TNsG on Annex I inclusion

Technical Notes for Guidance in Support of 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

April 2002

ECB, February 2008

The Technical Notes for Guidance on Annex I inclusion were formatted and edited in one single document in pdf format.

No changes have been made with respect to the content of the Guidance Document.

Foreword

The Biocidal Products Directive (Directive 98/8/EC of the European Parliament and of the Council)[1] lays down rules and procedures for authorisation of biocidal products in Member States.

The Directive foresees that the Commission shall draw up technical notes for guidance (TNsG) on the implementation of the authorisation procedures, the entry of active substances in the appropriate Annexes, the Annexes relating to data requirements and the Annex dealing with the common principles for evaluation of dossiers for biocidal products. Furthermore guidance on structure and content of dossiers is under preparation (the TNsG on Practicalities)

This TNsG deals with the Annex I inclusion of active substances of biocidal products. The document has gone through a long process of writing and negotiations. Firstly, from February 1997 to December 1998 on the basis of a contract with the Commission KEMI (the Swedish National Chemicals Inspectorate) drafted a proposal for a TNsG. Under the responsibility of the Commission (JRC-ECB) this draft was then discussed in a number of small expert groups in which Member States and Industry participated. Furthermore, the document has been discussed with all member states at several technical meetings. All Member States, Industry and NGOs have been invited to these meetings. At each stage updated versions of the document have been circulated for all parties to comment upon.

At a meeting of the Competent Authorities of Member States on the 12-13 December 2001, it was agreed to use the document for inclusion of active substances into Annex I, IA or IB of the Biocides Directive after a last round of written comments. In light of the experience gained through use the TNsG may then be updated in the future.

[1] OJ L 123, 24.4.1998, p. 1.

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List of Abbreviations

Standard term / Abbreviation	Explanation
µg	microgram(s)
ADI	Acceptable Daily Intake
ADME	Absorption Distribution Metabolism and Excretion
AF	Assessment Factor
Ann.	Annex
AOEL	Acceptable Operator Exposure Level
ASTM	American Society of Testing Methods
BBA	Biologische Bundesanstalt (*Germany*)
BCF	Bioconcentration factor
BIOEXPO	Project for risk reassessment of biocidal products for authorisation purposes *(Germany, January of 1998)*
BPD	Biocidal Products Directive
b.w.	body weight
°C	degree(s) Celsius (centigrade)
CA	Chemical Abstracts
CA	Competent Authority
CAS	Chemical Abstracts Service
CEC	Commission of the European Communities
CEFIC	European Chemical Industry Council
CEN	European Committee for Normalisation
CEPE	European Committee for Paints and Inks
Ch.	Chapter
CIPAC	Collaborative International Pesticides Analytical Council
CO_2	carbon dioxide
COST	European Co-operation in the field of Scientific and Technical Research
d	day(s)
DG	Directorate General
DIN (TTC,INT)	Deutsches Institut für Normung e.V. (*German Institute for Standardisation*)
DIS	Draft International Standard (*ISO*)
DRP	Detailed Review Paper (*from OECD)*
DT	Dissipation time (for field studies)
DT	Degradation time (for laboratory studies)
DT_{50}	period required for 50 percent dissipation (*define method of estimation*)
DT_{50lab}	period required for 50 percent dissipation under laboratory conditions (*define method of estimation*)
DT_{90}	period required for 90 percent dissipation (*define method of estimation*)
$DT_{90field}$	period required for 90 percent dissipation under field conditions (*define method of estimation*)
DDT	1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane
dw, d.wt.	dry weight
EC	European Communities or European Commission
EC_{50}	median effective concentration
ECCO	European Commission Co-ordination
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of Notified Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency

(DK, USA)	
EPAS	European Producers of Antimicrobacterial Substances
EPFP	European Producers of Formulated Preservatives
EPPO/OEPP	European and Mediterranean Plant Protection Organisation *(Paris, France)*
ESD	Emission Scenario Document
ESPE46/51	Evaluation System for Pesticides
EU	European Union
EUSES	European Union System for the Evaluation of Substances
EWPM	European Wood Preservation Manufacturers
FELS	fish early-life stage
F_{mol}	fractional equivalent of the metabolite's molecular weight compared to the active substance [-]
f_{oc}	organic carbon factor (*compartment dependent*)
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use (*European pesticide project for risk assessment)*
g	gram(s)
GEP	Good Experimental Practice
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
gw	gram weight
h	hour(s)
ha	hectare(s)
HPLC	high pressure (or performance) liquid chromatography
IARC	International Agency for Research on Cancer
IC_{50}	median immobilisation concentration or median inhibitory concentration
INT	2-p-Iodophenyl-3-p-nitrophenyl-5-phenyltetrazoliumchloride testing method (*please refer to DIN)*
IOBC	International Organisation for Biological Control
IR	InfraRed range of spectrum
ISBN	international standard book number
ISO	International Organisation for Standardisation
ISO (TC, SC, WG)	Technical Committee, Scientific Committee, Working Group
IUPAC	International Unions of Pure and Applied Chemistry
k	kilo
k	rate constant for biodegradation
Ka	acid dissociation coefficient
Kb	base dissociation coefficient
Kd	dissorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	solid-water partitioning coefficient of suspended matter
kPa	kilopascals(s)
$L(E)C_{50}$	lethal concentration, median
LD_0	highest non-Lethal Dose
LD_{50}	median Lethal Dose
l	litre(s)
LOAEL	Lowest Observed Adverse Effect Level
log	*logarithm to the basis 10*
m	metre
MAM	Minimum Acceptable Margin of Exposure
MEC	Measured Environmental Concentration

mg	milligram(s)
MITI	Ministry of International Trade and Industry (*Japan)* *(inherent biodegradability tests)*
MMAD	mass median aerodynamic diameter
MMM	methods, models and measurements
MOE	Margin of Exposure
MOS	Margin Of Safety
MS	Member State
MSDS	Material Safety Data Sheet
MT	material test
MRL	maximum residue limit
NMR	nuclear magnetic resonance
no**.,** n°	number
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
OECD	Organisation for Economic Co-operation and Development
OH	hydroxide
OJ	Official Journal
OPPTS	Office of Prevention, Pesticides, and Toxic Substances (*U.S.-EPA)*
Pa	Pascal unit(s)
PBT	Persistent, Bioaccumulating and Toxic (substances)
PEC	predicted environmental concentration
pH	potential hydrogen, negative *logarithm* (*to the basis 10*) of the hydrogen ion concentration
pKa	negative *logarithm* (*to the basis 10*) of the acid dissociation constant
pKb	negative *logarithm* (*to the basis 10*) of the base dissociation constant
PNEC(s)	predicted no effect concentration(s)
$PNEC_{water}$	predicted no effect concentration in water
POP	Persistent Organic Pollutant
Pow	Octanol/water partition coefficient
PPE	Personal Protective Equipment
PT	product type
PT (CEN)	Project Team CEN
QA	Quality Assurance
QAU	Quality Assurance Unit
QSAR	Quantitative Structure Activity Relationship
RA	Risk Assessment
$Rate_{a.s.}$	use rate of active ingredient [kg /ha]
$Rate_{metabolite}$	application rate at which metabolite should be tested in screen (kg/ha)
RENI	Registry Nomenclature Information System (*computerised database nomenclature and standardised diagnostic criteria for classifying tumours)*
RIVM	Netherlands National Institute of Public Health and Environmental Protection
RMS	Rapporteur Member State
RPE	Respiratory Protective Equipment
RSD	Relative Standard Deviation
SAR	Structure Activity Relationship
S/L	short term to long term ratio
SCB	Standing Committee on Biocides
SCAS	semi-continuous activated sludge (*inherent biodegradability tests*)
SETAC	Society of Environmental Toxicology and Chemistry
SMEs	Small and Medium sized Enterprises
STP	Sewage Treatment Plant

TBT	Tributyltin
TDI	Tolerable Daily Intake
TER	Toxicity Exposure Ratio(s)
TG	Technical Guideline(s), Technical Group(s)
TGD	Technical Guidance Document in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances and Directive 98/8/EC concerning the placing of biocidal products on the market.
TNsG	Technical Notes for Guidance
TNsG on Data Requirements	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
TNsG on product evaluation	Technical Notes for Guidance in support of Annex VI of 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 Annex I inclusion	TNsG on Annex I - Technical Notes for Guidance in support of 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
TNO	Netherlands Organisation for Applied Scientific Research
TTC	2,3,5-Triphenyltetrazoliumchloride
UBA	Umweltbundesamt *(Germany, Austria)*
UV	UltraViolet range of spectrum
UVC	Unknown or Variable composition, Complex reaction products
UVCB	Undefined or Variable composition, Complex reaction products or Biological material
v/v	volume per volume ratio
VIS	visible range of spectrum
w/w	weight per weight ratio
WHO	World Health Organisation
WPRS	West Palearctic Regional Section

1. Introduction and objectives

The Biocidal Products Directive (Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market) lays down rules and procedures for authorisation of biocidal products in Member States, and for approval of the active substances in biocidal products at the Community level. The aim of the Directive is to remove barriers to trade between Member States and at the same time to ensure a harmonised high level of protection for humans, animals and the environment with regard to biocidal products.

Due to the wide scope of the Biocidal Products Directive and the extensive variation of exposure and risks of different biocidal products, the general rules given in the Directive and its Annexes have to be specified in order to ensure efficient and harmonised day-to-day implementation of the Directive. As written in Article 33, the Commission, in accordance with the procedure laid down in Article 28(2), shall draw up technical notes for guidance to facilitate the day-to-day implementation of this directive.

In accordance with Article 11 or 15(2) (provisional authorisation) of the Directive an applicant wishing for an active substance to be listed on an annex of the guidance will forward to a competent authority of one of the Member States, a dossier for the active substance and a dossier for at least one biocidal product containing that active substance. However, the simultaneous submission of sufficient representative product dossiers to cover the full range of risk and efficacy assessments likely to be necessary for the subsequent product uses for that active substance will optimise the efficiency of the process.

A detailed methodology for the risk assessment of chemicals is described in the Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances. This guidance is currently (2001) being updated to also support assessments under the Biocidal Products Directive. The environmental assessment (for hazard, exposure and risk) and the human health hazard assessment of active substances will follow this guidance. The exposure assessment for humans is being elaborated in a separate guidance and the risk assessment for humans shall be given here in this document, the TNsG for Annex I inclusion. The methodology outlined in the TGD can also be applied to substances of concern and, regarding the methodology, to the biocidal products themselves.

The assessment shall be carried out by the responsible authority (known as the Competent Authority) of the Member State that receives the first biocidal product application or by a Member State decided upon by the Commission in accordance with the procedure laid down in Article 28(3) in combination with, where relevant, Article 11(3). The assessment shall include a proposal for inclusion, or otherwise, of the active substance in an annex, associated conditions for this entry or whatever specific risk reduction measures should be considered necessary for the risk management of the active substance. Copies of the evaluation with a proposal for decision shall be sent to the Commission, the other Member States and the applicant (Article 11(2)).

This TNsG on Annex I inclusion is issued at Community level identifying criteria for unacceptable/acceptable effects and associated conditions for inclusion of active substances in Annex I, IA (for active substances that can be used in low risk products) or IB (basic substances). The TNsG is intended primarily for the competent authorities of the Member States who shall assess the active substances and the biocidal products containing them, but also as guidance for the applicant.

The chapter addressing risk characterisation (Chapter 4) discusses the relevant endpoints for human health in terms of the population exposed (professional, non-professional and those exposed via the environment), followed by clarification of the roles of quantitative and qualitative risk characterisation. The environmental effects are discussed in terms of direct or indirect exposure to the different environmental compartments.

1.1 Provisions in the Directive

In the preamble and the legal text of the BPD a number of principles and general provisions are laid down which have bearing on the administrative decision whether or not an active substance in a biocidal product will be included on the ”positive lists”, Annex I, IA or IB of the Directive.

Articles 5(1) and 10 of the BPD state that a biocidal product, and thereby the active substance(s) it contains, shall be authorised for use only if it has no unacceptable effects directly or indirectly on human or animal health or the environment. This statement clearly reflects the aim of the Directive to ensure a harmonised high level of protection for humans, animals and the environment with regard to the use of biocidal products. In addition, Article 5(1)(c) lists the following properties which give rise to concern for the active substance: “[Member States shall authorise a biocidal product only if] …the nature and quantity of its active substances and, where appropriate, any toxicologically or ecotoxicologically significant impurities and co-formulants, and its residues of toxicological or environmental significance, which result from authorised uses, can be determined according to the relevant requirements in Annex IIA, IIB, IIIA, IIIB, IVA or IVB”.

In addition, Art.5 (2) points to a specific limitation in the use of products:

> “A biocidal products 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.”

In Article 10 conditions are set up for inclusion in Annex I, Annex IA or Annex IB of active substances used in biocidal products, low-risk biocidal products or as basic substances with a minor use as biocides, respectively. In Article 10(1) it is stated that the cumulative effects from the use of biocidal products containing the same active substance shall be considered where relevant. In Article 10(2) a number of general conditions and requirements are listed which, when appropriate shall be associated with Annex I, IA or IB inclusion of an active substance.

Of relevance is for example the establishment of scientifically derived values such as MOE[2], ADI, AOEL, NOAEL and PEC/PNEC ratio necessary for risk characterisation of the active substance during the intended use of the biocidal product.

Subject to Article 10(1) “An active substance shall not be included in Annex IA if it is classified according to Directive 67/548/EEC as:

- carcinogenic,
- mutagenic,
- toxic to reproduction,
- sensitising, or
- is bioaccumulative and does not readily degrade”

Article 10(2) exemplifies a number of requirements which, where appropriate, shall be linked to the inclusion of an active substance in Annex I.

Article 10(5) outlines general conditions for comparative assessment and substitution of (an) active substance(s) in biocidal products of the same product type (use area) by an active substance which presents significantly less risk to human health or to the environment.

In addition, Annex VI on evaluation of biocidal products contains some paragraphs that refer to properties and effects of the active substance(s) that give rise to concern and therefore may be judged unacceptable where criteria for acceptability are not passed. These reflect also the intention of the BPD that a qualitative risk assessment should be made in the case where, for various reasons, it is not feasible to make a quantitative risk characterisation for these properties or effects:

[2] Directive 98/8/EC refers to the expression ‘Margin of Safety’ when describing the ratio between the exposure at which no effect (or a defined effect) was seen during hazard identification studies and the estimated exposure to a human as the result of the use of a biocidal product/active substance. It was later agreed that the term ‘Margin of Exposure’ was more accurate and it is this term (and the abbreviation MOE) that will be used in this guidance document, unless the relevant part of the Directive is being directly quoted.

- para. 38 focuses on the significance of persistence, bio-accumulation and endocrine effects. These properties give grounds for concern even though they may not lead to classification of the active substances.
- Unacceptable impacts on non-target species in the aquatic, marine or estuarine environments (para. 81), in surface water or its sediments (para. 83), or in soil (para. 85) or unacceptable effects on the air compartment (para. 86) are listed in Annex VI of the Directive.
- It is also unacceptable if the foreseeable concentration of the active substance or of its relevant metabolites, breakdown or reaction products in groundwater (para. 82), or in the surface water in or from the area of envisaged use is intended for the abstraction of drinking water (para. 83) exceeds the maximum permissible concentration laid down by Directives 75/440/EEC and 80/778/EEC as amended by 98/83/EC after use of the biocidal product under the proposed conditions of use.
- Furthermore, bioaccumulation (para. 87 and 88) in non-target organisms and persistence in soil (para. 85) are mentioned for consideration as unacceptable impacts.

1.2 Completeness check

In accordance with Article 11 or 15(2) (provisional authorisation) of the Directive an applicant will forward to the competent authority of one of the Member States a dossier for the active substance and a dossier for at least one biocidal product containing that active substance. The competent authorities must ensure that the dossiers satisfy the requirements of the Directive for the intended use pattern(s) of the active substance and product(s). Annexes IIA and IIIA list the data that may be required on the active substance and further guidance is given in the TNsG for data requirements. It is the responsibility of the receiving competent authority to ensure that the dossier for the active substance is complete and adequate. This should be a formal check of the applicant's right to use the data in the dossier and the technical standard with no detailed evaluation of the studies. The applicant should have been in contact with the RMS before submitting the dossier to discuss any gaps, problems or points of uncertainty. This should simplify and accelerate the official completeness check and help to meet deadlines where they apply. The applicant should also have ensured that the BPD applies to the use of the active substance. Further guidance on the completeness check is given as part of the TNsG on product evaluation and the TNsG on Practicalities.

When the RMS has verified that the dossier submitted is complete it will require that the applicant forwards a summary of the dossiers to the Commission and the other Member States (Article 11, 1, b). The summary shall contain all endpoints and other relevant information. Article 18(2) describes the case of one of the other MS identifying an incompleteness in the dossier from the summary. They shall immediately communicate it to the RMS and, if necessary, inform the Commission and other MS without undue delay.

2. Hazard and Effects Assessment of an active substance

This section outlines briefly the purpose of hazard and effects assessment and gives the references to where the information on hazard and effects assessment is described.

The hazard assessment is performed on the active substance itself and, in addition, on relevant transformation products and impurities.

This guidance initially considers the evaluation of reports of regulatory hazard studies. However, data requirements can also be addressed by means of published reports from the literature (or any other source of data that provides adequate information) and by means of justifications as to why data are not required for a particular endpoint. Further guidance on the data to be submitted is given in the TNsG on Data Requirements.

The hazard identification should critically evaluate each study or item in detail, as described in the TNsG on Practicalities. Further guidance on data evaluation of study reports and published studies is given in the TNsG for data requirements and in the TNsG in support of annex VI for evaluation of studies relevant to the product assessment.

The data are grouped as follows:

- Data on the identity of the active substance
- Data regarding the physico-chemical properties of the active substance
- Data regarding the hazard identification for human health risk assessment
- Data regarding the hazard identification for environmental risk assessment

In addition, a dossier contains information on analytical methods, efficacy, resistance and protection measures.

The data required in each group are listed in Annexes II and III of the Directive and further guidance on the tests to perform is given in the TNsG on Data Requirements.

These studies are also used for the classification with regard to inherent properties according to Council Directive on Classification, Packaging and Labelling of Dangerous Substances (67/548/EEC).

2.1 Hazard Assessment for Physico-Chemical Properties

The hazards should be assessed from each of the physico-chemical properties of an active substance according to the data requirements described in the TNsG on Data Requirements. The assessment can be carried out to the same principles described in chapter 3 of the TNsG on Product Evaluation.

2.2 Procedure for Toxicological Hazard and Effects Assessment

The toxicological effects assessment comprises the following steps of the risk assessment procedure:

- Hazard Identification: the aim of the hazard identification is to identify the effects of concern.
- Dose (concentration) – response (effect) assessment: at this step the relevant no observed adverse effect level (NOAEL), shall, where possible, be determined.

The human health effects are addressed by studies on:

- Acute toxicity
- Irritation and Corrosivity
- Sensitisation
- Repeated dose toxicity
- Genotoxicity

- Carcininogenicity
- Reproductive (and developmental) toxicity
- Neurotoxicity
- Other (for example on endocrine effects and immunotoxicity)

Useful data for human health risk assessment can also be obtained from epidemiological studies, for example human case reports and case studies. However, the quality of these often varies between anecdotal information to full studies conducted to Good Clinical/Laboratory Practice guidelines. Although toxicity endpoints are usually addressed by animal data, the evaluation of human data is important since it can supplement findings in animal studies, for example for skin sensitisation.

Experimental human toxicity studies must not be conducted specifically for the purpose of Annex I, IA or IB inclusion.

2.2.1 Derived limit values of the hazard identification for human health

Detailed guidance on how to evaluate the available data for all the above end-points and for toxicokinetics is provided in the Technical Guidance Document on Risk Assessment for New and Existing Substances and Biocides. This process should be used to identify relevant No Observed Adverse Effect Levels (NOAELs) or NOAECs (or LOAEL, LD_{50}s or LC_{50}s where necessary), dose-response curves and endpoints for which thresholds for effects do not exist. Special consideration should be given to dose-response information that would affect the interpretation of the risk characterisation. This applies to both individual endpoints and to the overall pattern of effects observed at increasing dose. The irreversible effects and additive effects also need to be noted with respect to the setting of an assessment factor.

For certain use areas, and especially where the biocide can enter the food chain, it will be appropriate for values to be calculated for the ADI/ TDI and the MRLs for the active substance/metabolites. ADI and MRL values are set by the WHO/FAO Joint Meeting on Pesticide Residues or the WHO/FAO Joint Expert Committee on Food Additives and Contaminants and by the Standing Committee on Plant Health for the inclusion of active substances in Annex 1 of Directive 91/414/EC. Where possible the EU-values should be taken into consideration. Where no ADI (for MRL setting) or MRL itself exists, competent authorities should not attempt to determine them for the purposes of the BPD alone but make comments/proposals on what data should be considered by the appropriate bodies.

An ADI is derived by dividing the most appropriate NOAEL (usually from long-term studies) by the appropriate assessment factors (usually 100, but may be higher or lower in justified cases). The ADI is usually expressed as mg active substance per kg body weight per day.

MRLs are defined as the maximum residue limits in specified food and are usually expressed in mg of active substance per kg food.

When used the AOEL is derived by choosing the most relevant NOAEL (or LOAEL if no NOAEL is available) and applying an assessment factor. The Margin of Exposure (MOE) is derived by dividing the most relevant NOAEL (or LOAEL) by the estimated exposure to the person from the use of an active substance.

2.2.2 Data regarding the hazard identification for human health risk assessment

This guidance is not intended to be an exhaustive list of what information should be included in evaluations. Expert judgement will always be required to determine the type and extent of information that should be provided.

The evaluation of toxicity studies should identify the various outputs that can be used in risk characterisation. Some outputs will be:

- the direct endpoints that can be used for risk characterisation for example LD_{50}s, NOAELs, LOAELs;
- the derived endpoints such as the ADI, AOEL or MOE (where appropriate);

- classification according to Directive 67/548/EEC as appropriate;
- any qualitative information that would contribute to the assessment of the potential effects of the active substance on human health, for example irreversible effects, or additive effects such as acetylcholinesterase inhibition.

2.3 Procedure for Environmental Hazard and Effects Assessment

The environmental effects assessment comprises the following steps of the risk assessment procedure:

- Hazard Identification: the aim of the hazard identification is to identify the effects of concern.
- Dose (concentration) – response (effect) assessment: at this step the predicted no effect concentration (PNEC), shall, where possible, be determined.

A PNEC is regarded as a concentration below which an unacceptable effect will, most likely, not occur. In principle, the PNEC is calculated by dividing the lowest short term $L(E)C_{50}$ or long term NOEC value by an appropriate assessment factor. The assessment factors reflect the degree of uncertainty in extrapolation from laboratory toxicity test data for a limited number of species to the 'real' environment. Assessment factors applied for long term tests are smaller as the uncertainty of the extrapolation from laboratory data to the natural environment is reduced. For this reason long term data are preferred to short term data. Results from field tests or mesocosm studies can also be used to derive a PNEC on a case by case basis.

The environmental hazard identification, that is identification of the inherent properties of a substance, is an important step in the risk assessment. The hazard identification is based on information about:

- Physical and chemical data
- Fate and behaviour in the Environment (including degradation and mobility)
- Effects on aquatic organisms (including sediment-dwellers)
- Effects on terrestrial organisms (including mammals and birds)

Using the data above, a PNEC has to be derived for each of the protection goals for the environment, as given below:

- Fresh water aquatic ecosystem (including the sediment)
- Marine aquatic ecosystem (including the sediment)
- Terrestrial ecosystem
- Microbial activity in a sewage treatment plant
- Secondary poisoning (top predators)
- The atmosphere

In cases where it is not possible to establish a PNEC, a qualitative estimate has to be made.

If, during the transformation of the substance, relevant metabolites/transformation products are formed, an effect assessment for the concerned compartments will have to be carried out. Guidance for Metabolites is under development under Directive 91/414/EEC. When available this guidance can be useful for risk characterisation under the BPD as appropriate.

The methodology for establishing these PNECs is presented in the Technical Guidance Document on Risk Assessment.

The data to be submitted according to the Directive and detailed in the TNsG on data requirements allows for deriving PNECs for all relevant environmental compartments.

PBT criteria are being discussed under a future revision of the TGD. Once agreed, these criteria will also apply to biocides.

This view is consistent with the current international programmes on chemical control. The prevention of pollution of substances that are persistent and liable to bioaccumulate is addressed in the Esbjerg

Declaration on the protection of the North Sea, and in the Regional UNECE Protocol and global UNEP Convention on Persistent Organic Pollutants (POP).

3. Exposure Assessment

Each application for inclusion of an active substance on to either Annex I or Annex IA must be accompanied by a dossier on at least one biocidal product (Article 11(1, a) ii)). In general, the exposure part of the risk characterisation for the active substance (Annex VI, para. 3) will be based on the exposure patterns for the accompanying product(s), as well as taking into account relevant cumulative exposures (Art. 10(1)). Where relevant the manufacture and use of the active substance itself should also be taken into account based on the information from Annex IIA 2.10 of the Directive.
Ongoing work on exposure models will be introduced here when finalised. Where appropriate exposure data are available these should be used in preference to models. In the absence of actual exposure data, suitable models can be used. Should no suitable models be available, competent authorities should employ a qualitative approach to risk characterisation according to experience.

The purpose of this chapter is to give relevant references to exposure assessment guidance documents, not to describe the detailed assessment methods themselves.

The exposure assessment is divided into environmental exposure assessment and human exposure assessment.

3.1 Human exposure

The exposure is characterised in two ways:

1. By the level (how much?), frequency (how often?) and duration (how long?)
2. By being primary (the person knows he is being exposed) or secondary (the person does not know he is being exposed).

These terms are elaborated in more detail in the TNsG for Data Requirements, chapter 1.4.

Depending on the severity of the effect(s) and the characteristics of the exposure with regard to 1) and 2) the exposure will, or will not, be of concern. Basically the 'concern' is triggered if the estimated or measured dose exceeds an appropriate reference dose or the most relevant NOAEL(C) divided by an assessment factor. However, it is good practice in product design and product use that exposure should always be reduced to as low a level as is reasonably possible.

The human exposure assessment for biocides is addressed in a report "Assessment of human exposures to biocides" from October 1998. It is available on the ECB web site at http://ecb.jrc.it/biocides . Currently (July 2001) a follow-up project to this report is on-going with the aim to give methods, models and measurements for describing the human exposure so that they can be directly applied to exposure assessments for active biocidal substances in products.

3.1.1 Categories of human populations exposed

Below is given a brief description of the different categories of users as mentioned in the Directive. In addition to these categories, Chapter 1.4 of the TNsG on Data Requirements (guidance on non-submission of data) identified the general public as a group, and furthermore the necessity for all groups to distinguish between primary and secondary exposure.

Professional users

The professional users of biocidal products are assumed to have some skill and knowledge in the handling of chemicals. They are expected to take realistic precautions using Personal Protective Equipment (PPE) including Respiratory Protective Equipment (RPE), where necessary. PPE does not abolish exposure even if it is used to high occupational hygiene standards. Suitable engineering controls should be used in preference to PPE whenever practical. However, proper use of PPE is assumed to keep inhalation and dermal exposure at a low level. Professional users shall also include those professionals who may come in contact with the biocide for example when handling and processing newly treated material.

Further detail regarding the exposure to the product is given in the TNsG on human exposure (in preparation). The assessments of unacceptable effects depend very much on the purpose and method of use of the product associated with the application for inclusion of an active substance on to an Annex.

The range of scenarios is wide and ranges from those where exposure is well-controlled by engineering in, for example, an industrial plant to those where someone is spraying a biocidal product in cramped conditions where exposure is difficult to control.

Non-professional users including the general public

Non-professionals are assumed to have no training in the safe handling of biocidal products. They are assumed to read and, in general, to follow the label instructions including the risk and safety phrases but it should be borne in mind that the range of "normal" exposure from a particular use could exceed the level of exposure of professional users significantly (realistic worst case exposure). They are assumed to have no means of protection from exposure to the products in the form of protective clothing or respiratory equipment paragraph 73 of Annex VI of the BPD). The range of products and exposure scenarios varies greatly for non-professionals from ready-prepared baits that require no direct contact to liquids that will be sprayed or brushed, possibly in windy conditions. Products could be used occasionally (such as coating wood once every few years) to using a product every day for months (such as fly sprays).

In the Directive in Article 5(2), particular reference is made to the restrictions placed on the use of products with certain classifications under the Council Directive on the classification, packaging and labelling of Preparations (1999/45/EC). The concentration of an active substance in biocidal products purely for non-professional use ("the general public", Article 5(2)) will, therefore, have to be within the limits set by these directives if the active substance has the relevant classifications.

Those exposed indirectly via the environment

Like non-professionals/general public one assumes that those exposed to active substances through their environment (the surroundings, which can also be inside buildings) are without protection against exposure. According to the agreement at the OECD workshop in Canada in June 2000 the exposure via the environment falls under what was defined as 'secondary exposure' for which the exposed person may not know of his exposure (for example handling treated material, consumption of residues in food or drinking water) which may even be long-term (inhalation exposure after indoor use). Therefore the risk characterisation has to take account of foreseeable exposure from normal product use and use of the treated article and so, once again, information on the patterns of use of the associated products is important. Critical endpoints also have to be considered for risk assessments on foreseeable misuse for example the accidental ingestion of a product, dermal exposure to residues that should have been removed, and oral exposure to residues in food, drinking water and feed stuff.

The toxicity end-points that must be evaluated are the same for any exposed population group. As mentioned before, according to the Directive the actions to take will depend on which population groups are exposed. Further guidance is given the TGD on Risk Assessment.

Combined exposure

As set out in the TNsG on Practicalities Section 1.5 of Document IIC, a risk assessment for "Combined exposure" is required. In order to conduct this risk assessment, one first has to calculate the possible combined exposure.

A person can have multiple exposures to an active substance within one product type on a single day. Whereas each of the individual exposures might prove acceptable during risk assessment, it can occur that risks from possible, realistic multiple exposures combine to reach an unacceptable level. In order to assess the risk, the exposure assessment must first be conducted and this can be known as the "combined exposure".

Combined exposure occurs when someone is a member of different exposure populations during a period. For example, a person could use product(s) containing the active substance as an operator (for example applying a fly spray, rodenticide or wood preservative) and then be exposed to the same active substance for the same use as a bystander or user at home. In addition, there could be an exposure from food and drink via environmental exposure. Therefore it can involve both primary and secondary exposures.

Where multiple exposures are considered possible, the relevant exposure scenarios should be presented and explained in the exposure assessment. The individual exposure values, as derived in the three previous sections, should be totalled and carried forward to the risk characterisation.

3.2 Environmental Exposure

The assessment of environmental exposure consists of:

- the estimation of emissions into the different environmental compartments, those are fresh and marine water, ground water, soil, air and sewage treatment plant;
- the assessment of the degradation and transformation processes;
- the assessment of distribution over the different compartments;
- the exposure of organisms within those compartments, either directly or indirectly via the food chain.

Further guidance on exposure assessment is provided in the TGD on Risk Assessment and in the EUBEES project described on the ECB home page.
For the estimates of environmental exposure and in order to cover also processes and uses that may be specific for biocides, emission scenario documents (ESDs) are being developed and will be incorporated in the TGD. An overview of existing ESDs, also applicable to biocides, is available (an overview report on ESDs can be found at the ECB web page). ESDs are under development with the aim to have them for all 23 product types. The ESDs describe the expected exposure of the different environmental compartments: Air, Water (marine, fresh, sediment, ground water) and Soil and STP.

3.3 Cumulative Exposure

Article 10(1) states that the risks from the cumulative use of an active substance in biocidal products shall be taken into account. There is no established methodology for this type of exposure estimate neither for the environment nor for human exposure and it is not yet known whether fully quantitative assessments will be possible in every case. However, the following principles should be followed as closely as possible.

For the first evaluation of the active substance the applicant (in the dossier) and the Competent Authority (in the report) should consider what combination of exposures to the active substance from all the representative uses is realistically possible. This should be based on the combined exposures for each use. A relevant time period for the pattern of use of the products and the nature of the active substance should be decided and explained in each case. The assessment should reflect normal lifestyles and emission patterns. Realistic worst case possible combinations of exposures should also be considered.

When using measured concentrations in exposure assessment it is not necessary to differentiate the sources of exposure in detail as long as it can be verified that at a general level the measurements are representative for the exposure situation in question. There is for example no need to differentiate in detail between primary and secondary exposure or differentiate if there are some minor non-biocidal emission sources involved. The measured data should therefore typically represent cumulative exposure from concentrations of natural origin and releases from all biocidal uses. When it comes to cumulative exposure of a substance used also outside the scope of the BPD (for example in plant protection products) and may be regulated with another directive, there is currently still a need for a common EU decision on how to handle such cases. Exclusion of other than only biocidal uses from the assessment causes difficulties when using monitoring data or comparing measured residue data with Maximum Residue Limits and should not be attempted.

For later evaluations the need for a revision of the cumulative exposure assessment should be considered. The influence of the level of use of authorised products should also be taken into account.

4. Risk Characterisation

It is always necessary to carry out a risk characterisation, taking into account the identified hazards leading to classification and labelling according to the criteria given in Directive 67/548/EEC, as well as other grounds for concern. Such concerns could be that criteria for classification of a specific effect are not yet developed. This is for example the case for the terrestrial environment, endocrine disrupting effects, and for anaerobic degradation in environments not covered by test methods in Annex V of Directive 67/548/EEC.

According to Annex VI of the BPD, risk characterisation is defined as:

> **Risk characterisation**: this is the estimation of the incidence and severity of the adverse effects likely to occur in a human population, animals or environmental compartments due to actual or predicted exposure to any active substance or substance of concern in a biocidal product. This may include "risk estimation", i.e. the quantification of that likelihood.

In the context of the Biocides Directive the risk characterisation is thus an assessment of the risk associated with the exposure to the active substance through the use of the biocidal products.

Risk characterisation for human health is based on a comparison of the critical toxicity endpoints of the active substance and the exposure scenario for the proposed pattern(s) of use. The possible critical role in risk characterisation of each of the different toxicity endpoints are discussed below in terms of the population that will be exposed.

This section does not distinguish between the use of animal model data and human epidemiology data. This will have been taken into account in the evaluation of the data, and the setting of the assessment factors.

The specific conditions in the Directive relating to inherent properties and inclusion into either of the Annexes I, IA or IB are given in Chapter 1.1 (Provisions in the Directive).

The risk assessment of an active substance is an essential part of the assessment procedure for the product. In the Directive, "whereas" clause number 14 describes the principles for assessment of the active substances which are to be used, by referring to the principles for industrial chemicals laid down in Directive 92/32/EEC and Council Regulation (EC) 793/93.

Many of the existing active substances will have been on the market for a long time, often also for purposes other than for use in biocidal products. To ensure close co-ordination with existing legislation and concerns, "whereas" clause number 20 specifically mentions the Plant Protection Products Directive, Directive 91/414/EC, the Water Framework Directive and the directives concerning GMOs.

The methodology for risk assessment of the active substance can be defined as the combined processes of (a) hazard identification, (b) identification of the dose-response relationship, (c) exposure assessment and (d) risk characterisation. The hazard assessment and the dose-response relationship will be elucidated once for the active substance. This evaluation is then used in the product evaluations. The exposure assessment for the Annex I, IA and IB inclusion of the active substance should take into account (Art 10(1)) "where relevant, cumulation effects from the use of biocidal products containing the same active substances." and the exposure data from Annex IIA of the directive. The risk characterisation is a combination of (a), (b) and (c). A detailed methodology for risk assessment applicable to active substances is described in the Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances which is being revised (year 2001) and will in the future also support assessments under the Biocidal Products Directive. The TGD on Risk Assessment covers the hazard assessment, and for the ecotoxicological part of the assessment, the TGD also covers the exposure assessment and the risk characterisation. For Human Health the current TNsG covers the steps from risk characterisation onwards.

It is assumed that the results of the risk characterisation can be applied to pets and other domestic animals.

Effects data are obtained from the hazard identification (see Chapter 2) and these are compared with estimates of exposure (see chapter 3) within the risk characterisation. Where possible, the no-effect doses or concentrations of the active substance obtained from the scientific studies are compared with the predicted or monitored, overall exposure during relevant stages of the product life cycle. The ratio between measured/predicted and acceptable exposure then forms the basis for the decision on whether or not the substance can be included in Annex I, IA or IB. Assessment factors are used in the characterisation of the ratio between effective doses or concentrations and exposure and, when appropriate, to calculate a derived value (for example MOE, AOEL, ADI, TDI and PNEC values). Annex VI states that where a quantified risk assessment is not possible a qualitative risk characterisation can be conducted. A qualitative assessment will have to be carried out when reliable exposure data are missing and/or when no effect dose levels relevant for an adequate assessment of risks to non-target organisms are not established. There may also be cases where test guidelines for a specific endpoint considered relevant for a quantitative assessment are unavailable.
When sufficient data for an adequate risk assessment are not available, justified precautions may have to be included in the decision-making to fulfil the aims of the Directive. If in one part of the risk assessment a highly unacceptable risk has been identified then, the remaining part of the Risk Assessment can be done at a more general level.

4.1 Quantitative Human Health risk characterisation

Where a critical effect is threshold-based and exposure data are reliable, quantitative risk characterisations should be carried out for each exposed population, product type and method of application relevant for the accompanying product(s) as indicated by the exposure assessment. The most appropriate endpoint(s) for use in risk characterisation must also be identified and then compared with the exposure estimate for the relevant use situations. The risk characterisation should, for a period, be performed using both the MOE and the AOEL approach.

4.1.1 Choosing a NOAEL

The choice of NOAEL depends above all on the toxicological profile of the active substance. Selection of the most sensitive NOAEL on which to base, for example, an AOEL needs to be made on a case-by-case basis, and requires expert judgement. The choice of NOAEL should derive from the identification of the critical effect in the most relevant and sensitive animal species. If the chosen NOAEL is an external dose (applied dose) it might be necessary to convert it to an internal value by using a correction factor for systemic availability and for this purpose adequate absorption data should be provided. The duration of the study from which the NOAEL is chosen should be appropriate to the pattern of use of the product. The choice of a NOAEL is inappropriate if serious effects such as non-threshold carcinogenicity or other specific effects have been identified.

For long-term exposure for example from indoor use of preservatives/preservative-treated material, NOAELs should normally be derived from chronic toxicity/carcinogenicity studies. NOAELs from studies with the relevant route of administration should be used where possible.
When the most appropriate study does not provide a NOAEL, the lowest dose may be used as a LOAEL but this situation must be reflected in choosing and justifying the assessment factor.

4.1.2 Determining reference doses and margins of exposure

Reference doses can be ascertained as a threshold estimation of a daily or interrupted route specific exposure to the human population that is likely to be without an appreciable risk of adverse effects during a specified lifetime period.

The Biocidal Products Directive, Article 10(2) states that “Inclusion of an active substance in Annexes I, IA or IB shall, where appropriate, be subject to the following:…” and continues “…(ii) the establishment of the following reference doses:

(a) acceptable operator exposure level (AOEL), if necessary,
(b) where relevant, an acceptable daily intake for man (ADI) and a maximum residue limit (MRL),…”

Annex VI, para. 71 states that for the authorisation of biocidal products ”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.”

Thus the Directive opens for the use both of the AOEL and MOE approaches.

A future choice for either including only an AOEL or a MOE approach should be made on the following items: consistency with other legislative texts, transparency of the method and flexibility of the method. For the time being, both methods will be used in risk assessment so that all evaluators gain experience in order to make an informed choice at a later stage.

4.1.3 Determining assessment factors

Both methods require the determination of assessment factors that account for uncertainties in the extrapolation of information from toxicity data to the exposed human population. The same issues influence the setting of these factors for a given dossier and exposure scenario. Therefore they should be the same for both methods of risk characterisation for a specific scenario.

The setting of the overall assessment factor is a critical step and one that has proved very difficult in other areas of regulatory risk assessment. The points to consider include:

- interspecies variation;
- intraspecies variation;
- the type and severity of the effect;
- the human population which is exposed;
- possible differences in exposure characteristics between the calculated exposure and the exposure in the study providing the NOAEL (route of exposure, exposure duration, frequency, exposure pattern);
- correction from LOAEL to NOAEL if necessary;
- the dose-response relationship observed;

Factors for interspecies and intraspecies variation are usually both 10, although some Member States have used lower factors for the intraspecies variation factor for the working population. Other factors could be multiples or fractions depending on their role in the process. An additional assessment factor of 10 would be used for the most severe effects. However, it is unlikely that standard factors could be set that would be used in every case. Experience in other assessment programmes indicates that simply multiplying standard factors can result in an unnecessarily over-conservative assessment. It might be possible to set standard factors after some years’ experience. However, for now it is recommended that assessors should choose what they consider to be appropriate factors and then explain them in the dossier or report so that the decision process can be followed step by step. Chemical-specific factors can be used where the database supports them. The application of these is being investigated by a WHO/IPCS working group and application of the guidance produced by it should be considered where appropriate (see http://www.ipcsharmonize.org).

4.1.4 The AOEL approach

The following text explaining the concept and the establishment of an AOEL is primarily based on the draft EU Guidance Document on setting the AOEL. It should be noted that that guidance document is prepared within the scope of Directive 91/414/EEC for plant protection products.

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 AOEL is a health-based limit-value and will be established on the basis of the full toxicological package required for Annex I inclusion. The default AOEL represents the internal (absorbed) dose available for systemic distribution from any route of absorption and is expressed as an internal level (mg/kg bw/d). The concept of the AOEL as such has relevant legislative consequences and serves primarily as an important tool for operator risk assessment. Exposure estimates exceeding the AOEL do not allow an inclusion of active substances in Annex I of Directive 91/414/EC.

For active substances in biocidal products, it may still permit the decision for Annex I inclusion, depending on the agreements of the involved EU Scientific Committees.

The AOEL should be based on the (overall) NOAEL in the most sensitive relevant animal species. This selection is performed on a case-by-case basis. It is set on the basis of the full data set available for oral studies provided that no major route-specific differences are anticipated. When fundamental differences in the toxicological effects (for example first-pass-mechanism) exist between exposure routes, route-specific studies should be considered for AOEL setting but the external NOAEL from such a study should be converted to an internal value since the AOEL is defined as an internal systemic limit value (except for some inhalatory and dermal effects).

Although establishment of an AOEL relies heavily on expert judgement, its derivation needs to be reported as transparently as possible. Any agreed AOEL might need to be reassessed in the light of new data.

To translate the selected NOAEL into an AOEL, the NOAEL is divided by the assessment factors described above. Since the target tissues, critical effects, and the NOAELs may differ depending on the exposure time, more than one AOEL may be established to allow for flexibility considering the anticipated exposure situations. However, as a default procedure, only one AOEL is set for an exposure period appropriate to the frequency and duration of exposure of operators (including contractors) and re-entry workers. This is typically short-term exposure, for example repeated exposure during a total of up to 3 months per year.
The default AOEL will be a systemic AOEL based on the NOAEL from an oral short-term toxicity study 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.

A number of aspects in the AOEL approach are still subject to discussion at the EU-level. Major points of discussion are the number of AOELs to be set in a default procedure (one or three (acute, short-term, and long-term AOELs), whether external route specific AOELs should be set (such as an $AOEL_{inhalatory}$ or an $AOEL_{local\ dermal}$), and which assessment factors to be used for the working population. Further guidance on setting an AOEL should be available in the future from the work done under Directive 91/414/EEC. When available this guidance can be applied to risk characterisation under the Biocidal Products Directive as appropriate.

4.1.5 The MOE approach

The text below is from the 1996 version of the TGD on risk assessment.

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:

$$MOE = \frac{\text{NOAEL (mg/kg bw/d)}}{\text{Exposure (mg/kg bw/d)}} \quad \text{or} = \frac{\text{NOAEC (mg/m}^3\text{)}}{\text{Exposure (mg/m}^3\text{)}}$$

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 (see section 2.1 regarding suitable human studies). The selection of endpoints and studies involves expert judgement on a case-by-case basis. According to the TGD for new and existing substances a 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 would indicate whether the risk was now acceptable. This process should be exceptional since the applicant should have resolved these situations while conducting the risk assessment with their dossier.
Further guidance will be available from the revised TGD on Risk Assessment. This guidance can be applied to risk characterisation under the Biocidal Products Directive as appropriate.

4.1.6 The ADI approach

For the assessment of health risk after subchronic or chronic exposure to pesticides, the ADI has been established. The World Health Organisation 1989 publication "Guidelines for predicting the dietary intake of pesticide residues" (WHO, 1989) had formed the basis for this ADI approach of consumer risk assessments of food residues. The ADI is usually based on NOAELs from lifespan or subchronic studies. Concerns have been recently expressed that acute toxic effects may sometimes be elicited following consumption of food containing residues of certain pesticides. The 1994 JMPR (FAO/WHO, 1994) considered that situations in which the ADI derived from subchronic or long-term studies were probably not an appropriate toxicological benchmark for assessing risk posed by short-term exposure to acutely toxic residues. Certain biocides might present an acute hazard, however, so that such excesses are of toxicological concern. As a matter of standard practice in the risk assessment of residues in food and drinking water, the case for setting an acute reference dose (ARfD) should be considered for all compounds (EC2001 b). The ARfD of a chemical was defined by the 1998 JMPR as 'an estimate of a substance in food or drinking water, expressed on body weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of evaluation' (FAO/WHO, 1998).

4.1.7 Exposure – Differences between residential and occupational settings

Both the AOEL- and the MOE approach serve as instruments for risk assessment. In other words, the risk assessor has to conclude whether a certain active substance in a certain product, involving a specific usage and hence a specific exposure scenario, can be applied safely or not (concern).
As already indicated, biocides include a wide range of different products ranging from disinfectants in closed circulating systems to insect repellents directly rubbed on the skin. This involves a very wide range of exposure scenarios, for example from a single acute exposure once or a few times a year for the general public to daily contact for professional users.

Primary exposure of professional users to biocides is mostly characterised by some form of regular procedure because they perform certain standard activities on a regular basis. For example, disinfectants in a closed circulation system are removed and refilled every week or month, whereas spraying some types of insecticide occurs daily during a specific period of the year. In other words, in certain cases occupational exposure to biocides can be categorised into rather standardised exposure scenarios. Therefore, a concept of the AOEL (in which one or a few value is/are established) may be able to cover adequately the rather standardised exposure scenarios of occupational settings.

In contrast, exposure of private users – especially in the case of residential exposure – involves a large diversity of products and a large variation in product use and consumer behaviour. Similar conditions may apply to secondary exposure in occupational settings. In addition, residential use of biocides involves the whole population whereas the working population does not include children or the elderly. Therefore, exposure scenarios of widely differing time scales and, in addition, different toxicity endpoints relevant for specific subpopulations are anticipated. This requires a risk assessment methodology that allows maximal flexibility in order to perform risk characterisations to take account of, for example, different

exposure durations, different toxicity endpoints and different exposed populations, to protect the most sensitive subpopulation in the most relevant time frame applying the precautionary principle. Therefore, exposure of all relevant subpopulations of the general public (private users and bystanders (such as children) as well as through secondary exposure) is too diverse to be covered by a single (or a limited number of) health-based limit value(s).

4.1.8 Outcomes

If, when the comparison is made, estimated exposure is lower than the derived exposure limits the risk characterisation indicates no cause for concern. Ideally an applicant should have addressed any potential case where an exposure limit would be exceeded during the compilation of the dossier. However, differences in opinion on, for example, the most appropriate NOAEL can occur. Consequently it is possible that during the evaluation by the Rapporteur Member State or during discussions between Member States, the outcome of the risk characterisation is that the limit is exceeded. The exposure estimates and NOAEL values should be the optimal for the specific exposure scenario so no refinement of these should be necessary. However, it may be possible for the exposure scenario to be modified in a limited way to take account of risk management tools. This is for the applicant to decide at the earliest possible time after the problem is identified. The new scenario may provide a different estimated exposure and the risk characterisation can be adapted.

4.2 Qualitative Human Health risk characterisation

Qualitative risk characterisation will be relevant for endpoints such as irritation/corrosivity, sensitisation (if non-irritant or non-sensitising concentration thresholds have not been adequately identified), genotoxicity and carcinogenicity where no threshold mechanism and no threshold have been adequately identified. However, if determined, the dose-response-relationship should be taken into consideration.

Consideration of the severity of the effect will usually only be relevant for irritation/corrosivity where, for a given exposure, the effect could range from mild to severe with irreversible damage. Sensitising active substances have different potencies but at the present time these are usually not sufficiently well-characterised to influence the risk characterisation. The most important information on exposure needed in case of sensitising and genotoxic properties is a clear task analysis that provides details of how exposure occurs during the preparation and use of the active substance itself (according to 98/8/EC, Annex IIA, No.II.2.10, annex VI, para.3) and of the product. A description of what happens to the active substance afterwards should also be provided where relevant (for example, where surface residues remain). This should allow the identification of the occasions of potential exposure and a consideration of the availability and effectiveness of tools for risk management. Quantitative exposure data may also be helpful to indicate to what extent exposure is expected to occur. In general, the potential for exposure to active substances with these hazardous properties would need to be nil or negligible.

4.3 Evaluation of each human health endpoint

Toxicokinetics and dermal absorption

Data on toxicokinetics will provide information on the possible fate of the active substance in the human body. Sufficient information on absorption should be available to support route-to-route extrapolation in the risk characterisation for product types where it is needed or to address species-specific mechanisms if relevant.

Studies on, for example dermal absorption may contribute indirectly to risk characterisation. They may also provide information on the possible toxic behaviour of the active substance for example it may indicate a potential for dermal toxicity or a dermal deposit leading to the possibility of skin sensitisation or carcinogenic effects. Dermal absorption must also be taken into account, since dermal exposure may be higher and prolonged if a product is not washed off the skin.

Acute toxicity

Acute toxicity will not often feature as a critical endpoint in risk assessments for professional use. Most exposure will probably be via the dermal route and also by inhalation. Risk characterisation will be quantitative since acute effects usually have a threshold, and thus can be based on a $LD(C)_0$ or $LD(C)_{50}$ value. While acute toxicity is usually not characterised by a NOAEL(C) (or LOAEL(C)), these can be used if available from sub-acute toxicity studies. $LD(C)_{50}$ values are the most frequently available data but are not so suitable for risk characterisation since they are based on the endpoint of lethality. Additional assessment factors are needed as described in 4.1.3. Occasionally information from human case reports of poisoning may be available. The use of this for risk characterisation will depend upon expert judgement on the reliability of the reported information. Problems include the availability of an effect level but no information on a no-effect level or a dose-response relationship. Oral toxicity will have an impact upon risk assessment where ingestion may occur for example through poor occupational hygiene. A substance would normally have to be very toxic or toxic for this to be an issue of concern.

Non-professional users may use large quantities of some active substances on an occasional basis and with less control over exposure than professional users (for example, in wood preservative products and antifouling products). Non-professionals will not usually use protective equipment and, in fact, cannot depend on it to reduce risk to an acceptable level, (Annex VI para. 73 and 74) so, in practice, dermal and inhalation exposure may be considerably greater than for professional users for the same pattern of use.

For the general public the most relevant acute toxicological endpoint is oral for exposure following accidental/intentional ingestion of an active substance. Risks based on oral toxicity of active substances shall be considered for all product types due to the risk of accidental ingestion by young children. Dermal exposure to for example treated fabrics or soft furnishings would usually be low level and would be compared to data from a repeated dose study. Inhalation exposure is especially relevant where volatile active substances have been applied recently indoors.

Irritation and corrosivity

The risk to professionals from irritation and corrosivity should be considered in the first place without taking into account the risk reduction provided by personal protective equipment and respiratory protective equipment. The risk for dermal and inhalation exposure and contact with the eyes should be considered.

These toxicity endpoints are more significant for products for non-professional use since one must assume that no PPE is worn during application of products. Dermal contact could be significant depending on the formulation type and method of application for the product. Formal quantitative risk characterisation is not usually possible but comparison of information on the maximum non-irritating dose and the proposed product concentration (and in-use concentration, where relevant) may be possible if sufficient information is available. The severity of the irritant effect of the product and the predicted frequency of use should also be taken into account. A measure of that severity is provided by the classification criteria for which the active substance qualifies under directive 67/548/EC.

Particular attention should be given to an active substance which is classified as corrosive or severely irritant to the skin or eyes when it is likely to trigger the classification of biocidal products under 99/45/EC as severely irritant or corrosive or as irritant to the respiratory tract. Exposure during all stages of use of typical products should be described for prescribed conditions of use taking into account the presentation and/or delivery of the product, and also realistic worst case conditions. Data from Poison Control Centers could also be used in the assessment process. The full range of risk management procedures should be used to reduce the possible risk arising from the use of biocidal products classified as severely irritant or corrosive to an acceptable level, bearing in mind for non-professional use paragraph 73 of Annex VI of the Biocidal Products Directive[3]. Risk management could play a key role for the final acceptability of the use of products and would, therefore, be influential in the decision as to whether the risk from use of the active substance is acceptable. Consequently, the risk from these effects of particular concern will have to be considered on a case-by-case basis for both active substances and products.

[3] This remark relates to biocidal products whose evaluation should be carried out in accordance with the guidelines prepared on Annex VI of the BPD. Therefore if the risk is decreased in a subsequent biocidal product, this submission should be evaluated on its own merits/on a case-by-case basis.

In some cases, use of biocidal products will leave residues that cannot be removed, or are not intended to be, removed. It is, therefore, important to consider the potential for irritation effects, especially when exposure is frequent. For example, dermal exposure might occur for those handling treated wood, or working in areas that are frequently cleaned with biocidal products (for example furniture polish).
Important for the risk characterisation of these effects could also be that an active substance, as it dries may increase in concentration within the residue to a level that causes irritation.

Irritation can also be an important endpoint for the assessment of risks to children. These may spend a larger proportion of their time in contact with treated surfaces, for example carpets and textiles. This applies also to companion animals (pets).

Sensitisation

Risk characterisation for skin sensitisation is more difficult to formalise than for many other toxic endpoints. Test methods to detect the potential sensitising effects, and classification and labelling guidelines are well-established. However, the potency with which sensitising substances cause skin sensitisation appears to vary widely, depending on chemical class and structure. Less well developed is a method to either quantify the risk of sensitisation following exposure, or compare the potency between substances. Data from the Local Lymph Node Assay will provide useful information on these points when they are available for an active substance and, in the longer term, its use may develop to form the basis of a formalised method of comparing potency within groups of substances.

In the meantime, the risk assessment of sensitising active substances will often have to be conducted on a more semi-quantitative basis. Actual or estimated exposure can be compared with either the NOAEL in the LLNA or the potency (expressed as the amount of the chemical per unit area of skin required to cause a defined response) when reliable data is available. When such data are not available, judgements will have to be made on a case-by-case basis as to whether the potential for skin sensitisation described in an animal study report constitutes a cause for concern. Such judgements will take into account all available data from animal studies, evidence from human case reports (including concentrations/formulations resulting in effects and frequency of exposure required to elicit an effect) and estimates of likely exposure. Information from closely related formulations may also be useful in the risk assessment. Structural alerts and signs of ability of the substance to cause respiratory sensitisation or hypersensitivity must also be taken into account. The irreversibility of sensitisation and the apparent variation of sensitivity amongst the human population will influence the caution with which the acceptability of the risk is interpreted.

It is recognised that the role of the whole range of available risk management procedures will be extremely influential on the risk assessment for sensitisation. The reliability of the control of exposure will be of paramount importance for the acceptability of risk from the use of products by both professionals and non-professionals.

In some cases the use of biocidal products will leave residues. It is, therefore, important to consider the potential for sensitisation, especially when exposure is frequent. For example, dermal exposure might occur for those handling treated wood, or working in areas that are frequently cleaned with biocidal products (for example, furniture polish). It should also be taken into account that, as it dries, an active substance may increase in concentration within the residue to a level that causes sensitisation or elicit an allergic reaction.

Sensitisation can also be an important endpoint for the assessment of risks to children. They may spend a larger proportion of their time in contact with treated surfaces such as carpets and textiles. This applies also to companion animals (pets).

The potential of active substances to cause respiratory sensitisation appears to vary widely. Where criteria (Dir. 67/548/EEC) for classification as a respiratory sensitiser are met, a case-by-case evaluation has to be performed to determine if the risk from exposure to the substance is acceptable or not.

Repeated dose effects

Repeated dose effects (as interpreted from the 28 day study, the 90-day study and the long term toxicity study, for observations of genotoxicity or carcinogenicity see following sections) will be of concern whenever exposure is on a regular and/or frequent basis and especially if the effects have been observed to be irreversible or only partially reversible.

Most effects can be assessed using quantitative risk characterisation and therefore depend upon the difference in dose levels at which adverse effects are seen in animals (or humans) and the estimated exposure for the accompanying product. The key factors are the most sensitive, relevant NOAEL, the effects it is based upon and the dose response that occurs at higher doses. If the effects are irreversible a greater assessment factor will be required between the NOAEL and the exposure for humans.

Effects noted in repeated dose studies are critical endpoints for secondary exposure (man via the environment and via occupational settings) because exposure can be repeated for various reasons. It might be that the same individuals enter treated areas immediately following regular treatments (including staff in hospitals, offices, shipyards) or that they frequently handle treated goods (such as carpenters). Long-term, low level inhalation exposure is also possible from indoor use of treated material. Exposure in the diet via residues should normally be compared to chronic NOAELs.

Genotoxicity

When a positive result has been obtained in genotoxicity studies the strategy to be followed for further testing is detailed in Annex IIA and is amplified in the TNsG on data requirements.

Since it is usually assumed that a threshold does not exist for genotoxicity (with the possible exception of aneuploidy) these studies cannot provide any quantitative input to the risk characterisation. However, a conclusion that potential for genotoxic activity exists is a fundamental qualitative input to risk characterisation.

Genotoxicity will be a critical endpoint for all active substances, but especially those used in non-professional products. The BPD (Art.5 (2)) states that "A biocidal product classified according to " Council Directive 1999/45/EC "as….a category 1 or 2 mutagen….shall not be authorised for marketing to, or use by the general public." The risk to the general public from secondary exposure to these substances would also usually be unacceptable.

Genotoxicity will be a critical endpoint for most active substances where positive results are obtained in appropriate studies. In general the risk from these substances will be unacceptable if exposure is likely to occur but will depend upon the available measures to control and limit exposure. Furthermore, if genotoxic substances are listed on Annex I, they should be considered as strong candidates for comparative assessment, see chapter 8. It is essential that such active substances be subject to strict risk management.

The criterion in 67/548/EEC for category 3 mutagens states that indications of possible genotoxic effects in somatic cells cause concern for humans but there is insufficient evidence to place the substance in category 2. The risk from a category 3 mutagenic substance in a biocidal product for non-professional users only, who are assumed to be unprotected from exposure, may be considered acceptable on a case-by-case basis, for example, where exposure via a route of concern is not likely to occur. The significance of adverse effects in genotoxicity studies for those exposed via the environment would be the same as for non-professionals in the sense that one must assume that they are not protected from exposure. However, whereas non-professionals cannot use products containing category 1 or 2 mutagens, they may be exposed to these substances from the environment following use of products by professionals. A thorough assessment of possible groups entering treated areas or handling treated goods is essential. The possibility of exposure and the available measures to control and limit exposure would also influence whether the risk was so low as to be acceptable.

The developments in the field of carcinogenicity testing strategies should be followed and applied to biocides where relevant. Sometimes a substance can be classified as a Cat 3 Mutagen. The supplier will then handle the substance with caution and may consider that further testing, for carcinogenic potential is unnecessary as the results of the testing will not affect how the substance is handled. In this case the substance is never formally classified into Cat 2 for carcinogenicity. However, it should be considered that, if it should be possible to waive studies in these circumstances, then the restrictions under BPD that are placed on substances classified in Cat 2 should apply.

Carcinogenicity

The acceptability of the risk from active substances for which carcinogenic potential exists will depend upon the appropriate category of carcinogenic classification, the likely mechanism of carcinogenicity and the extent of exposure.

The BPD (Art.5 (2)) states that "A biocidal product classified according to "Council Directive 1999/45/EC "as….a category 1 or 2 carcinogen….shall not be authorised for marketing to, or use by the general public." The risk to the general public from secondary exposure to these substances would also usually be unacceptable. The risk from active substances that meet criteria for categories 1 or 2 carcinogenicity under 67/548/EEC will not be acceptable where exposure is likely to occur. Furthermore, if they are listed on Annex I, they should be considered as strong candidates for comparative assessment, see chapter 8. It is essential that such active substances be subject to strict risk management (see Annex VI para.75).

The inclusion of active substances meeting the criteria for category 3 classification under 67/548/EEC will be strongly dependent upon the mechanism and levels of exposure. If the most likely mechanism has a threshold then a normal risk assessment approach can be taken. However an assessment factor of 1000 might be used to the critical carcinogenic effect (such as increased incidence of tumours). If more data on the mechanism is awaited (one of the criteria for category 3) or if it is believed that a genotoxic (non-threshold) effect may be responsible for the carcinogenic potential then a threshold approach to risk assessment is not possible and the acceptability of the risk must be carefully considered qualitatively.

Toxicity to reproduction and development

The BPD (Art.5 (2)) states that "A biocidal product classified according to "Council Directive 1999/45/EC "as….classified as toxic for reproduction category 1 or 2….shall not be authorised for marketing to, or use by the general public." The risk to the general public from secondary exposure to these substances would also usually be unacceptable

Active substances that meet criteria for categories 1 and 2 as toxic to reproduction under 67/548/EEC and cause effects on reproduction at dose levels which do not produce other signs of toxicity in animals should, in general, be considered as strong candidates for comparative assessment (see Chapter 8). It is essential that such active substances be subject to strict risk management (see Annex VI para. 75).

Effects on the reproductive system are often threshold-based allowing a quantitative risk characterisation to be carried out. However, effects on the development of offspring can be due to a genotoxic mechanism and the potential for this needs to be considered since a qualitative risk characterisation would then be appropriate.

If an active substance is classified as category 1 or 2 toxic to reproduction and is subject to quantitative risk characterisation, then an assessment factor of 1000 applied to the critical reproductive toxicity effect (such as increased incidence of malformations) might normally be used. The assessment factor for category 3 substances will depend upon the severity of effects, their relationship to toxicity observed in the mothers and the exposure level at which they occurred compared with effects seen in other animals. It should also be remembered that the general public is unprotected from exposure and that the people concerned may not be aware of their exposure, which implies the use of a very stringent assessment factor.

Fertility and developmental effects are relevant endpoints for exposure scenarios involving repeated exposure. However, developmental effects can occur following short-term exposure if this happens to coincide with the critical formative stages of embryonic and foetal development. Furthermore, effects on fertility have been reported already following short-term exposure so this risk should also be characterised where indicated.

Other Toxicity End-points

In addition to the above-mentioned effects, other effects such as endocrine disruption, immunotoxicity and neurotoxicity must be risk assessed.

The toxicity endpoints neurotoxicity, immunotoxicity, behavioural toxicity and endocrine effects may be as significant for professional as for non-professional users. They may also be significant for secondary exposed persons, among them children, especially if the use of the biocidal product leaves residues that cannot, or are not intended to be, removed.

For these effects there are no specific criteria for classification according to 67/548/EC. Consequently, judgement as to the entry onto Annex I must be made on a case-by-case basis, taking into account the use pattern and consequent potential primary and secondary exposures.

The effects may be of concern after any type of exposure (ranging from acute to chronic); they may be reversible or irreversible. In any case, the acceptability of the effects will be reflected by the relevant NOAEL and the assessed exposure.

4.4 Risk characterisation for combined and cumulative exposures

Two aspects need to be considered for the risk characterisation of the combined exposure for the use under consideration in the application. Firstly, whether the cumulative exposure poses an unacceptable risk in comparison to the endpoints considered for the separate exposures and secondly, whether the combination of exposures will give rise to risks that did not arise for the individual populations.

It can be argued that combined and cumulative exposure estimates are subject to greater variation than the individual population exposure estimates due to the combination of scenarios and dependence on an individual's behaviour, possibly over an extended time period. To try and take account of this, risk characterisations should reflect normal use as well as realistic worst case combinations.

The appropriate risk characterisations must be revised when an exposure assessment for cumulative exposures from different biocidal uses of the same active substance is updated. This can occur following the addition of new uses or the extensive use of existing uses already listed on an annex. If the change in exposure is so great as to change the decision on the outcome of the risk characterisation and influence the risk assessment of the active substance, then the Standing Committee must reconsider the inclusion of the active substance on the annex of the Directive.

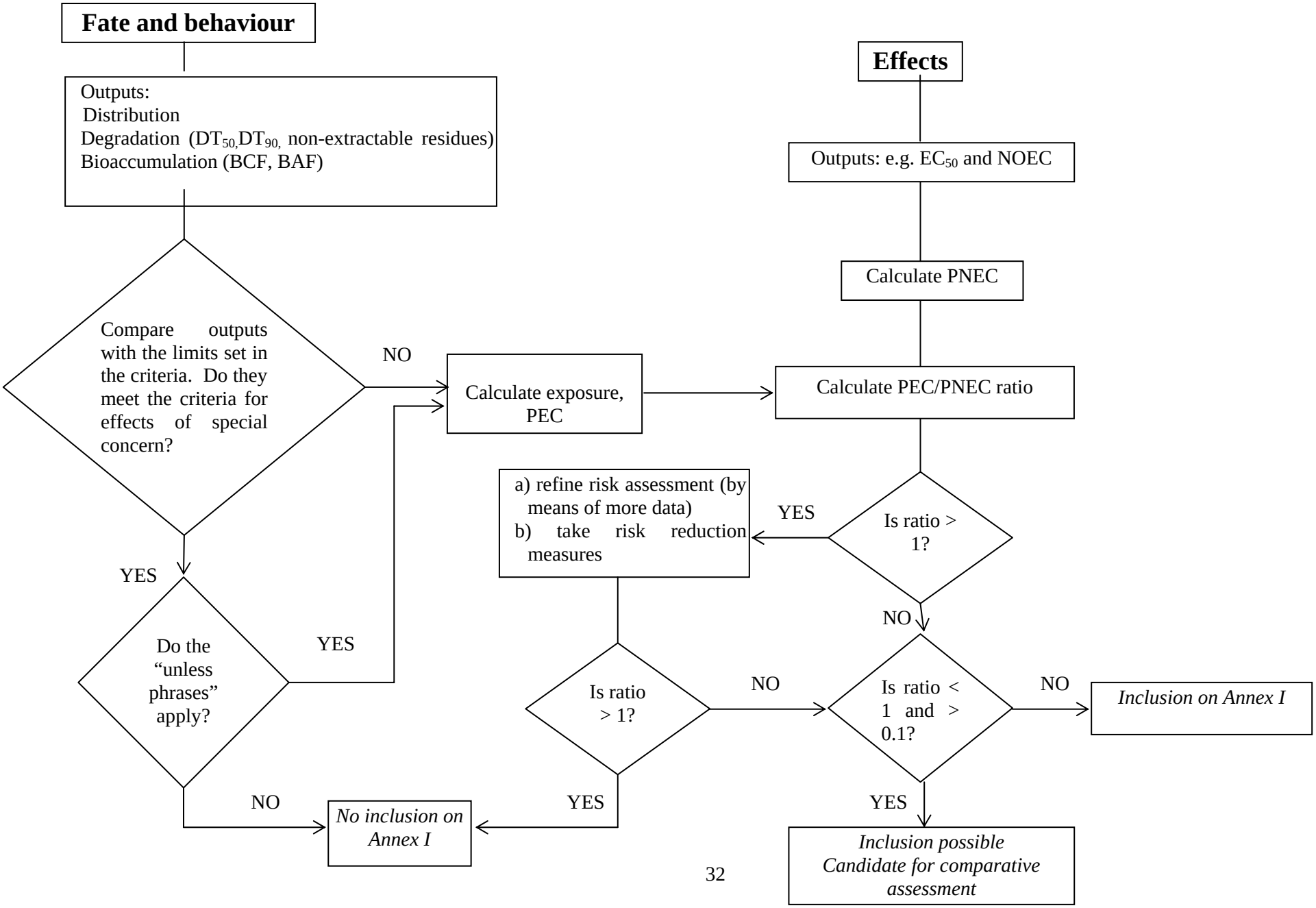
4.5 Environmental risk characterisation

The risk characterisation for the environment must consider both the behaviour of the active substance in the environment and its effects upon non-target organisms.

For any given environmental compartment, the risk characterisation shall, as far as possible, entail comparison of the PEC with the PNEC so that a PEC/PNEC ratio may be derived. If it has not been possible to derive a PEC/PNEC ratio, the risk characterisation shall entail a qualitative evaluation of the likelihood that an effect is occurring under the current conditions of exposure or will occur under the expected conditions of exposure.

The risk assessment for the environment will follow the methodology outlined in the TGD. A schematic overview is given in fig. 4.

Figure 4 Scheme of decision-making process for environmental risk assessment



4.6 Risk characterisation of active substances for Annex IA

The section on risk characterisation of active substances applies to active substances for inclusion on to all Annexes. However, inclusion of an active substance on to Annex IA will also depend upon compliance with the specific criteria laid down in Article 10(1) of the Directive and repeated in Chapter 5.

4.7 Procedures for Assessment and risk characterisation of active substances for Annex IB

The procedures for assessing an active substance for entry on to Annex IB will be similar to those for other active substances in terms of completeness checks and the hazard identification.
Each safety study or justification for a data gap will be assessed in the same way as for active substances to be listed on Annex I and Annex IA.

When basic substances are being considered as active substances for entry to Annex IB the risk characterisation process will have to take into account the fact that there will be no accompanying product. There will only be a description of how the substance is used and the competent authority/applicant will have to identify the product exposure scenario that most closely resembles the use pattern for the basic substance (see Chapter 7). Guidance on data requirements for basic substances is given in the TNsG for Data Requirements.

5. Criteria for Annex I, IA and IB inclusion

The Directive gives criteria for inclusion of active substances into Annex I, IA and IB based both on hazard identification expressed according to Directive 67/548/EEC and the product properties assessed according to Annex VI of the Directive. The criteria relates to environmental and toxicological aspects. Furthermore, there are a number of general criteria relating to other properties of the substance and the quality of the dossier.

5.1 General Criteria for inclusion in Annexes I, IA and/or IB

Documentation

An active substance may be included in Annex I, IA or IB if, as a minimum, a dossier deemed to be complete has been submitted on both the active substance and at least one representative biocidal product.

Composition of the Active Substance and Physico-Chemical Properties

- The minimum degree of purity must be defined.
- The identity of the impurities and their maximum content, and where relevant identity and content of isomers / diastereo-isomers and additives.
- Impurities of toxicological or environmental concern are within acceptable limits.
- The specification is within FAO specification where relevant.

Annex VI para. 50 “If there are indications that any other unacceptable effects may occur the Member State shall evaluate the possibility of such effects occurring. An example of such an unacceptable effect would be an adverse reaction to fastenings and fittings used in wood following the application of a wood preservative.”

Methods of Analysis

- The method of analysis of the active substance as manufactured and for the determination of impurities and co-formulants of toxicological, ecotoxicological or environmental concern or which are present in quantities $\geq$ 1g/kg in the active substance as manufactured has been validated and shown to be sufficiently specific, linear, accurate and precise.
- The method of analysis of the active substance’s residues of toxicological or environmental significance, which result from authorised uses, has been validated and shown to be sufficiently specific, linear, accurate and precise.
- The method for analysis in environmental matrices, as appropriate, must have been validated and shown to be sufficiently sensitive with respect to the levels of concern.

Other criteria related to the proposed uses

The Annex VI of the Directive lists some unacceptable effects of the substances:

- Unnecessary suffering of the target organisms (Annex VI, para 48)
- The development of resistance (Annex VI, para 49)
- The indications of any other unacceptable effects (Annex VI, para 50)

Furthermore, the biocidal product has to have a demonstrated efficacy (Annex VI, para 51).

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[4], 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

[4] Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

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.

5.3 Environmental Criteria for exclusion from Annexes I, IA and/or IB

For all the environmental compartments, a condition for the inclusion of the active substance in Annex I is that the final PEC/PNEC ratio is <1 for the following protection goals (taking into account both the active substance and its transformation products):

- aquatic fresh water and marine ecosystem (including the sediment);
- terrestrial ecosystem (for example other non-target arthropods);
- micro-organisms in sewage treatment plants;
- top-predators (secondary poisoning);

According to Annex VI, the active substance can be included into Annex I if it is clearly established in the risk assessment that under field conditions no unacceptable effects occur after use of the biocidal product according to the proposed conditions of use. The risk assessment should be as comprehensive as the available data allow. Further data that are provided after an initial risk assessment (including results from field tests) will have an influence upon the exposure and the effects assessment and thereby on the PEC/PNEC ratio or on the additional criteria listed below. At the end, the risk assessment will use all data and the final decision will be based on the final PEC/PNEC ratio and on the additional criteria listed below. The degree to which field data cover the EU area may affect the flexibility of the Annex I inclusion.

There is an exemption for antifouling products from this criterion in relation to non-target aquatic organisms if similar antifouling control cannot be achieved by other practical means for a period of up to 10 years from the date on which the BPD entered into force (ref. BPD, Annex VI, para. 88).

Effects of concern

The biocidal active substance should normally not be listed on an annex if, at the end of the iterative procedure, the final PEC will exceed the PNEC at the intended use.

Air

An active substance (including relevant transformation products)

- which has the potential to have adverse effects and
- has a vapour pressure >0.01 Pa (at 20 °C) or a Henry's law constant > 0.03 Pa x m^3 x mol^{-1} and the atmospheric DT_{50} > 2 days or
- is measured at elevated levels in remote regions.

shall be carefully considered before inclusion in Annex I.

Substances which have adverse effects on the atmospheric environment by contributing to:

- degrading air quality (visibility, effects on human health, bad smell, effects on plants)
- tropospheric ozone building
- acidification
- ozone layer depletion
- global warming
- long range transport.

shall be carefully considered before inclusion in Annex I.

Soil

According to Annex VI para. 85, an active substance shall not be included in Annex I if:

- during tests in the field, it persists in soil for more than one year (a substance can be considered to persist for more than a year if, in soil field tests, its DT_{90} > 1 year and DT_{50} > 3 months), or

- during laboratory tests, it forms not extractable residues in amounts exceeding 70 % of the initial dose after 100 days with a mineralisation rate of less than 5 % in 100 days, or
- has unacceptable consequences or effects on non-target organisms

unless it is scientifically demonstrated under field conditions that there are no unacceptable effects or unacceptable accumulation in soil.

The consequences or effects on non-target organisms will already have been assessed in the risk assessment.

In addition to the above criteria, the active substance shall not be included into Annex I if it has a DT_{50} > 6 months at 20 ºC in soil metabolism studies. However, this does not necessarily apply if the active substance is included in Annex I with regard to areas of use where a long lasting service-life of the treated material is essential and it is scientifically demonstrated that under field conditions there is no unacceptable accumulation in soil (e.g. that the PEC/PNEC < 1 in soil during the service-life of the treated article). This derogation is an interpretation of the above mentioned "unless clause).

Similarly, an active substance containing a metal or a semi-metal element shall not be included in annex I if the use will cause significant accumulation above the natural background levels.

Surface Water

According to Annex VI, an active substance shall not be included in Annex I "if under the proposed conditions of use, the foreseeable concentration of the active substance or of any other substance of concern or of relevant metabolites or breakdown or reaction products in water (or its sediments) has an unacceptable impact on non-target species in the aquatic, marine or estuarine environment unless it is scientifically demonstrated that under relevant field conditions there is no unacceptable effect."

The consequences or effects on non-target organisms will already have been assessed in the risk assessment.

Furthermore, according to Annex VI, an active substance shall not be included into Annex I "if the foreseeable concentration of the active substance or…. of relevant metabolites, breakdown or reaction products to be expected in surface water or its sediments after use of the biocidal product under the proposed conditions of use:

- exceeds, where the surface water in or from the area of envisaged use is intended for the abstraction of drinking water, the values fixed by
    - Council Directive 75/440/EEC of 16 June 1975 concerning the quality required of surface water intended for the abstraction of drinking water in the member states,
    - Directive 98/83/EC or
- has an impact deemed unacceptable on non-target species

unless it is scientifically demonstrated that under relevant field conditions this concentration is not exceeded.

The consequences or effects on non-target organisms will already have been assessed in the risk assessment. The following directives may also be relevant for limit concentrations in surface water: Directive 75/440/EEC and the Water Framework Directive 2000/60/EC.

Furthermore, an active substance should not be included in Annex I if

- it shows in the sediment of a laboratory water/sediment system a DT_{50} > 6 months at 20 °C or
- during laboratory tests in aerobic sediment/water system (20-25 °C) it forms non-extractable residues in amounts exceeding 70% of the initial dose after 100 days with a mineralisation rate of less than 5% in 100 days

unless it is scientifically demonstrated that under relevant field conditions there is no unacceptable accumulation in sediment.

An active substance containing a metal or a semi-metal element shall not be included in annex I if the use will cause significant accumulation above the natural background levels.

Ground water

According to Annex VI para. 82, an active substance shall not be included in Annex I "if, under the proposed conditions of use, the foreseeable concentration of the active substance or of any other substance of concern or of relevant metabolites or breakdown or reaction products in groundwater exceeds the lower of the following concentrations:

- the maximum permissible concentration laid down by Directive 80/778/EEC as amended by 98/83/EC, or
- the maximum concentration as laid down following the procedure for including the active substance in Annex I, IA or IB to this Directive, on the basis of appropriate data, in particular toxicological data.

unless it is scientifically demonstrated that under relevant field conditions this concentration is not exceeded.

The second bullet point is already taken into account within the risk assessment (indirect exposure of man via the environment).

Bioaccumulation

According to Annex VI para. 88, an active substance shall not be included in Annex I if "the bioconcentration factor (BCF) is greater than 1000 for substances which are readily biodegradable or greater than 100 for those which are not readily biodegradable unless it is clearly established in the risk assessment that under field conditions no unacceptable impact, either directly or indirectly, occurs on the viability of exposed organisms including marine and estuarine organisms after use of the biocidal product according to the proposed conditions of use." There is an exemption for antifouling products from this criterion in relation to non-target aquatic organisms if similar antifouling control cannot be achieved by other practical means for a period of up to 10 years from the date on which the BPD entered into force (ref. BPD, Annex VI, paragraph 88)."

According to the TGD, substances which are not readily biodegradable, but have a half life < 15 days (based on full mineralisation, that is more than 90% mineralised) in surface water or in sediment/water simulation tests should be considered as "readily biodegradable" in the sense of the above paragraph. Inversely, readily biodegradable substances which have a half life > 15 days (based on full mineralisation) in surface water or sediment/water simulation tests should be considered as "not-readily biodegradable" in the sense of the above paragraph.

As an interpretation of the above mentioned "unless clause", a tiered approach can be proposed:

If an active substance fulfils the above exclusion criteria, but with a BCF < 2000, and the risk assessment for predators due to secondary poisoning and for man exposed via the environment show that there is no risk, the active substance can still be included in Annex I.

Criteria for Persistent, Bioaccumulating and Toxic (PBT) substances and very Persistent and very Bioaccumulating (vPvB) substances is currently being discussed in the EU and more detailed guidance will be presented in the TGD on risk assessment. The PBT assessment approach should be considered case-by-case when a BCF is between 2000 and 5000.

An active substance with a BCF > 5000 shall not be included in Annex I.

According to Annex VI para. 87, an active substance shall not be included in Annex I if "the bioaccumulation factor (BCF) related to fat tissues in non-target vertebrates is above 1 unless it is clearly established in the risk assessment that under field conditions no unacceptable effects occur, either directly or indirectly, after use of the biocidal product according to the proposed conditions of use."

Currently no guidance can be proposed regarding the interpretation of this criterion. Further work will be necessary to do so.

Persistent, Bioaccumulative and toxic substances

Recently, international agreement was reached within a UNEP convention to limit world-wide the emissions to the environment of Persistent Organic Pollutants (POPs), those are chemicals with a high

potential for persistence, bioaccumulation, long range environmental transport and adverse effects to human health and the environment.

Active substances which fulfil the selection criteria under the UNEP-POPs convention shall not be included in Annex I.

A practical implementation of the UNEP-POPs criteria will be included in the TGD. These will therefore automatically apply to active biocidal substances.

The criteria below are the preliminary PBT criteria of the TGD and should be updated when the final PBT criteria are available.

Substances which fulfil the following PBT or vPvB criteria shall not be included in Annex I unless releases to the environment can be effectively prevented:

	PBT-criteria	**vPvB-criteria**
P	Half-life > 60 d in marine water or half-life > 180 d in marine sediment	Half-life > 60 d marine or freshwater or >180 d in marine or fresh water sediment
B	BCF > 2000	BCF > 5000
T	Chronic NOEC < 0.01 mg/l or CMR or endocrine disrupting effects	Not applicable

5.4 Criteria for active substances to be listed on Annex IA

The inclusion of a substance on to Annex IA may be subject to conditions, for example regarding categories of users where the use does not seem to pose risk of concern. Certain criteria for the placing of active substances on to Annex IA are specified by the Directive itself (Article 10(2)).

An active substance cannot be included in Annex IA if it is classified according to Directive 67/548/EEC as:

- carcinogenic,
- mutagenic,
- toxic for reproduction,
- sensitising, or
- is bioaccumulating and does not readily biodegrade

The criteria for the inclusion of active substances on Annex I also apply.

In addition to the above, an active substance can only be listed on Annex IA if a dossier is submitted demonstrating that the representative product(s) meet(s) the definition of Article 2(1)(b) of the Directive and the criteria described in the TNsG on Product Evaluation.

5.5 Criteria for active substances to be listed on Annex IB

The criteria for inclusion in Annex I apply except that there is no accompanying product.

6. Guidance for the inclusion of active substances on to Annex IA

The Directive defines a low-risk biocidal product as: “A biocidal product which contains as active substance(s) only one or more of those listed in Annex IA and which does not contain any substance(s) of concern. Under the conditions of use, the biocidal product shall pose only a low risk to humans, animals and the environment.” (Article 2 (1) b)).

It is one of the intentions of the Directive to provide a simplified procedure for the registration of low-risk biocidal products (Article 8). The active substances and accompanying representative products are subject to the full requirements of Annex IIA and IIB, and IIIA and IIIB of the Directive but there is a derogation from the requirements of Annex IIB and Annex IIIB of the Directive (data requirements for products) for subsequent products. There is no derogation from Annexes IIA and IIIA (data requirements for active substances). Therefore the procedure for the listing of a substance on Annex IA will be similar to that for listing a substance on Annex I (see Chapters 2 & 3).

Evaluation of the data set required for the active substance will be consistent with the guidance provided for assessment of substances to be entered on to Annex I. Aspects of the assessment that are particular to active substances to be used in low-risk products are discussed below.

An active substance that is to be included in low-risk products has to fulfil certain requirements as stipulated in the Directive. Further criteria are specified for the identification of low risk products and described in the TNsG on product evaluation. The data which should be submitted in support of an active substance to be included in low risk products is the same as those for entry on to Annex I for the same product type and exposure scenario as described in the TNsG on data requirements. Once the active substance is entered on to Annex IA then the simplified procedure of registration of products can be implemented. Guidance on this procedure is provided in the TNsG on Product Evaluation.

Candidate active substances for Annex IA may be identified either by the applicant during the submission of the dossiers or by a competent authority during the evaluation of data originally submitted for entry of an active substance either on to Annex I.

6.1 Entries on Annexes I and IA for the same active substance

An active substance listed in Annex IA is automatically listed in Annex I. The entry on Annex IA would be similar to an Annex I entry, but there may be different conditions indicated as for instance the indicative permissible maximum concentration of the active substance for use in low risk products, lower than permitted in other products. (The minimum required concentration determined for the purposes of efficacy would remain the same). The entry on Annex I would then represent all those exposure scenarios in product types where authorisation of individual products under the requirements of Article 5(1) would be possible but where the criteria for low-risk products are not met. It may, of course, be associated with conditions and limits of its own.

A hypothetical example where the maximum active substance concentration permissible under low-risk criteria for an enclosed bait station might be 25% but for a ready-for-use liquid formulation it might be only 2%. There is a higher user exposure to the product when applying liquid formulations than for baits. In order for user exposure to remain within the low-risk criteria (that is, still with the same large margins of safety) the liquid formulation may not be able to contain more than 2% active substance (the product would also have to be efficacious at that concentration). In addition, some entries may require a limit on the application rate (for example mg or mg active substance per ml formulation) together with the number and timings of applications (for example four applications made, one per week) to ensure that exposure during use of the product remains at an acceptable level.

7. Guidance for the inclusion of basic substances on to Annex IB

7.1 Definition and introduction

This chapter discusses the conditions that basic substances must meet in order to be entered as active biocidal substances on to Annex IB. The Directive defines a basic substance as,

> "A substance which is listed in Annex IB, whose major use is non-pesticidal but which has some minor use as a biocide either directly or in a product consisting of the substance and a simple diluent which itself is not a substance of concern, which is not directly marketed for this biocidal use.
>
> The substances which could potentially enter Annex IB in accordance with the procedure laid down in Articles 10 and 11, are *inter alia* the following:
>
> carbon dioxide
> nitrogen
> ethanol
> 2-propanol
> acetic acid
> kieselguhr."

Applicants must demonstrate that the proposed substance adheres to the directive's definition of an active basic substance.

Although the above list is not exhaustive, it is assumed that only a limited number of substances are currently used in this way and would meet the criteria for Annex IB inclusion.

Guidance on the data requirements for these substances is provided separately (TNsG on data requirements, chapter 5.4). The evaluation of these data will be similar to that for active substances to be entered on to Annex I and the appropriate guidance for this can be found in Chapter 2 of this document. This chapter discusses the current use of basic substances and the conditions for what constitutes a basic substance. A flow diagram illustrates the process of considering an application and a structure for the Annex IB entry is proposed (Table 7.1).

This guidance is written on the basis of some Member States' experience with basic substances prior to the implementation of the BPD. It must be remembered that the wide scope of the Directive will probably introduce basic substances for regulation that have not been considered before and new issues may arise that have not been addressed here. Competent authorities will have to resolve new problems on a case-by-case basis.

7.2 The use of basic substances

The Directive provides for the placing on the market and the use of basic substances or simple products on condition that they are not sold, supplied, or advertised specifically for biocidal use. The basic substance is purchased from general suppliers and it does not carry specific information or conditions about use as a biocide. However, when the substance is used for biocidal purposes this must be done in accordance with the conditions laid out in the Annex IB inclusion, chapter 7.3. The uses are often specific to particular trades or activities (such as preservation of objects of historic interest in museums) and, in cases where the users are professional, they are trained in the use of the basic substance as part of the training for their work in general.

Suppliers cannot market a biocidal product or label the substance specifically for biocidal use. If a supplier should wish to market a product containing a basic substance for a specific biocidal purpose then full authorisation of the product would be required and the substance would have to be evaluated for inclusion in Annex I or Annex IA.

Table 7.1: Structure for Annex IB entry examples

PARAMETER	INPUT
Active Substance: Common name, EC no., CAS no. Other numbers	Substance x EC no: Zzz-zzz-z, CAS no.: xxxxxx-xx-x
Chemical name (IUPAC, CAS)	> 99%
Minimum degree of purity	
Identity & maximum content of certain impurities	
Product Type	14: Rodenticides 18: Insecticides, acaricides and products to control other arthropods
Manner and area of use and use pattern	Control of rodents, insects and mites in sealed enclosures. Used in public hygiene situations, commercial/ industrial premises, ships, aircraft and containers
Categories of users (industrial, professional or non-professional)	Professional
Other particular conditions	The treatment area has to be kept free from the presence of unprotected persons and non-target animals.
Enforcement date	
Expiry date of Annex IB inclusion	

7.3 Conditions for Annex IB inclusion

7.3.1 Minor use

The biocidal use of the chemical must be minor compared to other uses of the same chemical. "Minor" is not defined in the Directive but it is suggested here that the proportion of the total usage of the substance should be not more than 5%. Such a percentage may not be easy for an applicant to document but a best attempt should be made. However, the total quantity placed on the market for biocidal purposes should also be taken into account. Overall, it will be the duty of the applicant to satisfy the competent authority that the use is minor.

It is the duty of the applicant to provide an explanation of the major uses of the basic substance demonstrating that they are non-pesticidal, and it will be the duty of the competent authority to ensure that the major use is non-pesticidal under other regulations; for example, that it falls outside the scope of other directives where pesticidal effect is claimed, such as 91/414/EEC (Plant Protection Products Directive) and 81/851/EEC (the directive for the licensing of Veterinary Medicines).

7.3.2 Human and environmental health effects and efficacy

In addition to the above, specific, conditions for basic substances the general conditions that there must be no unacceptable effects to humans or the environment (Articles 5 and 10 of the Directive) will also have to be met. Some evidence of efficacy must be provided in accordance with the guidance on data requirements (TNsG on Data Requirements).
If the conclusion of the risk assessment is that the risk associated with the biocidal use of the basic substance warrants refusal of entry onto Annex IB, a restriction for biocidal use via Directive 76/769/EEC may be necessary.

7.4 Evaluation of data for Annex IB inclusion

The applicant shall provide a dossier and data as outlined in the guidance on Annexes IIA and IIIA, as specified in the TNsG on data requirements for basic substances, together with some evidence of efficacy.

Hazard identification will then be carried out on the data for the same endpoints as for active substances considered for Annexes I or IA for the same use (see Chapter 2). The exposure assessment and risk characterisation for the intended use are also carried out to the same procedures and criteria as for products based on active substances listed on Annex I or IA. This compares the identified hazards to the exposure during the specific tasks to be carried out. Although there is no product upon which to conduct the exposure assessment, sufficient information on the use pattern of the basic substance should be provided by the applicant to demonstrate that they have used the most suitable exposure scenario the assessment.

If the outcome of the risk characterisation does not meet the criteria for Annex IB inclusion, listing on Annex IB is refused. If the inclusion criteria are met, the active substance can be added to Annex IB specifying the necessary conditions for safe use (the entry will be fairly detailed as it will have to define the conditions that would normally put on individual product labels). The structure of the Annex IB inclusion is provided in Table 7.1.

7.5 Discussion

7.5.1 Form and origin of the dossier

It is believed that the range and quality of data available for current basic substances varies widely. Some of the information is in the public domain and other reports are owned by separate parties. In order to provide the required complete dossier, the formation of Task Forces will be the appropriate means. It is also likely that data will be available less frequently than for other active substances. An applicant (or Task Force) wishing to submit a dossier that contains data gaps must provide a justification as to why the data gap need not be filled. Guidance on the content and presentation of these justifications is provided in the TNsG on data requirements. In addition, when data are provided it is acknowledged that it may come from various sources (such as published literature or safety data sheets) and will not always be composed of proprietary study reports.

The nature of basic substances currently in use in some Member States ranges widely. For some substances (for example liquid nitrogen) a carefully constructed justification might address many toxicological endpoints. For other substances, (for example ethanol) a more extensive evaluation of information would be required. This would more closely resemble the assessment of active substances for entry on to Annex I. The extent of the data set required and the acceptability of justifications would have to be assessed by the competent authority on a case-by-case basis.

It is the responsibility solely of the applicant to provide the data, and not of competent authorities (unless they took on the responsibility as they could under the first review regulation 1896/2000). However, it might be possible to adopt an existing evaluation where the substance has been reviewed recently under other EU legislation. This should encourage a consistent approach between the different fields of chemical regulation and avoid duplication of effort in reviewing the same substance twice.

7.5.2 Description of use pattern

An application would need to be accompanied by a sufficient description of how the substance might be used in order to facilitate the risk assessment process. In many cases this would need to be quite detailed and would include the concentration at which the substance is used, the type of user (professional or non-professional) and what protection they might have, the duration and frequency of use, the environmental compartments that will probably be exposed and the potential extent of that exposure, and the means of disposal of the used substance and materials treated with it.

8. Guidance on the application of comparative assessment

8.1 Introduction

The intention of this part of the guidance is to give a more precise description of how comparative assessment shall be performed in practice. The approach for comparative assessment in accordance with Article 10(5) is described here and examples based on current national applications of comparative assessment are presented.

The application of comparative assessment is, when justified, in line with the perspectives and goals of the Directive. The procedure is a tool for risk reduction and, carefully performed, it should lead to a progressive removal or restriction of use of those active substances which pose a risk to health and/or the environment and which may be replaced by others showing significantly less risk. It should also prevent new substances that raise a significant concern when used from unnecessarily entering the market. In addition, the concept of comparative assessment should promote the development of new substances posing lower risks.

The application of comparative assessment should also imply a more efficient review process for the Annex I entries as comparative assessment will enable a qualified ranking of risks within a defined group of substances where one or more substances are considered to give rise to concern.

Comparative assessment can briefly be defined as a procedure to determine whether there is an alternative active substance in Annex I, (IA or IB) intended for the same purpose which:

1. presents significantly less risk to human health or the environment, or both, but in no case an increased risk to the other,
2. can be used for sufficient control of the target organism(s) and which
3. can be used without significant economic or practical disadvantages for the user.

8.2 Conditions for comparative assessment

The indicative examples and criteria presented later are representative conditions for comparative assessment mainly based on a significant difference in risk to humans or the environment. Many of these are also essentially based on the reasoning and criteria of Annex VI. The high level of ambition of the Directive laid down both in the preambles and in the legal text has also been taken into account.

According to the definition of the Article 10(5) i) of the Directive, candidates for comparative assessment are active substances

- ”that, under normal conditions/...../still give rise to concern”.

Active substances that comply with the proposed criteria for unacceptable effects on health or the environment (as defined in Chapters 3.4 and 3.5) shall not, pursuant to the Articles 5 and 10, be included in Annex I. However, there may be active substances meeting these criteria that, for substantiated reasons, will still be allowed for use in authorised biocidal products under restrictive safety conditions and/or for a limited period of time. These substances are obvious candidates for comparative assessment.

Candidates for comparative assessment should also be active substances that, even though fulfilling the conditions for inclusion in Annex I, still give rise to an actual concern. The reason for concern could be the nature of the critical effects (such as sensitisation, corrosivity, neurotoxicity, carcinogenicity, mutagenicity and reproductive toxicity, high toxicity to environmental organisms and bioaccumulation), which, in combination with the use/exposure patterns, imply use situations that cause concern. This is particularly the case when the quantitative assessment shows that the AOEL is exceeded by the exposure estimate when not using personal protective equipment.

The Article 10(5) i) of the Directive further stipulates that when a removal or refusal of an Annex I, IA or IB inclusion in favour of an alternative substance is considered, the alternative must show significantly lower risk to health or the environment. An assessment of the alternative substance shall take place to

demonstrate whether it can be used with similar effect on the target organism and without significant economic and practical disadvantages to the user or not.

Further conditions for a refusal or removal of an Annex I, IA or IB inclusion, related to this document, laid down in Article 10(5(ii)) are:

- the chemical diversity of the active substances included on Annex I should be adequate to minimise the occurrence of resistance in the target organism;
- it should be applied only to active substances which, when used in authorised biocidal products, present a significantly different level of risk;
- it should only be applied to active substances used in products of the same product type (specifically the same purpose; for example an insecticide for professional indoor control of cockroaches);
- it should be applied only after allowing the possibility, where necessary of acquiring experience from use in practice, if it is not already available;
- complete data dossiers are required (a decision cannot be made on a partial assessment);

8.2.1 Need for sufficient control

To secure sufficient control of a target organism, and minimise the development of resistance, the use of a specific active substance or a selection of substances may be needed. The possibility to remove one or more of these substances from the market will then be limited. If one (or more) of these substances give rise to concern, the applicant(s) shall give the full scientific and/or technical justifications for the need of the specific substance(s). If a substance is proven indispensable based on scientific and technical reasons at the time of assessment, it will remain a candidate for comparative assessment.

8.2.2 Definitions

8.2.2.1 Significant difference in risk

A significant difference in risk shall be identified on a case-by-case basis by the competent authorities. The critical endpoints, the criteria for different population subgroups and exposure categories (described in Chapter 3) should be taken into account. Other factors such as the stringency of imposed use restrictions and prescribed PPE may also have to be considered.

For the environment, a factor of 10 between the PEC/PNEC ratios of different active substances is considered a significant difference in risk.

8.2.2.2 Environmental Effects of concern:

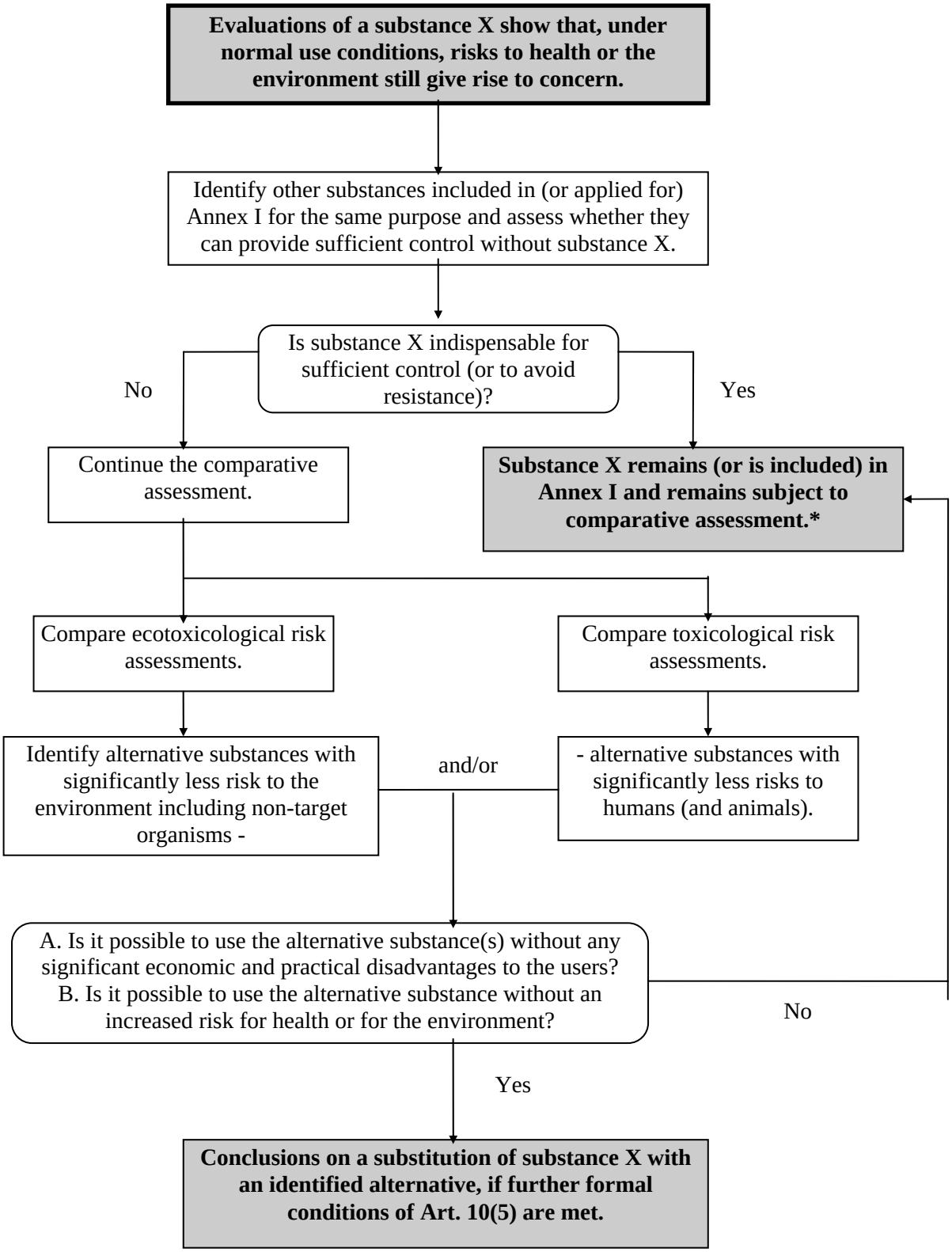
An active substance shows effects of concern if:

- PEC/PNEC ratio < 1 and > 0.1 (the result of the risk assessment indicates a residual probability that adverse effects can occur).

Examples demonstrating cases with identified concerns and differences in risk are given in Section 8.4.

An active substance could be a candidate for comparative assessment if any of the “unless” clauses of the exclusion criteria have been applied when deciding on the entry of the substance on to Annex I or if the use of the substance is restricted within Directive 76/769/EEC.

Figure 8.1



* This should be clearly indicated in the Annex I inclusion

8.2.2.3 Significant practical or economic disadvantages

Significant practical or economic disadvantage to the user is defined as a quantifiable major impairment of working practices or business activity leading to an inability to maintain sufficient control of the target organism. Such a major impairment might be, for example, when no technical facilities for the use of the alternative substance(s) are available or economically feasible.

If a comparative assessment indicates that restrictions/prohibitions of use of an active substance could cause such disadvantage then this will be taken into account in the decision-making process. This situation must be substantiated.

8.3 Procedure

Figure 8.1 outlines the procedure and more details are given below.

8.3.1 When?

Comparative assessment shall be applied in the following situations when the use of an active substance gives rise to (a definable) concern. Care should though be taken not to shift risk from one area to another.

- when assessing existing active substances during the review programme.
- when an active substance already included in Annex I still gives rise to concern and a new active substance submitted for inclusion for the same purpose poses a significantly lower risk for health or the environment;
- when an active substance submitted for Annex I gives rise to concern and can be compared to active substances already listed for the same purpose;
- when new information on a substance in Annex I is available that changes the outcome of the risk assessment demonstrating a significantly increased risk for health or the environment.

8.3.2 How?

Comparative assessment shall be carried out between substances in biocidal products within the same product type and intended for the same purpose.

1. Identify the active substance in the products/areas of use where it gives rise to concern and should therefore be subject to comparative assessment.
2. Consider whether sufficient control of target organisms can be maintained if the use of the substance that gives rise to concern(s) is restricted/prohibited. If the substance is proven to be indispensable or not interchangeable then go to step 5.
3. Compare with available active substances to see if a significant difference in risk is identified. Alternative substances should present significantly less risk to one or more end-points, while at the same time not presenting significantly increased risks for other risk end-points.
4. Consider if a restriction of use of the active substance in question or the use of the proposed alternative substances leads to significant practical or economic disadvantages as justified by the applicant.
5. Conclusions on a removal, refusal or inclusion of the Annex I substance according to further conditions in Article 10(5). A substance that will be included /remain on Annex I even though it gives rise to concern should remain a candidate for comparative assessment.

The identification of a concern shall be clearly explained and the comparison of the outcome of the risk characterisations should be done with expert judgements.

The outcome of the risk characterisation should be compared for the environmental or health risks separately as a comparative valuation of effects in these areas is usually not possible. If the difference in risk is not significant or is unclear, substitution is not justified.

8.3.3 Who?

The comparative assessment should be performed by the rapporteur Member States who have evaluated the substances being compared and flagged possible candidates for comparative assessment.

8.4 Examples

The examples given below are modified from current national application of comparative assessment, adapted to fictitious situations according to the BPD, and will be substituted by real examples from the application of the BPD as soon as these become available.

The examples do not claim to give an exhaustive description of the procedure and implications of Comparative assessment. Moreover, the examples should not be read standing by themselves but in the light of the general conditions stated in Article 10(5) and amplified in Sections 4.1-4.3 of the TNsG.

To ”equate” risk with hazard in the decision process of comparative assessment is appropriate only in cases where the exposure situations, with all relevant factors taken into account, are so similar (or the difference is so small that it is deemed insignificant) that the exposure can be discounted. In other cases crucial differences in physico-chemical properties, dosing and other parameters that may significantly affect the exposure shall be considered in a final comparison of risk.

Possible measures to decrease/eliminate the difference in risk have not been considered in the examples. If the applicant can prove that realistic methods are available to significantly decrease the risk from the substance, these should be given due consideration in the decision process.

The documentation of the substances addressed in the examples is assumed to be sufficient for evaluation, assessment and decision-making in all cases.

Example A

There are eight substances included in Annex I for the same area of use and application methods. The risk assessments show that an exposure to the environment of the active substance or relevant metabolites is not negligible. A concern is identified regarding the bioconcentration factor, BCF (in fish) and persistence in the environment; Substance *A* has a BCF of 100 and is readily biodegradable. Substance *B* has a BCF around 950 and a DT_{50} in water/sediment of 3½ months and the six other substances have BCF of 10-30 and are readily biodegradable.

In this case it is preferable that the six substances with the BCF of 10-30 are used, but it is not clear that substance *A* with the BCF around 100 implies a significantly higher risk compared to the other six substances. However, the risk for the more persistent substance *B* with a BCF of 950 could be assessed as significantly higher compared to the rest of the substances and *B* could therefore be replaced or removed if further conditions are met.

Example B

There are nine substances, already included in Annex I, that are contained in nine different products used for the same purpose, for example as slimicides in paper mill process water.

Seven of the products are classified as skin sensitisers and a qualitative risk assessment does not prove that the risk for sensitisation is negligible. Thus, although all nine substances are included on Annex I, seven of them still give rise to concern and two of them do not. Also, a significant difference in risk is identified.

In this case it could be preferable that only the two not classified products are used. However, for this area of use it is justified by the industry as necessary to have a selection of at least the nine different active substances already on the market to counteract resistance, changing physico-chemical conditions and the fluctuating biological diversity of the target organisms. No alternatives showing significantly lower risk that could replace any of the seven sensitising substances, are available. Thus, the sensitising substances in this case cannot be replaced or removed using comparative assessment due to the need for

sufficient control. The seven substances, however, remain candidates for comparative assessment for the use described in this case.

Example C

A substance is on the market for use as an active substance in products for non-professional use to control micro-organisms in chemical toilets and is subject to assessment in the review programme for existing active substances. For practical reasons regarding dilution factors, such products are delivered as rather concentrated in-can solutions. The concentration of the active substance leads to a product classification of harmful if swallowed, irritating to skin and risk of serious damage to the eye. The handling of the products is open and manual and considered frequent and exposure to eye and skin is possible. Due to its non-professional use, personal protection such as safety glasses cannot (normally) be required. Thus, an obvious concern is identified.

Another substance for the same use is assessed at the same time. It does not fulfil the criteria for classification or other grounds for concern and, hence, a significant difference in risk is identified. This alternative substance is proven to give sufficient control and does not lead to a significantly higher economic or practical burden to the users as the prices and application methods are comparable. The latter but not the first substance should then be included in Annex I for use against micro-organisms in chemical toilets if the remaining conditions for refusal based on comparative assessment are met.

Example E

There are two substances used on the market for insect control in empty premises, such as transport containers. They both are active in the gaseous phase, possibly by a volatilisation step. The human toxicological profiles of both substances are very different as indicated by both the classification and the risk assessment:

- one substance is classified with rather severe symbols as T or C, the other substance is unclassified;
- the human health risk is very different for both substances, especially for the workers concerned and maybe for the bystanders too. The heavily classified substance requires, on the basis of the risk assessment, a rather sophisticated health protection regimen, such as elaborated working procedures, minimum bystander distance requirements or a burdensome personal protection regime.

The difference in health risk justifies the inclusion of the less hazardous substance in Annex I, and the exclusion of the severely classified substance, unless special uses for this substance should remain for which a very restricted Annex I inclusion can then be considered.

9. Assessment of the efficacy at Annex I/IA listing stage

9.1 Purpose of this guidance

The objective of this chapter is to provide guidance on efficacy during the evaluation of the application for Annex I/IA listing of an active substance.

> Efficacy is described in the Directive (Annex IIB [5.10] and Annex VI, paragraph 51) as the ability of a biocidal product to fulfil the label claims for it on the proposed product label. It is clear therefore that the emphasis for the assessment of biocidal efficacy rests at the product level and is closely related to the label claims made for that product.
>
> Full assessment of efficacy is conducted on applications for product authorisations at a national level (that is, within individual Member States) and will be conducted according to the detailed principles set out in the TNsG for product evaluation.

However, for the purposes of inclusion onto Annex I, some assessment of the inherent activity of both the candidate active substance and an accompanying product is required.

9.2 Efficacy data requirements for the active substance

The data requirements on the efficacy of an active substance are listed in Annex IIA [5.1 – 5.5] of the Directive. They are summarised below and are further amplified in the TNsG for data requirements.

- Function, for example fungicide, rodenticide, insecticide, bactericide
- Organism(s) to be controlled and products, organisms or objects to be protected
- Effects on target organisms, and likely concentrations at which the substance will be used
- Mode of action (including time delay)
- Field of use envisaged

9.2.1 Nature of the available data

There is a need to recognise the differences in the data required for a candidate active substance and that required for a formulated biocidal product.

Three types of efficacy data may be considered when evaluating an efficacy data package. These are laboratory studies, simulated use studies and field studies (further descriptions and examples for these can be found the TNsG on product evaluation). Laboratory studies are the most appropriate for the assessment of the inherent efficacy of an active substance.

Data generated from simulated use tests and field studies are unlikely to be available for the active substance. Such data are designed to test the use of a product in situations that mirror the intended field of use and the test materials are applied in accordance with proposed label directions for a biocidal product. These data together with simple laboratory data are likely to be provided to support applications for product authorisations (see Chapter 6 of TNsG on product evaluation).

9.2.2. Laboratory studies

The efficacy of an active substance may be demonstrated by a “screening” laboratory test using either the undiluted active substance, the active substance in a solvent carrier or the active substance presented in a simple formulation. Test data are designed and intended to establish the innate biocidal efficacy of the substance against specific organisms under carefully controlled and reproducible conditions and may include dose-response tests. For example, such tests could include:

- Rate of Kill tests or Minimum Cidal Concentration tests (suspension tests) to demonstrate bactericidal activity against gram negative bacteria (such as *Escherichia coli*, *Pseudomonas aeruginosa*) and gram positive bacteria (such as *Staphylococcus aureus* and *Bacillus subtilis*) at a range of dose levels and exposure times (for example PT11 or PT12)
- Direct cuticle application of an active substance in a simple solvent to Oriental cockroaches (*Blatta orientalis*) to assess contact toxicity (for example PT 18, contact residual surface spray against cockroaches)
- Active substance present in a range of concentrations in flea-rearing medium containing cat flea (*Ctenocephalides felis*) eggs (PT18, residual surface spray against fleas)
- Saw-toothed grain beetle (*Oryzaephilus surinamensis*) introduced into petri dishes containing a surface coating of a dust formulation for a defined period of time (PT18, contact dust – stored product insects)
- Miniblock (block/agar or block/soil) test screens using the active substance in a carrier solvent or simple formulation exposed to wood-rotting basidiomycetes fungi via a suitable culture medium (PT8, wood preservatives – fungicides)
- *In vitro* toxicity screening tests to demonstrate activity as an anti-weed or anti-animal agent (PT21, antifouling products)
- General surface biocide – application of a range of concentrations of the active substance absorbed onto assay discs applied to a suitable nutrient agar medium seeded with either fungi or algae and following a suitable incubation period, the determination of the zone of growth inhibition (PT10, Masonry preservatives)

9.2.3 Evaluation of the efficacy data

On the basis of the laboratory data presented in support of the Annex IIA requirements [5.1-5.5] the Rapporteur Member State should conclude whether an active substance possesses a sufficient level of biocidal efficacy (for example bactericidal, fungicidal, insecticidal) at the recommended concentrations for use.

9.3 Accompanying biocidal product

Each application for inclusion on Annex I or Annex IA must contain a dossier for at least one biocidal product (Article 11 (1) ii). Furthermore an active substance can only be listed on Annex I or Annex IA if at least one product meets the requirements of Article 5(1) b)[5].

9.3.1 Efficacy data requirements for the biocidal product

The efficacy data requirements for a biocidal product are listed in Annex IIB [5.1-5.8 and 5.10-5.11]. They are summarised below and are further amplified in the TNsG on data requirements and the TNsG on product evaluation.

- Product type and field of use envisaged
- Method of application including description of system used
- Application rate and if appropriate, the final concentration of the biocidal product and active substance in the system in which the preparation is to be used, such as cooling water, surface water, water used for heating purposes
- Number and timing of applications, and where relevant, any particular information relating to geographical variations, climatic variations, or necessary waiting periods to protect humans and animals

[5] A biocidal product may contain one or more active substances. In the first case a more in-depth evaluation of the efficacy of the active substance is possible.

- Function, for example fungicide, rodenticide, insecticide, bactericide
- Pest organism(s) to be controlled and products, organisms or objects to be protected
- Effects on target organisms
- Mode of action (including time delay)

Efficacy data

- The proposed label claims for the product and efficacy data to support these claims, including any available standard protocols used, laboratory tests, or field trials, where appropriate
- Any other known limitations on efficacy including resistance

9.3.2 Nature of the available data

In order to substantiate the efficacy of a biocidal product, it is necessary to demonstrate either through testing the biocidal product, or by presenting data generated on a product within the meaning of frame formulations, that the product is efficacious when used in accordance with the label instructions.

Efficacy test data submitted for evaluation will usually comprise a combination of one or more of three types of studies: laboratory, simulated use tests or field studies.

The TNsG on product evaluation provides more detail on the types of test available and experimental design.

Test guidelines

Annex VI (paragraph 52) states that testing should be carried out according to community guidelines if these are available and applicable. However it also recognises that where appropriate, other methods can be used such as:

- ISO, CEN or other international standard method
- National standard method
- Industry standard method (accepted by competent authority)
- Individual producer standard (accepted by competent authority)
- Data from actual development of the biocidal product (accepted by competent authority)

A useful list of available efficacy test methods for biocidal product types has been collated and referenced by the OECD and is available on its website ***(www.oecd.org/ehs/Biocides/efficacy-overview.htm).***

Note The lack of standardisation and method validation in many cases requires the competent authority to assess efficacy data on their own merits (whether the test be an EN, ASTM, AOAC, a national standard or "non-standard" data) when considering efficacy data against label claims. Assessment of individual studies or groups of studies should, therefore, be considered in terms of: robustness; quality; adequacy; completeness. Further guidance on these aspects with regard to efficacy are discussed in the TNsG on product evaluation.

9.3.3 Evaluation of available data for the accompanying product(s)

With regard to the assessment of the efficacy of the accompanying product(s) this will require the evaluation of the summary of the Annex IIB dossier of the candidate product(s) to enable the Rapporteur Member State to satisfy itself that these data provide sufficient evidence that the proposed product(s) is(are) sufficiently effective (Article 10 referring to Article 5).

An evaluation of the summary dossier of the Annex IIB data supplied in support of the efficacy of the product should address the following:

Product type

Information on the proposed product type for the biocidal product and the proposed product label should be provided.

Target organisms/spectrum of activity

The range of target organisms for which claims are made and from which principal organisms representative of the biological challenge can be selected should, wherever possible, be identified on the label. It follows that efficacy claims within a particular product type may often be very specific in nature with respect to target organisms or alternatively they can be very broad. In the case of broad label claims it is not always appropriate or realistic to include on the product label and associated literature the entire range of organisms against which the product is intended to be used.

Mode of action/effects on the target organism(s)

The available data must be relevant to the claimed mode of action or intended effect on the target organisms.

Area of Use/Site of Application

A detailed description of the use patterns proposed for the product must be provided. In addition the available data must reflect the intended use pattern/area of use for the candidate product.

Directions for use

The data (and proposed product label) should also include the information that defines the way in which the biocidal product is handled and applied and typically should encompass the following:

- Preparation of the formulation for use
- application method/delivery technique (including details of dilution and diluent, if appropriate);
- dose rate/treatment frequency;
- other information/limitations pertinent to the efficacy of the candidate product (for example details whether delivery of the product is by means of a specialised device or whether the product enclosed within a particular container such as a bait station).

The Rapporteur Member State should ensure that the appropriate information relevant to the application has been provided.

9.3.4. Overall evaluation of efficacy data for accompanying product

The proposed criteria are essentially based on the principles and reasoning outlined for efficacy assessment in the TNsG on product evaluation. The Rapporteur Member State should ensure:

- that the summary dossier for the accompanying product is complete, in other words that there are no apparent major gaps which might prevent a decision being made with regard to the efficacy of the product for its intended uses.

- Adequacy: the appropriateness of the submission, that is that the data are relevant to the intended label claims and use patterns for the accompanying product

9.4. Annex I/IA listing decision

If the Rapporteur Member State is satisfied that:

- the assessment of biocidal activity of the candidate active substance demonstrates that the active substance has a sufficient level of efficacy against the target organism(s) avoiding unnecessary suffering of target organisms; and
- the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious,

then the Rapporteur Member State can recommend inclusion of the active substance on to Annex I and/or Annex IA with respect to efficacy.

10. Assessment for the potential for resistance to the active substance

Annex IIA of the Directive requires information on the occurrence and possible development of resistance, and appropriate resistance management strategies, for chemical active substances.

- Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (Annex IIA, [5.7])

10.1 Introduction

Evaluation of resistance to an active substance must be done on a case-by-case basis.

A number of factors need to be considered:

10.1.1. Resistance

This term refers to a genetically inherited characteristic, which cannot be acquired during the lifetime of the organism. It may be defined as a significant loss of performance due to the ability of the target organism to withstand the effects of normally applied concentrations of the biocide. The term 'resistance' is often used loosely, and incorrectly, to explain treatment failure which may be attributed to inadequate treatment, behavioural resistance, target pest tolerance or other contributory factors.

The level of resistance of a particular genetic strain can be quantified in laboratory studies by the *resistance factor* (*or ratio*), which is the number of times the amount of biocide given to a resistant strain has to be increased above the normal dose to achieve the same effect as that dose in the normal strain. Cross-resistance, where target organisms resistant to one active substance are also resistant to others to which they have not been previously exposed, can also occur.

The level of resistance, its geographical spread and frequency of occurrence can all change with time for any one biocide (indeed there can be a wide variation in resistance levels across a single country). It should be noted that some biocides will continue to have a commercial usefulness even at reduced levels of efficacy towards a particular target species.

10.1.2. Behavioural resistance

Treatment failure as a result of behavioural resistance can be displayed in a number of ways, such as bait preference and neophobia. Behavioural resistance does not involve actual systemic resistance to a biocide's action, and it can be reversible.

An example of bait preference is the altering of feeding habits by ants from protein to carbohydrate baits. Obviously if bait preference changes or is different depending on the change in the life cycle of the pest, then the biocidal product will have varying degrees of efficacy.

Neophobia or "new object reaction" is exhibited by some rodent species, and refers to individuals who avoid a new object (such as a bait) placed in the environment until they become used to it. As a result the individual may only take a small, sub-lethal amounts of bait, and may consequently avoid the bait if it learns to associate it with an unpleasant response.

Some of these behavioural aspects can be anticipated and tested through experimental design when biocidal products are being developed but others can only be overcome by the expert use of the biocide by trained professional operators.

10.1.2. Tolerance

Tolerance can be defined as the ability of an organism to withstand the effect of a normally lethal dose of a biocide by ingestion of increasingly large sub-lethal doses over a short period of time. An example of this has been reported for the use of alphachoralose against mice.

Tolerance is different from resistance because if the normal lethal dose is administered in single dose the individual will die (resistant individuals will not)

It can be seen from the above points that the potential for actual resistance must be identified to establish that a resistant management strategy is required.

Where relevant the rapporteur Member State should evaluate the extent and nature of existing resistance to an active substance by the target organism, and anticipate its development, so that a balanced Annex I inclusion decision can be made.

10.2. Types and availability of data

Whilst data should be relevant to the target species, requirements must be flexible because of the variable nature of resistance. Evidence of resistance may come from:

- Laboratory studies specifically addressing resistance (including simulated use and dose response tests) such as efficacy studies on strains that are known to be resistant to the active substance. Baseline studies should be presented[6]. For vertebrates there may be specific, non-lethal methods of resistance assessment such as blood-clotting tests for anticoagulant rodenticides; or
- field studies (in which data are generated using the biocidal product under actual service conditions and in the manner described on the product label)[7].

Field observations may also be provided as additional evidence.

Resistance data will usually be available for existing active substances following review for Annex I inclusion, but there are unlikely to be any data for new active substances. However the rapporteur Member State may be able to make a decision based on relevant information on products containing an active substance from the same chemical class with a similar mode of action.

10.3. Evaluation

10.3.1. General Principles

Available data should include, where relevant, all information necessary to allow a reasonable evaluation of target organisms resistance to a biocidal active substance at the recommended in-use concentrations when used in an appropriate way to the intended use patterns. The rapporteur Member State competent authority should perform the evaluation according to the general principles set out in Chapter 6 of the TNsG for product evaluation with regard to

- Test objective
- Study content and methodology;
- Acceptability of the method
- Robustness
- Quality assurance
- Completeness; and
- Adequacy (its reliability and relevance to the proposed use)
- field data from any source should be taken into account

Expert judgement is needed for proper interpretation of resistance data. Apparent resistance may also be caused by behavioural factors, such as neophobia. For this reason, the rapporteur Member State may need evidence to show that other possible causes of treatment failure have been excluded.

[6] Baseline studies are studies of the level of resistance without the organism ever having been in contact with the active substance.
[7] EPPO guideline 213 (Resistance) is relevant here.

10.3.2. Cross-resistance

The issue of cross-resistance will need to be assessed when the active substance under review has a similar mode of action (or belongs) to a particular chemical class which is known to have resistance problems in particular situations (for example pyrethroids used to control fly problems in intensive animal rearing units). Relevant information should be provided in meeting the Annex IIA data requirements.

10.3.3. Development of Resistance

As well as assessing the immediate likelihood of resistance, the rapporteur Member State must, where relevant, evaluate the possibility of the development of resistance to the active substance by the target organism. However, it is likely that resistance development will only become evident as products are used. The ability of laboratory tests to predict such development can be low, because they often show only the symptoms of resistance rather than the underlying cause. Factors that may encourage the development of resistance are related to the lifestyle of the target organism and the proposed use pattern of the biocidal product. Examples of such factors include:

- Active substances acting by a "one site" mechanism (as opposed to a "multi-site" mechanism) are more liable to lead to resistance;
- Target organisms with rapid breeding cycles (resulting in many generations per year)
- Pest infestations that are confined in some way (where resistant individuals are unable to disperse and so remain localised);
- Use of the biocide over large areas and/or for long periods with frequent application rates (creating a continual evolutionary selection pressure on the target population);
- Use of a number of biocidal products against the same pest that contain either the same active substance or active substances with similar modes of action; and
- Use of active substances which expose "multi-generations" as opposed to single generations to one application is more liable to cause resistance.

10.4. Resistance management strategies

Where resistance is considered likely to be a significant problem for a particular active substance an overall management strategy to help delay the onset or likelihood of development of resistance (or cross-resistance) must be developed.

10.4.1. What is a resistance management strategy?

The immediate aim of resistance management is to prevent or retard the development of resistance to a given biocidal active substance while permitting its continued use, as far as possible without being counterproductive. The ultimate aim is to reduce or eliminate the adverse consequences of resistance. The central concept is that this can be done more effectively and cost-efficiently by integrated, cohesive and systematic action than by the normal, default option in which all the parties involved improvise their own ways of addressing the problem. In this sense the approach has much in common with IPM (integrated pest management), and uses the same wide range of techniques.
Where relevant, contact should be sought with the International Resistance Action Committees (RACs)[8]

Without question, the deployment of a suitable range of alternative active substances is necessary for the management of resistance and to prolong the useful lifespan of those active substances to which resistance has become a problem. The following practices are among a number of the more feasible options available to retard the onset of resistance, where resistance is identified as a significant problem.

- Not using the biocidal active substance in isolation. Consideration of application with one or more biocides of a different type (biocidal diversity), or as one component in a rotation of different treatments

[8] The RACs give advice on the use of pesticides. It will often be easy to broaden their field of work to biocides, such as in the cases of fungicides and insecticides which are used both in pesticidal and biocidal applications.

- Restriction of the number of treatments applied, and application only when strictly necessary
- An increase in the concentration of the currently used biocidal active substance for a short time to eradicate the less susceptible strains
- Use of non-chemical control techniques, where available
- A switch to another biocidal active substance to which resistance rarely or never develops
- Ensuring complete eradication with a specific biocide and resuming the current treatment
- Maintaining uncontrolled, susceptible populations *in refugia* (in isolated areas) from which emigration can occur

Note Supplementary strategies may be required later for individual products (see TNsG for product evaluation for further information).

10.4.2 Resistance Monitoring

When resistance has been detected and a resistance management strategy instituted, monitoring is necessary to determine its effectiveness. Some form of surveillance, such as questionnaire surveys, investigation of reports of inefficiency, or some other form of feedback reports, may also help towards early detection of new cases of resistance.

10.5 Decision making

If assessment for the potential for development of resistance concludes there is not a significant concern then the candidate active substance can be recommended for inclusion onto Annex I or Annex IA.

Where resistance is considered to be a significant problem for a particular active substance at the Annex I inclusion stage an overall management strategy to help delay or reduce the likelihood of development must be developed to minimise any consequences. In such cases this may involve the restriction or modification of subsequent product authorisations containing the active substance or even refusal of an authorisation.

11. Decision on the inclusion of an active substance on to an annex of the Directive

11.1 Decision-making process

The rapporteur competent authority should collate all the relevant information from the different parts of the active substance evaluation and form a proposal on whether entry on to an Annex should be recommended. Given the dependence of product authorisation upon the inclusion of the active substance in an annex (including the conditions associated with the entry (Article 5 (1, a)), the decision-making process shall take into account all aspects of the assessment, including those specified in Annex VI of the Directive (paragraph 63).

The steps in the decision making process can be summarised as follows:

1. The process begins with a comparison of the results of the risk assessment with the criteria listed in this document for the relevant annex. When an active substance does not meet the criteria, it should normally not be listed on any annex of the Directive.
2. The active substance should be efficacious at least at the concentration proposed in the representative product(s) and there should be no unresolved concerns regarding resistance.
3. All other required information (such as administrative information or analytical data) is available and acceptable.
4. The benefits of products containing the active substance should be considered. Especially in cases where there are concerns about the acceptability of the risks, the need for and benefits of biocidal products containing the substance should be considered carefully and weighed against the acceptable level of risk.
5. Comparative assessment: Where comparative assessment has been carried out, the inclusion of an active substance on to an Annex will depend upon the outcome of that assessment. If other active substances are listed on an annex for the same purpose and their use causes significantly less risk to humans or the environment (given acceptable efficacy), then entry on to an Annex may be refused. However, the refusal will have to be balanced against the need for the active substance (including chemical diversity of active substances available) and any significant economic or practical disadvantage that would result from the restriction or refusal of the use of the active substance. If the comparative assessment leads to a decision to replace a listed active substance, completely or for a specific use area, by an alternative creating less risk, the substance shall be removed from Annex I, IA or IB at the latest 4 years after the decision (Article 10 (5, iii)).
6. Product data: Article 10 of the Directive states that an active substance shall be included in an annex (other factors permitting) if “it may be expected” that biocidal products and commodity (basic) substances will comply with the respective definitions in Article 2(1) and will fulfil the conditions in Article 5(1) b), c) and d). The product dossiers submitted with the active substance dossier (in the cases of Annex I and IA) must therefore demonstrate this to the Standing Committee’s satisfaction.
7. Precautionary principle: The Precautionary Principle (COM (2000)1 final of 2.2.2000*)* should be applied in the decision making-process for inclusion of an active substance on to an annex, as well as reflected in the conditions and restrictions to be associated with the inclusion.

The proposal for the decision should be described in Document I of the Competent Authority’s report (see TNsG on Practicalities) in sufficient detail for the reader to follow how the proposal was reached.

11.2 When an active substance is not suitable for listing on Annex IA

If an application has been made for the entry of an active substance on to Annex IA but it is found not to fulfil the criteria for entry on to that Annex, it may be considered for entry on to Annex I.

11.3 Inclusion on to an Annex

A schematic description of the entry into an Annex is given here: If an active substance is accepted for entry on to Annex I or IA the conditions for its use in biocidal products should be listed as in Appendix 11.1. The Competent Authority shall send the completed evaluation to the Commission who "will prepare a proposal" in the form of a Decision for inclusion or non-inclusion in Annex I for the Standing Committee to decide upon within 12 months (Article 11(4)). Proposals in favour of inclusion in an annex can be expected to include a draft annex entry. Examples of how Annex I entries might appear are given in Appendix 11.2.

There may be cases where a certain use of an active substance is proven to be of utmost importance (that is the risk when not using the substance takes priority over the risk predicted by using the substance, for example when no alternative means of adequate biocidal control exist and where there is an imminent public interest in the availability of this substance). In these exceptional cases the benefit may take precedence over the risk and the substance would be allowed (if the other factors listed here are met) for Annex I inclusion, for that specific purpose. In these cases a detailed risk benefit analysis should be submitted.

11.4 When an existing active substance is unacceptable for inclusion on to any Annex

If an existing active substance is found unacceptable for entry on to any Annex it is proposed that it should be subject to limitations or phase-out schemes by an appropriate Community legal act. The extent of the limitations and the length of a phase-out scheme will depend upon the level of concern and the need for the continued use of the active substance while alternative means of biocidal control are obtained.

12. Background documents

- Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market. *Official Journal of the European Communities*, **1998**, L123. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Commission Regulation (EC) No 1896/2000 of 7 September 2000 on the first phase of the programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council on biocidal products. *Official Journal of the European Communities*, **2000**, L228. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Technical Guidance Documents in Support of the Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and the Commission Regulation (EC) 1488/94 on Risk Assessment for Existing Substances. In press as *Commission Publication*, **1996**. *Office for Official Publications of the European Communities, L-2985 Luxemburg*. UNDER REVISION TO INCLUDE BIOCIDES
- Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. Official Journal of the European Communities. *Official Journal of the European Communities*, **1991**, L230. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Development of a concept for environmental risk assessment of biocidal products for authorisation purposes (BIOEXPO). UBA Research Project No. 106 01065, Final Report January 1998. web page: http://ecb.jrc.it/biocides/
- CJ van Leeuwen, J.L.M. Hermens, Risk assessment of chemicals. An introduction. Kluwer Academic Publishers, 1995
- Directive 92/32/EEC of 30 April 1992 amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations, and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities*, **1992**, L154. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- EC (1994) Commission Regulation (EC) 1488/94 laying down the principles for the assessment of risks to man and the environment of existing substances in acc. with Council Regulation (EEC) 793/93, *Official Journal of the European Communities*, **1994**, L161. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Council regulation (EEC) 793/93 of 23rd March 1993 on the evaluation and control of the risks of existing substances. Official Journal of the European Communities. 1993. L84. Office for Official Publications of the European Communities. L-2985 Luxembourg.
- Council Directive (EEC) 67/548 of 27 July 1967 on the approximation of the laws, regulations and administrative provisions relating to classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities*, **1967**, L196. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Council Directive 75/440/EEC concerning the quality required of surface water intended for the abstraction of drinking water in the Member States. *Official Journal of the European Communities*, **1975**, L375. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Council Directive 80/778/EEC of 15 July 1980 relating to the quality of water intended for human consumption. *Official Journal of the European Communities*, **1980**, L229. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. *Official Journal of the European Communities*, **1998**, L330. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.

- Directive 1999/45/EC of the European Parliament and Council of the 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. *Official Journal of the European Communities*, **1999**, L200. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- Council Directive 81/851/EEC on the approximation of the laws of the Member States on Veterinary Medicinal products. *Official Journal of the European Communities*, **1981**, L317. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- EC (2001 a): Guidance for the setting of acceptable operator exposure levels (AOELs) Draft guidance document (7531/VI/95 rev.6 of 10/09/2001, DG SANCO.
- EC (2001 b): Guidance for the setting of an Acute Reference Dose (ARfD). Draft guidance document (7199/VI/99 rev. 5 of 05/07/2001), DG SANCO.
- UK Guidelines on the efficacy data requirements for approvals of non-agricultural pesticides (D. Dillon, Health and Safety Executive, Bootle, UK).
- Comité European de Normalisation, CEN
- OECD web page for Biocides, http://www.oecd.org//ehs/Biocides/
- Council Directive 76/769/EEC on the Restrictions in Marketing and Use of dangerous substances and preparations. *Official Journal of the European Communities*, **1976**, L398. *Office for Official Publications of the European Communities, L-2985 Luxemburg*.
- European Chemicals Bureau web page at http://ecb.jrc.it/
- "Development of Emission Scenario Documents for 23 Product Types. State of the Art report" by university of Dortmund (Germany). Can be downloaded from the ECB web page.
- POP convention: http://irptc.unep.ch/POPS/site_map.htm/ finding the document number UNEP/POPS/INC.5/7
- FAO/WHO, 1994: Pesticide Residues in Food – 1994, Report of the JMPR, FAO Plant Production and Protection Paper 127, FAO Rome.
- FAO/WHO, 1998: Pesticide Residues in Food – 1998, Report of the JMPR, FAO Plant Prodcution and Protection Paper 148, FAO Rome.
- Technical Notes for Guidance on Data Requirements, on the ECB home page under Biocides in the 'documents'.
- WHO, 1989: WHO Guidelines for Predicting Dietary Intakes of Pesticide Residues. Report prepared by the Joint UNEP/FAO/WHO Food Contamination Monitoring Programme in collaboration with the Codex Committee on Pesticide Rsidues, World Health Organisation, Geneva.

Annex I: Proposed structure for Annex I and IA entries

1. Identity

IUPAC nomenclature:
CAS-name (if different):
CAS No:
EC No:
Other numbers (if available, specification):

2. Particular conditions

2.1 Purity of the active substance
(And identities and maximum levels of impurities where necessary.)

2.2 Product type

The names and numbers of the product types (as defined in Annex V of the Biocidal Products Directive) for which risk characterisations were acceptable. Information on the following sub-points for each product type separately.

Efficacy

- Target organisms
- Articles or organisms to be protected

Use patterns, user categories

- Maximum content in biocidal products
- Frequency and duration of use (where necessary)

2.3 Conditions on particular uses:

2.4 Other conditions regarding the individual life-cycle of the active substance (for example disposal)

2.5 Future candidate for comparative assessment. If yes please give the reasons.

...

3. Expiry date of the inclusion