEG Opinions were not legally binding documents and they were indeed living documents which could be amended at any time, if necessary.

Members of the HEEG are appointed by the MS CAs, who can inform the Commission of a new member by sending an e-mail to ENV-BIOCIDES@ec.europa.eu. The list of current members and the coordinator is available in CIRCA: http://circa.europa.eu/ (Library/Human Health Related Issues/Human Exposure Expert Group/List of Members).

Pending further research or EU agreement, an exposure estimate is drawn up for these uses in the different Member States, based on expert judgement, and where appropriate on the basis of literature data or monitoring data.

For wood preservatives (product group 8), the exposure scenarios are together with the directions for use and the proposed default values included in the User Guidance (see Table 1 of the User Guidance [4]). Where the required information on the envisaged use (WG/GA) is available, the exposed population has been identified, the exposure routes together with –where appropriate- personal protection have been mapped, the exposure estimates for wood preservatives can by means of models be drawn up on the basis of the established default values and indicative values. The models are briefly described in the User Guidance and more extensively in the TNsG on Human Exposure.
The User Guidance contains several examples of exposure estimates for primary exposure to wood preservatives.

For rodenticides (product group 14) detailed directions for use (formulation, amount per application, duration, frequency) for professional as well as non-professional use, together with the scope of human exposure (application, post-application and disposal), are described in the User Guidance. Where the required information on the envisaged use (WG/GA) is available, the exposed population has been identified, the exposure routes together with –where appropriate- personal protection have been mapped, the exposure estimates can by means of theoretical models be drawn up on the basis of default values (no consensus) and indicative values. The models are briefly described in the User Guidance and more extensively in the TNsG on Human Exposure.
The User Guidance contains several examples of exposure estimates for primary exposure to rodenticides.

The specific models, approaches (mathematical) and agreements have been elaborated in the TNsG on human exposure [3]. For several situations additional HEEG opinions or opinions from other sources on primary exposure situations are available (see MOTA [5]).

*For the use of the TNsG on human exposure 2002 and/or 2007 the HEEG opinion endorsed in TM I 2008 is available. The HEEG Opinion on harmonising the use of new and old versions of the TNsG on human exposure and of BEAT agreed at TM IV 08 and at the 32nd CA meeting, February 2009 is available

*For models to be used in the exposure assessment for operators during the loading of products into vessels or systems in industrial scale the HEEG opinion endorsed in TM I 2008 is available.

*For the use of ConsExpo to assess professional exposure the HEEG opinion endorsed in TM IV 2008 is available.

*Specific guidance for the exposure assessment of metalworking fluids (PT13) is available in the HEEG opinion endorsed in TM III 2008.

*The source for the values to be used for anticoagulant rodenticides for the daily number of manipulations is the company survey document provided by CEFIC. As this HEEG opinion is based on data that are protected a Member State can only carry out the assessment using this data if a letter of access has been received from the applicant.

In the HEEG opinion agreed at TMIII2010 the harmonised number of manipulations in the assessment of rodenticides (anticoagulants) is described. In the HEEG opinion 12 the harmonised approach of rodenticides (anticoagulants) is described.

*For Antifouling the Antifouling painting model – Amendment of TNsG on Human exposure to biocidal products is available. This is a HEEG Opinion agreed at TM II 08

*Defaults and appropriate models to assess human exposure for dipping processes (PT 8) are described in the HEEG opinion (TM III 2009).

* For washing out of a brush which has been used to apply a paint there is a HEEG agreement made at TMIII2010.

*The application duration of 120 minutes is the most relevant exposure determinant and should be used as default for spraying applications in stables (TMIII2011) (agreed TMII 2012)

*Dislodgeable fraction used as a refinement for a child chewing/mouthing wood (TMII 2011) (agreed TMII 2012) (has to be included in the next version of the MOTA)

* The "HEEG Opinion on an approach to identification of worst-case human exposure scenario for PT6" was agreed at TMIII2012 (see next MOTA). The HEEG Opinion focused on how to assess the exposure, but management strategies about the use of PPE for consumers were not considered.

* The HEEG Opinion on the assessment of inhalation exposure of volatilised biocide active substance. HEEG Opinion agreed at TM IV 2011 (see MOTA).

Estimation secondary exposure
There is no limit to the number of possible secondary exposure scenarios.
The relevant forms of secondary exposure per application are therefore considered on a case-by-case basis.
The User Guidance contains various examples of exposure estimates for secondary exposure to wood preservatives.
The TNsG on Human Exposure still contains other examples of exposure estimates for secondary exposure.

The specific models, approaches (mathematical) and agreements have been elaborated in the TNsG on human exposure [3]. For several situations additional HEEG opinions or opinions from other sources on secondary exposure situations are available (see MOTA [5~~6~~]).

- For PT 2, 3 and 4 the HEEG opinion on the assessment of secondary exposure from a treated surface has been endorsed in TM I 2009.
- The exposure assessment take into account the possibility of children handling dead rodents is considered unrealistic where oral baits have been used. This was the conclusion of the anti-coagulant expert meeting of May 18th 2006 (TM II 2006 see MOTA).

Calculation systemically available dose
The risk evaluation is for primary as well as secondary exposure based on the systemically available dose (=internal dose=internal exposure). During uptake the substance passes lungs, gastro-intestinal tract and/or skin.
Systemic exposure occurs via respiration, dermal absorption and ingestion.
The risk evaluation carried out with an AEL (Acceptable Operator Exposure Level) approach is based on the systemically available doses, which must be calculated by using the dermal and/or respiratory absorption data. The metabolic processes determine the final biological availability of the substance in the body.

2.3.2 Tiered approach
Testing is based on the starting point that primary and secondary exposure are sufficiently safe for humans on the basis of a risk assessment.
The risk assessment will be carried out with the Margin Of Exposure (MOE) approach and/or the systemic and/or local AEL approach, and/or the Acceptable Daily Intake (ADI) approach, and/or the Acute Reference Dose (ARfD) approach, depending on the envisaged use and form of exposure (see Chapter human toxicity, EU part) and TNsG on Annex I Inclusion [6] for derivation of these limit values).

The MOE represents a direct comparison of exposure and toxicity. This is extensively described in the TNsG on Annex I inclusion and the adapted chapter 4.1 (see Chapter human toxicity, EU part).

The “overall assessment factor” depends on the safety factors used (see assessment fators in tox part). For the MOE approach, however, this is usually 100, based on a factor 10 for intraspecies and a factor 10 for interspecies.

The systemic AEL approach is based on an internal (absorbed) dose available for systemic distribution and is expressed as internal level (mg/kg bw/day). The local AEL approach is based on external values as concentration or percentage or mg/m^2. The ADI approach is based on an external dose expressed as external level (mg/kg bw/day).
The MOE approach is based on a direct comparison of exposure and toxicology. There will be no cause for concern (risk) if the estimated exposure is lower than the derived limit values.

Risk assessment based on AEL approach
A so-called tiered exposure estimation (TNsG Human Exposure) is applied in the risk assessment, where it is common to conduct the first exposure estimation by means of model calculations based on realistic “worst case” assumptions and the use of default values. If this risk assessment based on these “worst case” assumptions results in “no risk”, the risk assessment for the human population in question can be completed and a further refinement of the exposure estimate is not required. The exposure estimate must on the other hand be refined where the outcome leads to a risk of a biocide. This refinement will then be based on expert judgement while using additional data and/or reasonable arguments.
This tiered approach is a logical step process which will lead to a risk assessment with optimal use of the available information and to a reduction of unnecessary requirements as regards human exposure data or studies. The three tiers of the tiered exposure estimation in the risk assessment are described below.

Tier 1 Screening
The screening step in the exposure estimation must be kept simple. Starting point is a worst case exposure based on the highest value in an exposure study or an indicative value based on a generic model or a worst case value based on a mathematical model. Tier 1 estimates must be based on realistic worst-case time budget information (such as frequency and duration of use). Exposure-reducing measures, such as personal protection equipment do not need to be taken into account. Where available, data on dermal absorption, however, are used to determine systemic exposure.

A refined exposure estimate is required if this exposure estimate leads to an unacceptable risk.

Tier 2 Realistic exposure estimate

This step in the exposure estimation process is more complex and requires more specific data and/or reasonable arguments for drawing up a refined exposure estimate. The exposure studies/models are used in the same manner as in tier 1.
Specific data regarding frequency and duration of application, transmission factor and the effects of personal protection measures, however, are used to adjust the exposure estimate, where the limited use of personal protection equipment by consumers must be taken into account.
The possibilities of exposure-reducing measures and the corresponding default values are discussed in the TNsG on Human Exposure (Part 2.2.3) Surrogate exposure values with PPE are available in most models. Potential hand exposure can be calculated from actual measured exposure data (see agreement TM I 2008 in MOTA [5]). Default values for PPE can be used in other cases. At the TMI 2010 an HEEG opinion is agreed on default protection factors for protective clothing and gloves (see MOTA). It can be concluded that the default values are approximately the same as in the RGB (see also Chapter 4 human exposure, NL part).

A further refined exposure estimate is required if this exposure estimate leads to an unacceptable risk.

Tier 3 Exposure studies under representative field conditions
The most detailed level of risk estimation requires human exposure data or studies with the actual product or with a surrogate.
The exposure studies must be carried out under representative field conditions, where appropriate with biological monitoring. Where no biological monitoring is included in the exposure study, this study only leads to a refined exposure estimate if the setup of the exposure study yields more representative exposure values than a generic/mathematical model. Exposure studies must be carried out in compliance with the OECD guidelines (Organisation for Economic Co-operation and Development). Biological monitoring must be carried out in compliance with the Helsinki Declaration (Helsinki Convention1971)..

The adapted version of chapter 4.1 of the TNsG on Annex I Inclusion described the tiered approach for risk characterisation of active substances as follow (the text in gray frames form the TNsG follows the section.

4.1.9 Towards a Tiered Approach for Risk Characterisation of Active Substances

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.

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.

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. 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) . 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.[7]

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 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.

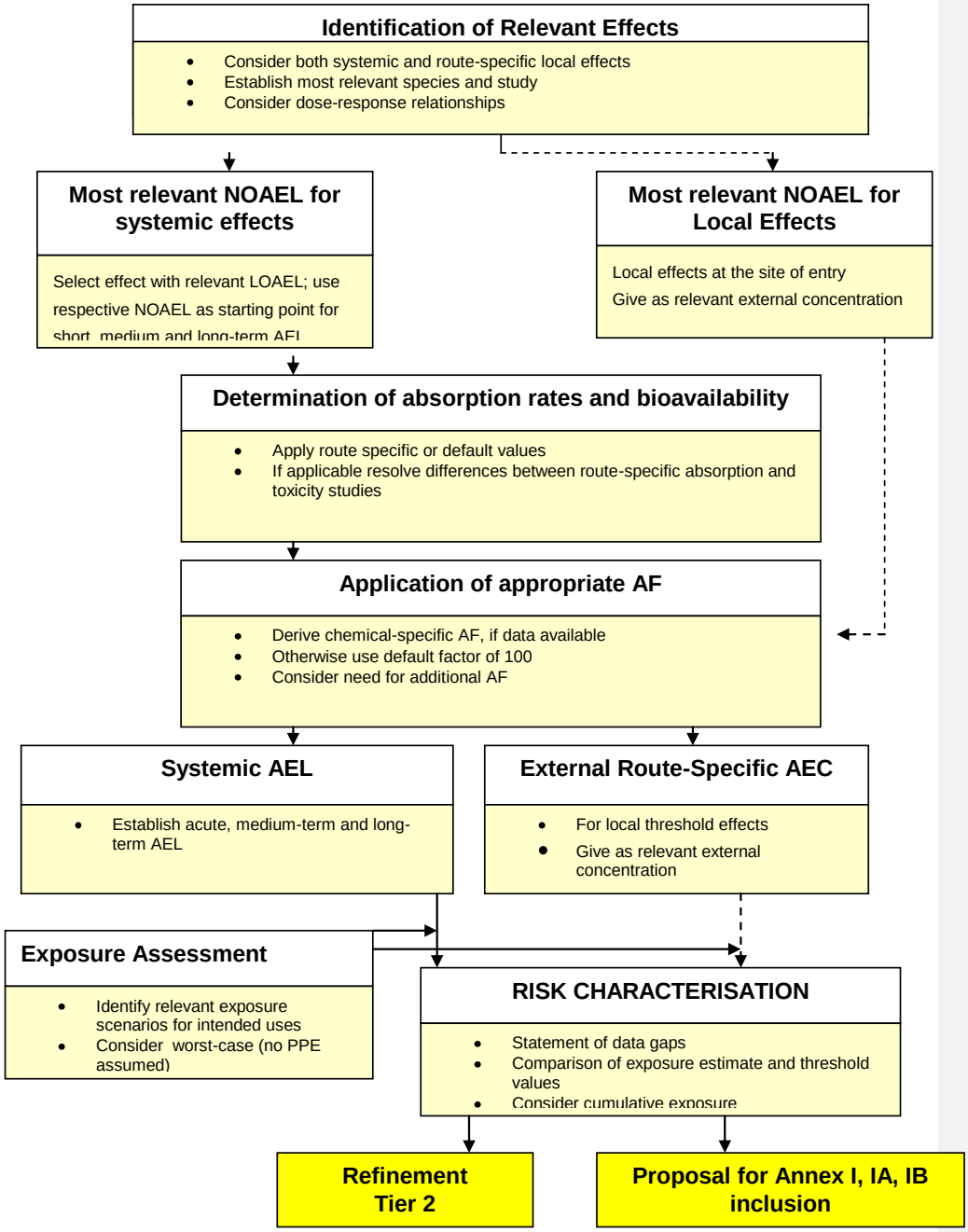
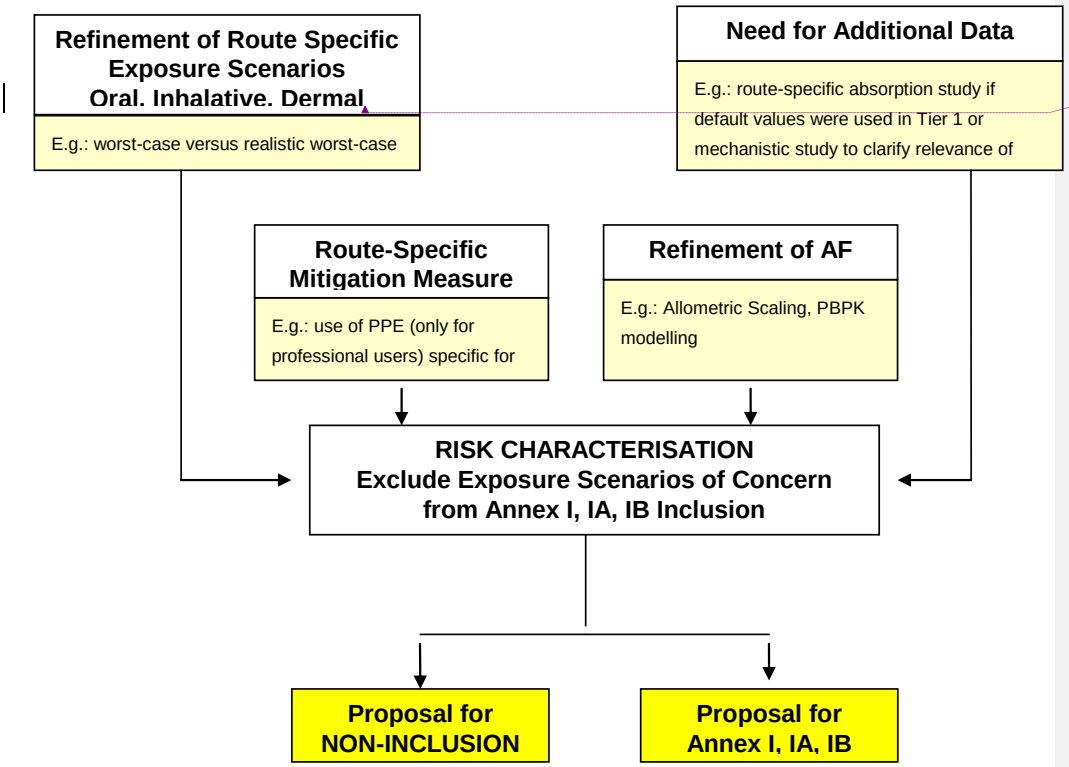


Figure 1A Tier Approach for Risk Characterisation: Tier 1 (basic step)



Met opmaak: Engels (Groot-Brittannië)

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

The tiered approach has been elaborated in the TNsG on human exposure adapted chapter 4.1 (see MOTA [5]). For several specific situations influencing the exposure assessment and/or the risk assessment agreements are available (see MOTA [5]).

- A guidance document was endorsed at the 22nd CA meeting about the consideration of exposure during manufacture in the risk assessment.
- For paints containing in-can preservatives the application of the paint by end users (TM II 2007 see MOTA) and mixing the in-can preservative into the products which is then to be used (for example, the addition of the in-can preservative to a formulation which is to be marketed as a laundry-washing detergent (TM II 2008 see MOTA), will be considered as primary exposure. Paints will not be authorised under the BPD, but the exposure through the use of the paint is relevant for the BPD. Paints are not covered by the BPD but the exposure should be assessed to find out if there is concern from the use of such products. Making dilutions of in-can preservatives can be considered equivalent to manufacture/formulation.
- A wood density of 0.4 g/cm^3 will be used as a worst case scenario. This is an average value for softwoods given in the website www/csudh.edu/oliver/chemdata/woods.htm (TM III 2008 see MOTA).
- The term “transient mouthing” is not recommended any more. Instead, the scenario should be called “Mouthing of poison bait - an exceptional scenario”. This scenario concerns the situation where an infant manages to access a bait block, despite the preventive measures taken, and then licks the block, or ingests a piece of the block. Exposure is thus acute and is expected to occur only exceptionally. In this scenario, licking of the hands can be disregarded as this would be a marginal addition to the mouthing exposure (TM III 2008 see MOTA).
- The HEEG opinion endorsed in TM I 2008 described whether potential hand exposure can be calculated from actual measured exposure data (see MOTA).
- Paper RISK MITIGATION MEASURES FOR ANTICOAGULANTS USED AS RODENTICIDES (ENV B.3/PC D(2007) - 21/03/2007) discussed at CA-March 07-Doc.6.3 final revised after 25th CA meeting.
- Application by spraying is allowed for non-professionals if exposure assessment and risk characterisation reveal no risk for the non-professionals. PPE required for safe use by non-professionals will not be allowed. (TM II 2007 see MOTA).

Risk assessment based on ADI/ARfD approach

The adapted version of chapter 4.1 of the TNsG on Annex I Inclusion described the tiered approach for risk characterisation of active substances as follow (the text in gray frames from the TNsG follows the section.

4.1.8 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 Limits (MRLs) for the active substance and metabolites.

The 1994 Joint Meeting on Pesticide Residues (JMPR, FAO/WHO, 1994) discussed situations in which ADIs derived from sub-chronic or long-term studies might not be appropriate for assessing risk posed by short-term exposure to acutely toxic residues.

Consequently, the ARfD was introduced.
If residues in food are expected to arise from the use of biocidal products, threshold 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. 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, the values for the inclusion of active substances in Annex I of Directive 91/414/EC (PPPs) or Regulation (EEC) No 2377/90 should be taken into consideration whenever possible. Where no ADI (for MRL setting), or MRL itself exists for the evaluation of an active substance as PPP or VMP, Competent Authorities should not attempt to determine them for the purposes of the BPD alone but make proposals on what data should be considered by the appropriate bodies. There is still ongoing discussion on how MRLs for residues from biocidal products will be set.

MRLs in food commodities should be set to ensure that consumer intakes will not exceed relevant ADIs and ARfDs. In general, MRLs are expressed in mg active substance/kg food. It is expected that MRLs already established for a substance under the EU regulations for VMP and PPP, are also applicable to residues from biocidal products. In such cases, the Annex I Inclusion in 98/8/EC would refer to the provisions already in force under the VMP and/or PPP legislation. When the use of a biocide might result in relevant residues in food or feed, an evaluation must be conducted to ascertain if the existing MRLs are still sufficient to account for the expected combined residue levels from all sources (VMP, PPP, biocidal products).

At present, in the determination of MRLs for PPPs the ALARA (As Low As Reasonably Achievable)-principle is followed. Based on the results of residue trials following Good Agricultural Practice, an achievable residue limit value is derived. So far, this limit value does not take into consideration additional residues in food or feeding stuffs due to the use of a biocidal product. From this point of view, it is necessary to conduct a combined risk assessment for different sources of residues.

Internationally harmonised ARfD, ADI, and MRL 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) for the risk management decisions of the Codex Committee of Pesticide Residues (CCPR). Similarly, threshold values are proposed by the Standing Committee on Plant Health (SCPH) for the inclusion of active substances in Annex I of Directive 91/414/EC. In conclusion, for MRL setting and risk assessment the same reference values need to be applied.

A dietary risk assessment expert working group (***DRAWG)*** *in* close co-operation with **EMEA** and **EFSA** has been formed. The initial objectives of this group are/were:

- To collect, develop and evaluate external animal exposure scenarios;
- To define data requirements for step 2 of refined external animal exposure scenarios;
- The framework paper for biocide DRA of food of animal origin will be re-drafted after the DRAWG has made some progress, in co-operation with EMEA.
- Other types of biocide DRA: The document relative to DRA for food of animal origin will be further progressed before deciding on other types of DRA. Meanwhile, reflection should continue on other types of dietary risk assessment and management:
    - For food of plant origin, the principles should be similar and the approach will have much in common; the relevant body for MRL setting is likely to be EFSA.

The issues will be treated either in a separate document or by extension of the document on food of animal origin.

- The direct exposure of food products of plant or animal origin to biocides, e.g. by contact with treated surfaces in food-processing facilities, will also have to be considered.

Directive 98/8/EC requires that a risk assessment be performed for products containing biocidal active substances including the quantification of residues in food and feed. Biocidal products are divided into 23 product types (PTs), some of which are used in areas or on objects where food or feed are produced, stored and/or processed. In this way or through direct treatment, biocidal active substances can be carried over into food or feed. In addition, through the use of biocides in animal husbandry, livestock can be exposed leading to residues in the food products obtained from livestock. Based on assessments performed in the course of EU-wide biocidal active substance evaluations, five basic groups of intended uses have been identified by way of which livestock animals can be exposed to biocidal active substances:

1. treatment of animal housing (mainly PT 3, 18, 19 and 21)
2. treatment of feedstuff and drinking water or of storage facilities (mainly PT 4, 5, 12 and 20)
3. treatment of materials that livestock animals may come in contact with (mainly PT 8)
4. direct treatment of livestock animals (mainly PT 3, 18 and 19)
5. treatment of aquaculture (mainly PT3 and PT21)

For each of these groups, possible methods for exposure estimation will be discussed in the final DRAWG (Dietary Risk Assessment Working Group) Draft Proposal Guidance on estimating livestock exposure to biocidal active substances (available on Circa).

The following PTs are likely to lead to an exposure of livestock animals:

PT3 veterinary hygiene biocidal products
PT4 food and feed area disinfectants
PT5 drinking water disinfectants
PT6 in-can preservatives (e.g. for inks and adhesives used in packaging of feedstuffs)
PT7 film preservatives (e.g. migration to feedstuffs from plastic packaging or plastic coated paper)
PT8 wood preservatives
PT9 fibre, leather, rubber and polymerised materials preservatives (migration to feedstuffs from paper, textile or polymerised packaging material)
T11 preservatives for liquid cooling and processing systems (migration to feedstuffs from preservatives used in process water or dosing systems for additives for paper/cardboard industry or process water in feed industry)
PT12 slimicides (used on wood/paper pulp for use as packaging of feedstuffs)
PT18 insecticides, acaricides etc.
PT19 repellents and attractants
PT20 preservatives for food and feedstock
PT21 antifouling products

For these PTs in particular, the possibility of livestock exposure must be considered and be addressed either by an exposure assessment or a waiver. Other PTs are unlikely to lead to livestock exposure, but this has to be considered on a case-by-case basis.

Concerning all dietary exposure assessment, the evaluation manual is mainly focused on livestock exposure assessment. Currently, the only available draft proposal guidance is indeed related to livestock exposure assessment to biocidal active substance. However, as mentioned in the first sentences other food or feed can also be contaminated after biocidal product treatment and this point could be more developed in the evaluation manual, even if guidance documents are still in preparation. The DRAWG has been mandated to work first on the livestock exposure assessment and is now working on estimating residues in foods exposed to biocidal active substances. When biocides are applied directly on animals or in their surrounding the animal health and welfare has to be considered. A risk assessment of animals may be needed (this can be relevant for PT 3 and PT 18). This is not always done in the CAR but left to the product authorisation level (see § 1.10 MOTA).

(see for further information with respect to the results of DRAWG the DRAWG Draft Proposal on Estimating Livestock Exposure to Biocidal Active Substances final 10075 (2010) available at Circa via the ECB website) and the DRAWG Draft Proposal Guidance on Estimating Transfer of Biocidal Active Substance into Foods discussed at TMIII2012

Regulation concerning the establishment of maximum residue levels for residues of active substances contained in biocidal products is described in a paper Doc.3.4a discussed at CA-Sept09 and available at Circa via the ECB website (http://ec.europa.eu/environment/biocides/annexi_and_ia.htm)..

2.3.3 Combination of two or more active substances in a product

Combination toxicity should be determined for a biocidal product containing at least two active substances or one active substance with at least one substance of concern, as well as for combinations of biocides. For biocides containing several active substances and/or substances of concern, the acute toxicity of the product can be estimated based on toxicological studies with the biocidal product or the calculation rules using the classification of all ingredients (= part of data requirements product) and the justified application of Directive 1999/45/EC and CLP-Regulation (EC) No 1272/2008 (see chapter 9 Classification, Labelling and Packaging). A risk assessment must, however, also be carried out for repeated exposure to a combination of two or more active substances and/or substances of concern.

A repeated dose study with the product or preparation with the different active substances is not part of the data requirements. In the Common Principles, Annex VI of the Biocidal Products Directive 98/8/EC and the TNsG on product evaluation however, attention is paid to this aspect. Combined exposure to active substances and/or substances of concern may possibly lead to a different toxicological profile than the profile derived for the individual active substances and/or substances of concern because they may influence each other's effect. Factors such as toxicological profile (critical effect, mode of action), metabolism of the active substances and/or substances of concern and whether the active substances and/or substances of concern cause enzyme induction shall be taken into account in the evaluation. The effect of two or more active substances and/or substances of concern may be independent, additive, synergistic or antagonistic. Both

synergistic as well as antagonistic effects could have an influence on the risk assessment in cases exposure takes place at or near the level at which undesirable effects of the individual active substances and/or substances of concern can be expected (in comparison with the AEL/ADI/ARfD). A proposal on combination toxicology (mixture toxicity), made available by France and commented by the other MSs will/ has been be discussed at the TM meetings in 2012-2013. Once accepted it will be incorporated in this manual.

2.4 Approval

According to the Directive of the European Parliament and the Council of 16 February 1998 concerning the placing on the market of biocides (98/8/EC) it should be investigated whether biocides when authorised, if correctly used for the envisaged purpose, in the light of the current scientific and technical knowledge, have no unacceptable effect on the health of humans (consideration 8). An unacceptable effect is in principle determined by the risk index. Where the risk index > 1 or the MOE is insufficiently high, an unacceptable effect may exist; exposure then exceeds the acceptable limit value based on the relevant toxicological properties of the substance.
A diagram of the risk assessment is given in Appendix 1; this originates from the TNsG on product evaluation [13].
Article 5. 1 (b) (iii) stipulates that Member States only authorise a biocide if this product

(iii) has no unacceptable effects itself or as a result of its residues, on human or animal health, directly or indirectly (e.g. through drinking, food or feed, indoor air or consequences in the place of work) or on surface water and groundwater,"

Article 5. 2 stipulates that
"A biocidal product classified according to Article 20(1) as toxic, very toxic or as a category 1 or 2 carcinogen, or as a category 1 or 2 mutagen or classified as toxic for reproduction category 1 or 2, shall not be authorised for marketing to, or use by the general public."

Article 10 (2 (ii) stipulates that inclusion of an active substance in Annex I, IA or IB is, where relevant, bound to the following conditions:
"ii) the establishment of the following:
(a) acceptable operator exposure level (AOEL), if necessary,
(b) where relevant, an acceptable daily intake for man (ADI) and a maximum residue limit (MRL);"

Instructions for the manner in which risk must be estimated are presented in several EU documents; these are the following documents:

- Technical Guidance document on Risk Assessment [2]
- TNsG on Annex I Inclusion 2002 and 2007 [6]
- TNsG Human Exposure to Biocidal Products; Guidance on exposure estimation [3]
- TGD on Data Requirements [7]
- TNsG on product evaluation [8]

2.4.1 Evaluation

Starting points for evaluation as regards the effects on humans are presented in the Common Principles (Annex VI to 98/8/EC). These are the relevant parts of the

introductory principles, the general principles, and the specific principles for effects on humans.
The specific principles for effects on humans are in the text below printed in a grey frame. This text, including numbering, is the literal text from Annex VI to Guideline 98/8/EC.

Effects on humans

20. The risk assessment shall take account of the following potential effects arising from the use of the biocidal product and the populations liable to exposure.
21. The effects previously mentioned result from the properties of the active substance and any substance of concern present. They are:
    — acute and chronic toxicity,
    — irritation,
    — corrosivity,
    — sensitisation,
    — repeated dose toxicity,
    — mutagenicity,
    — carcinogenicity,
    — reproduction toxicity,
    — neurotoxicity,
    — any other special properties of the active substance or substance of concern,
    — other effects due to physico-chemical properties.
22. The populations previously mentioned are:
    — professional users,
    — non-professional users,
    — humans exposed indirectly via the environment.
23. The hazard identification shall address the properties and potential adverse effects of the active substance and any substances of concern present in the biocidal product. If this results in the biocidal product being classified according to the requirements of Article 20 of this Directive then dose (concentration) — response (effect) assessment, exposure assessment and risk characterisation shall be required.
24. In those cases where the test appropriate to hazard identification in relation to a particular potential effect of an active substance or a substance of concern present in a biocidal product has been conducted but the results have not lead to classification of the biocidal product then risk characterisation in relation to that effect shall not be necessary unless there are other reasonable grounds for concern, e.g. adverse environmental effects or unacceptable residues.
25. The Member State shall apply paragraphs 26 to 29 when carrying out a dose (concentration) - response (effect) assessment on an active substance or a substance of concern present in a biocidal product.
26. For repeated dose toxicity and reproductive toxicity the dose response relationship shall be assessed for each active substance or substance of concern and, where possible, the no-observed-adverse-effect level (NOAEL) identified. If it is not possible to identify a NOAEL, the lowest-observed-adverse-effect level (LOAEL) shall be identified.
27. For acute toxicity, corrosivity and irritation, it is not usually possible to derive a NOAEL or LOAEL on the basis of tests conducted in accordance with the requirements of this Directive. For acute toxicity, the LD50 (median lethal dose) or LC50 (median lethal concentration) value or, where the fixed dose procedure has been used, the discriminating dose shall be derived. For the other effects it shall be sufficient to determine whether the active substance or substance of concern has an inherent capacity to cause such effects during use of the product.
28. For mutagenicity and carcinogenicity it shall be sufficient to determine whether the active substance or substance of concern has an inherent capacity to cause such

effects during use of the biocidal product. However, if it can be demonstrated that an active substance or a substance of concern identified as a carcinogen is non-genotoxic, it will be appropriate to identify a N(L)OAEL as described in paragraph 26.

29. With respect to skin sensitisation and respiratory sensitisation, in so far as there is no consensus on the possibility of identifying a dose/concentration below which adverse effects are unlikely to occur in a subject already sensitised to a given substance, it shall be sufficient to evaluate whether the active substance or substance of concern has an inherent capacity to cause such effects during use of the biocidal product.
30. Where toxicity data derived from observations of human exposure, e.g. information gained from manufacture, from poison centres or epidemiology surveys, are available special consideration shall be given to those data when carrying out the risk assessment.
31. An exposure assessment shall be carried out for each of the human populations (professional users, non-professional users and humans exposed indirectly via the environment) for which exposure to a biocidal product occurs or can reasonably be foreseen. The objective of the assessment shall be to make a quantitative or qualitative estimate of the dose/concentration of each active substance or substance of concern to which a population is, or may be exposed during use of the biocidal product.
32. The exposure assessment shall be based on the information in the technical dossier provided in conformity with Article 8 of this Directive and on any other available and relevant information. Particular account shall be taken, as appropriate, of:
— adequately measured exposure data,
— the form in which the product is marketed,
— the type of biocidal product,
— the application method and application rate,
— the physico-chemical properties of the product,
— the likely routes of exposure and potential for absorption,
— the frequency and duration of exposure,
— the type and size of specific exposed populations where such information is available.
33. Where adequately measured, representative exposure data are available, special consideration shall be given to them when conducting the exposure assessment. Where calculation methods are used for the estimation of exposure levels, adequate models shall be applied.
These models shall:
— make a best possible estimation of all relevant processes taking into account realistic parameters and assumptions,
— be subjected to an analysis taking into account possible elements of uncertainty,
— be reliably validated with measurements carried out under circumstances relevant for the use of the model,
— be relevant to the conditions in the area of use.
Relevant monitoring data from substances with analogous use and exposure patterns or analogous properties shall also be considered.
34. Where, for any of the effects set out in paragraph 21 a NOAEL or LOAEL had been identified, the risk characterisation shall entail comparison of the NOAEL or LOAEL with the evaluation of the dose/concentration to which the population will be exposed. Where a NOAEL or LOAEL cannot be established a qualitative comparison shall be made.

2.4.2 Decision making

Starting points for decision making as regards the effects on humans are presented in the

Common Principles (Annex VI to 98/8/EC). These are the relevant parts of the introductory principles, the general principles, and the specific principles for effects on humans.
The specific principles for effects on humans are in the text below printed in a grey frame. This text, including numbering, is the literal text from Annex VI to Guideline 98/8/EC.

Effects on humans

68. The Member State shall not authorise a biocidal product if the risk assessment confirms that, in foreseeable application including a realistic worst possible scenario, the product presents an unacceptable risk to humans.
69. The Member State shall consider possible effects on all human populations, namely professional users, non-professional users and humans exposed directly or indirectly through the environment when making a decision on the authorisation of a biocidal product.
70. The Member State shall examine the relationship between the exposure and the effect, and use this in the decision-making process. A number of factors need to be considered when examining this relationship and one of the most important is the nature of the adverse effect of the substance. These effects include acute toxicity, irritancy, corrosivity, sensitisation, repeated dose toxicity, mutagenicity, carcinogenicity, neurotoxicity, reproduction toxicity together with physico-chemical properties, and any other adverse properties of the active substance or substance of concern.
71. The Member State shall, where possible, compare the results obtained with those obtained from previous risk assessments for an identical or similar adverse effect and decide on an appropriate margin of safety (MOS) when making an authorisation decision. An appropriate MOS is typically 100 but an MOS higher or lower than this may be appropriate depending on, among other things, the nature of the critical toxicological effect.
72. The Member State shall, if appropriate, impose, as a condition of authorisation, the wearing of personal protective equipment such as respirators, breathing-masks, overalls, gloves and goggles in order to reduce exposure for professional operators. Such equipment must be readily available to them.
73. If for non-professional users the wearing of personal protective equipment would be the only possible method for reducing exposure, the product shall not normally be authorised.
74. If the relationship between the exposure and the effect cannot be reduced to an acceptable level then no authorisation can be given by the Member State for the biocidal product.
75. No biocidal product classified according to Article 20(1) of this Directive as toxic, very toxic or as a category 1 or 2 carcinogen, or as a category 1 or 2 mutagen, or classified as toxic for reproduction category 1 or 2, shall be authorised for use by the general public.

Chapter 5.2 of the TNsG on Annex I inclusion [6] also describes the starting points for decision making as regards the effects on humans.

The text below in the grey frame is from Chapter 5.2 of TNsG on Annex I inclusion. Numbering is the same as in Chapter 5.2 of TNsG on Annex I inclusion.

5.2 Criteria in relation to human health for the listing of an active substance on Annex I

Some criteria are laid down in the Directive text. These can be divided into two groups:

5.2.1 Criteria specified by the Directive

5.2.1.1 General Public Use

For use of biocidal products by the general public the Directive lays down the following criteria (Article 5(2)):

"A biocidal product classified according to Article 20(1) as toxic, very toxic or as a category 1 or 2 carcinogen, or as a category 1 or 2 mutagen or classified as toxic for reproduction category 1 or 2, shall not be authorised for marketing to, or use by the general public."

Products are classified and labelled according to Directive 1999/45/EC.

The above mentioned criteria have consequences for the authorisation of a biocidal product but also for the listing of an active substance on Annex I. If the products are only for use by the general public and the active substance is considered as meeting the criteria for any of the above classifications (Council Directive 67/548/EEC), then it cannot be listed on Annex I of the Biocidal Products Directive. If the active substance is for use by different user groups listing on the annex may be possible but the accompanying restrictions must specify that the active substance cannot be incorporated into products for use by the general public.

5.2.2 Criteria derived from the demands of the Directive

5.2.2.1 Non-general public use

For products for non-general public use, different criteria apply when considering whether an active substance should be listed on Annex I. The criteria are based on current scientific knowledge and usual regulatory policy. Decisions are taken in compliance with the requirements of Article 10(1) relating to active substances, and depend upon biocidal products containing the active substances being expected to comply with Article 5(1) b), c) and d). In this context, that specifically means that the active substance used in the product will have no unacceptable effects on human health either directly or indirectly.

An active substance may only be included in Annex I if, where relevant, an ADI, MRL and, if necessary, an AOEL can be established and they are not exceeded by the exposure estimates from at least one representative use. Assessment factors and margins of exposure are elaborated according to the TGD. If the margin of safety approach is used for risk characterisations then the active substance can be listed if the minimum or default value is not exceeded.

Furthermore, an active substance can also only be included in Annex I if,

(a) on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the provisions of Annex IIA point 6.6 and other available data and information, it is not or has not to be classified, in accordance with the provisions of Directive 67/548/EEC, as mutagen category 1 or 2, or if this classification is warranted, the formulation type and use conditions are such that exposure to humans is unlikely; and

(b) on the basis of assessment of carcinogenicity testing carried out in accordance with Annex IIA point 6.7 and other available data and information, it is not or has not to be classified, in accordance with the provisions of Directive 67/548/EEC, as a carcinogen category 1 or 2 unless the formulation type and use conditions are such that exposure to humans is unlikely; and

(c) on the basis of assessment of reproductive toxicity testing carried out in accordance with the provisions of Annex IIA point 6.8 and other available data and information, it is not or has not to be classified, in accordance with the provisions of Directive 67/548/EEC, as toxic for reproduction category 1 unless the formulation type and use conditions are such that exposure to humans is unlikely; and

(d) on the basis of assessment of reproductive toxicity testing carried out in accordance with the provisions of Annex IIA point 6.8 and other available data and information, it is not or has not to be classified, in accordance with the provisions of Directive 67/548/EEC, as toxic for reproduction category 2 unless the formulation type and use conditions are either such that

i) if there is a threshold for the effect there should be a safety factor of 1000 between the NOAEL and the predicted exposure to humans; or
ii) if there is no threshold for the effect, that exposure to humans is unlikely.

Comments on criteria

a) These criteria are set on the basis that active substances that meet the criteria for classification as mutagens categories 1 or 2 have no exposure threshold below which the effect does not occur. Therefore the only way to reduce the risk to an acceptable level is to control the exposure. While it is possible for an active substance to have a threshold for certain mutagenic effects, these cases would be exceptional. If the data demonstrate and support that a threshold can be set, then the criteria a) for inclusion would not be relevant. An additional assessment factor might be needed for the risk characterisation, but this would have to be decided upon on a case-by-case basis.

b) These criteria are also set on the basis that there is no threshold below which the effects do not occur and that the only way to reduce the risk is to control the exposure. Carcinogens that have threshold-based mechanisms are usually classified in category 3. However, if a category 1 or 2 carcinogen was demonstrated to have a threshold mechanism then the inclusion criteria b) would no longer be relevant. An additional assessment factor might be needed for the risk characterisation but this would have to be decided upon on a case-by-case basis.

c) These substances are known to impair fertility or to cause developmental toxicity in humans. While for these effects a threshold mechanism is likely the hazard is of high concern. Furthermore, it is usual regulatory practice to take special precautions when a substance can cause harm to an unborn child (the reasons include the fact that an exposed woman might not know she is pregnant). Consequently, an active substance classified in category 1 for toxicity to reproduction should not be included in biocidal products if exposure to humans is likely to occur.

d) According to the classification criteria, these substances are to be regarded as if they cause toxicity to reproduction in humans ("There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in …effects" (Council Directive 67/548/EEC, Annex VI, 4.2.3.1)).
However, when these effects have a mechanism with a proven threshold risk characterisation may indicate whether inclusion of the active substance in products for a given exposure scenario is tolerable. Decisions on inclusion of the active substance on to Annex I would depend on there being an assessment factor of 1000 between the NOAEL for the effect and the predicted human exposure for the use. This higher factor is justified by the serious nature of the effects.

Alternatively the active substance may exert an effect by a non-threshold mechanism or a threshold may not been determined. If this is the case then quantified risk characterisation is not possible and the active substance cannot be listed on Annex I if exposure is likely from the use scenario(s) specified.

5.2.2.2 All uses

For combined and cumulative exposures, exposure estimates will be compared with the same criteria for toxicological endpoints as for estimates from individual populations. Where the risk characterisation has identified additional concerns arising from the combined or cumulative exposures these should also be compared to the criteria.

Re. 5.2 It is not possible to allow the use for general public a substance classified as CMR as the BPD Article 5 (2) clearly indicates that CMR substances cannot be authorised for marketing to the general public or for use by the general public (taking into account the concentration limits).

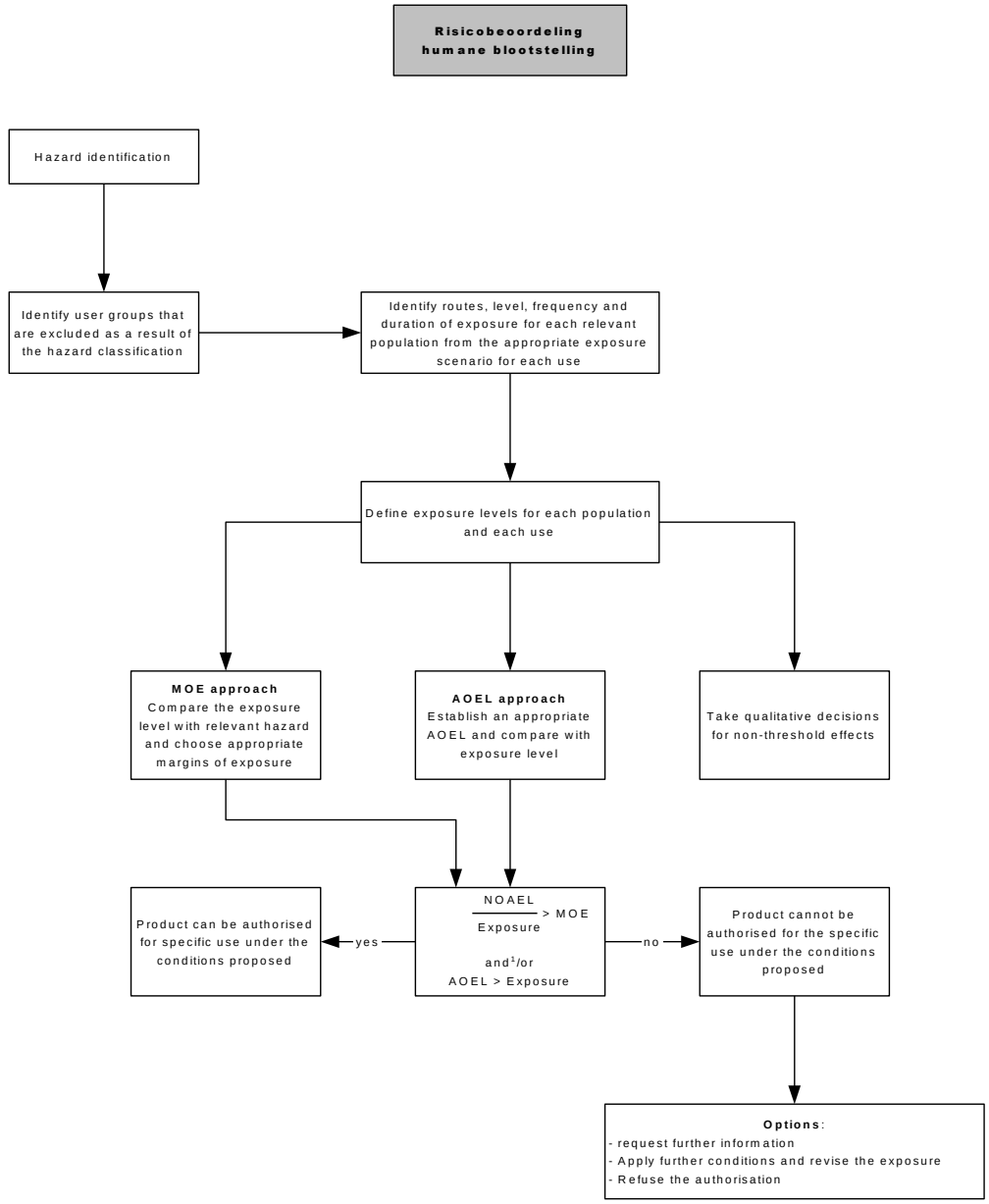
2.5 Developments

Biocides dossiers are currently being evaluated in EU framework. This process will result in amendments of the already existing TNsGs, and new documents will be prepared.
With the upcoming Biocidal Products Regulation coming into force on September 1st 2013 the TNsGs will be adapted.

3. APPENDICES

Appendix 1: Diagram risk assessment

The diagram below is from the TNsG on product evaluation.



[1] See under 4.4.1 Quantitative Human Health risk characterisation and 4.4.3 Decision Making. For both sections the relevant information is at the end of first paragraph.

4. REFERENCES

1 The biocide Directive: http://eur-lex.europa.eu/
LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0008:19980514:EN:PDF
2 Technical Guidance Document on Risk Assessment in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances, the Commission Regulation (EC) N0. 1488/94 on risk assessment for existing substances, published in 1996 and Directive 98/8/EC of the European Parliament and of the Council.
European Communities, 2003. This document can be downloaded via the ECB website: http://ecb.jrc.it/biocides/
3 Technical Notes for Guidance. Human Exposure to biocidal products. Guidance on exposure estimation. EC 2002 and 2007. This document can be downloaded via the ECB website: http://ecb.jrc.it/biocides/.
4 User guidance. Human exposure to biocidal products. version 1, June 2004.
This document can be downloaded via the ECB website: http://ecb.jrc.it/biocides/
5 Manual of technical Agreements (MOTA version 5) of the biocides Technical meeting publicly available at the biocides web-site of JRC-IHCP (growing document).
6 Technical Guidance Document in support of the directive 98/8/EC of the European Parliament and the council concerning the placing of biocidal products on the market. Principles and practical procedures for the inclusion of active substances in annexes I, IA and IB. (TNsG on Annex I inclusion) April 2002 final draft. This document can be downloaded via the ECB website: http://ecb.jrc.it/biocides/
7 Technical Guidance Document in support of the Directive 98/8/EC concerning the placing of biocidal products on the market. Guidance on data requirements for active substances and biocidal products. EC October 2000, version 4.3.2. This document can be downloaded via the ECB website: http://ecb.jrc.it/biocides/
8 Technical Guidance Document in support of the directive 98/8/EC of the European Parliament and the council concerning the placing of biocidal products on the market. Common principles and practical procedures for the authorisation and registration of products. (TNsG on product evaluation). Ver 10.0 july 2002, final draft. This document can be downloaded via the ECB website: http://ecb.jrc.it/biocides/