Technical Notes for Guidance

on the assessment of technical equivalence of substances regulated under Directive 98/8/EC

These Technical Notes for Guidance were adopted during the 29th meeting of representatives of Members States Competent Authorities for the implementation of Directive 98/8/EC concerning the placing of biocidal products on the market (28-30 May 2008)

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Contents

1. Introduction

As a general principle for the same active substance the level of hazard posed for health and environmental protection must be comparable for different sources of the substance. If the hazard is considered to be greater for the new source than the reference source, then an appropriate risk assessment should be conducted for the new source to determine if biocidal products containing the substance will fulfil the safety requirements laid down in Article 5 of Directive 98/8/EC.

This guidance document is intended to establish harmonised criteria and processes for assessing the equivalence of different sources of a substance versus the reference source. It will be used by Member States for assessing the equivalence of different sources during the evaluation for Annex I inclusion as well as during the authorisation process.

This paper does not address:

- Active substances that are micro-organisms
- UVCB substances (Substances of Unknown or Variable composition, Complex reaction products or Biological materials)
- Polymers

This paper applies to active substances, which have the same identity, in accordance with the rules established within the context of REACH[1].

2. Legal basis

The legal basis for this guidance document is Directive 98/8/EC.

3. Approach

In this document, a two-tiered approach is proposed in order to assess the equivalence of different sources of the active substance.

Tier I consists of the evaluation of analytical data. If equivalence can be ascertained from these data the Tier II assessment is not necessary.

If equivalence can not be established on the basis of the Tier I data, further consideration is necessary which may lead to specific requirements as indicated under **Tier II**.

4. Definitions

Substance (REACH Regulation)

A chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.

[1] See Guidance for identification and naming of substances under REACH (ECHA, 2007).

Active substance (Directive 98/8/EC)

A substance or micro-organism including a virus or a fungus having general or specific action on or against harmful organisms.

Active substance as manufactured

The active substance in its natural state or obtained by any production process, including any additive necessary to preserve the stability of the product(s) and any impurity deriving from the process used but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.

Constituent[1]

Any single species present in a substance that can be characterised by its unique chemical identity.

Main constituent[1]

A constituent, not being an additive or impurity, in a substance that makes a significant part of that substance and is therefore used in substance naming and detailed substance identification.

Mono-constituent substance[1]

As a general rule, a substance, defined by its composition, in which one main constituent is present to at least 80% (w/w).

Multi-constituent substance[1]

As a general rule, a substance, defined by its composition, in which more than one main constituent is present in a concentration ≥10% (w/w) and <80% (w/w).

UVCB[1]

Substances of Unknown or Variable composition, Complex reaction products or Biological materials, also called UVCB are substances that cannot be sufficiently identified by their chemical composition, because:

- The number of constituents is relatively large and/or
- The composition is, to a significant part, unknown and/or
- The variability of composition is relatively large or poorly predictable.

Polymer (REACH Regulation)

A substance consisting of molecules characterised by the sequence of one or more types of monomer units. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units. A polymer comprises the following:

(a) a simple weight majority of molecules containing at least three monomer units which are covalently bound to at least one other monomer unit or other reactant;

(b) less than a simple weight majority of molecules of the same molecular weight.
In the context of this definition a "monomer unit" means the reacted form of a monomer substance in a polymer.

Equivalence

Is the determination of the similarity of the chemical composition and hazard profile of a substance produced from different sources. If the substance from the new source presents a similar chemical composition and a similar, or lesser hazard, compared to the substance of the reference source, the new source can be considered equivalent to the reference source.

Reference source

The source on which the initial risk assessment was based.

In the context of this document **different sources** are intended to cover cases where, due to a change related to the manufacture of a substance, its chemical composition could be altered. The following cases are in particular covered:

- When the active substance comes from a new/different manufacturer.
- When there is a change of the manufacturing location, and/or addition of one or more alternative manufacturing locations.
- When there is a change in the manufacturing process (change in solvents, reactants, equipment, purification process) and/or quality of starting materials.

Impurity[1]

An unintended constituent present in a substance as produced. It may originate from the starting materials or be the result of secondary or incomplete reactions during the production process. While it is present in the final substance it was not intentionally added.

Significant impurity

An impurity is regarded as significant if it occurs or potentially occurs in a quantity ≥ 1 g/kg in the substance as manufactured. The impurity should be chemically identified if technically possible and included in the substance specification, with stated maximum concentration. A significant impurity may be considered relevant or non-relevant depending, in particular, on its known toxicological and eco-toxicological properties.

Relevant impurity/additive

An impurity/additive considered being of toxicological and/or eco-toxicological relevance.[2,3]

Additive[1]

A substance that has been intentionally added to stabilise the substance.

[2] An impurity may be relevant even if it presents in the substance < 1 g/kg (e.g. dioxine).
[3] Relevant impurities should be chemically identified, if technically possible, and included in the technical specification, with stated maximum concentrations.

5. Evaluation of equivalence of sources of the substance (Tier I)

5.1. Data requirements

In order to establish equivalence the following information is required for each new source of the substance:

- Applicant (name, address, etc.)
- Manufacturer (name, address, location of plant)
- Chemical name (IUPAC and CAS nomenclature) and Synonyms
- EC- and CAS-number (if allocated)
- Molecular and structural formula, molecular mass
- Method of manufacture
- Specification of the purity of the constituent(s) in g/kg
- Identity of all impurities and additives and their maximum content in g/kg
- Analytical profile of the substance of at least five different representative batches
- Validated methods for the analysis of the substance as manufactured[4].
- Limit of Quantification for significant and relevant impurities

5.2. Evaluation process

The evaluation should be based on the dry technical material. In case the substance is unstable, the technical material as manufactured should be considered instead.

For the evaluation of equivalence of different sources vs. the reference source, the following criteria should be considered in the Tier I approach. If all of the following conditions are met, the new source is deemed to be equivalent to the reference source and no further consideration is needed:

- The minimum degree of purity obtained with the new source is equal or higher than the one obtained with the reference source; and
- In case of a multi-constituent substance, each main constituent remains in the 10-80% range and the concentration of each main constituent does not deviate by more than 5% absolute or 10% relative, whichever is larger; and
- No new impurity or additive is present; and
- The limit of each relevant[5] impurity or additive is not exceeded; and

[4] The s*ubstance as manufactured* includes all the impurities and additives

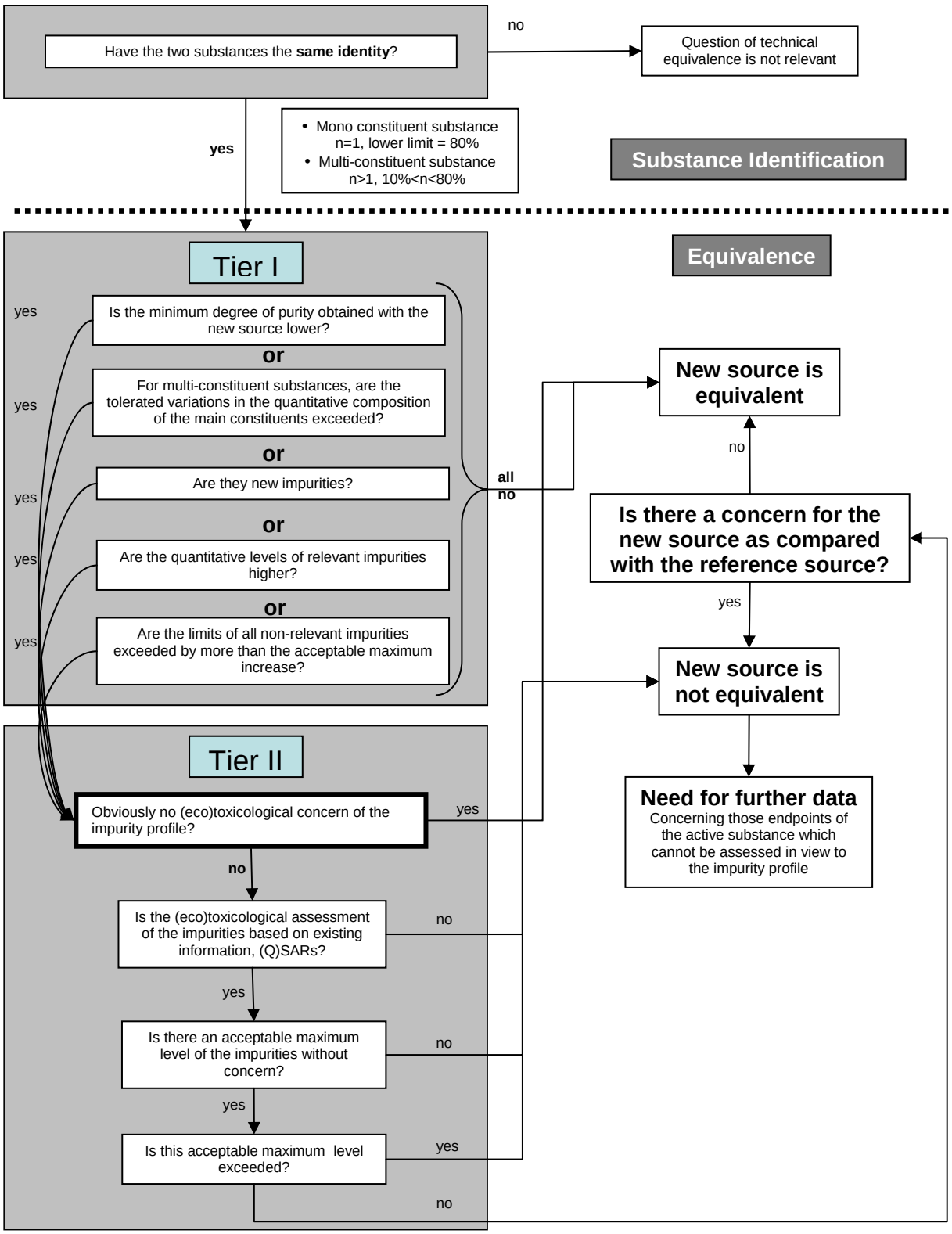
[5] To establish if a new impurity is of toxicological/ecotoxicological concern or not it will require toxicological/ecotoxicological input.

- The limits of all non-relevant impurities as certified on the basis of a 5-batch analysis for the reference source, are not exceeded by more than the following levels:

Limits of non-relevant impurities in the reference technical specifications	Acceptable maximum increase
≤ 6 g/kg	3 g/kg
> 6 g/kg	50 % of the certified limit

If one of these conditions is not met, equivalence between the two sources cannot be established based on Tier I criteria alone. Then it is necessary to move to Tier II and to assess whether the altered minimum purity or impurity profile results in an unacceptable increase of hazard of the new source as compared to the reference source.

Table I: Decision making tree on the equivalence of sources



6. Evaluation of equivalence of sources of the substance (Tier II)

6.1. Toxicity

6.1.1. Data requirements

The evaluation should mainly rely on information that is already available. Only when there are clear concerns that could impact adversely on the hazard assessment of the substance should further animal testing be conducted. The use of expert judgement is important when assessing toxicological data. The following guidance should therefore be used as starting point for decision-making, which should be done on a case-by-case basis. Rigid adherence to guidance may not be appropriate in all cases.

6.1.2. Evaluation process

The objective of the evaluation is to identify whether there is an unacceptable change in toxicity for the new source as compared to the reference source as a result of:

- The presence of any new relevant impurities or additives in the new source compared to the reference source and /or

- Increased levels of relevant impurities or additives that are present in both the new and reference sources

In the absence of appropriate test data for the reference source, an unacceptable increase in toxicity would generally be the case if either reference values such as MOE, ADI, AOEL, or ARfD would have to be lowered or a more severe hazard classification would result. If appropriate data for the reference source are available, the guidance given in this document should be followed.

If new relevant impurities or changes in the levels of relevant impurities occur, the applicant must provide a reasoned case and/or data to show that the new source is not more toxic than the reference source. If there is evidence that such changes will not have an adverse effect on the toxicity of the new source (when compared with the reference source), the new source is equivalent to the reference source. However, if there is evidence that such changes will have an adverse effect on the toxicity of the new source as compared with the reference source, the new source is not equivalent to the reference source.

The limits specified for relevant impurities in the new source should not exceed the limits as established and accepted in the reference source. If it is proposed that established limits should be amended, then the applicant will need to provide a very strong case to support such a proposal.

6.1.2.1. Assessment of the toxicity of the impurity profile

For the assessment of the toxicity of impurities, the flow chart in Table I and the considerations described below should be followed.

As a first step toxicologists should consider the case provided by the applicant, any available data for the impurity (as a pure substance or present as an impurity - see Appendix I) and whether the impurity is a structure of toxicological concern. Impurities of interest (because they are new or present at increased levels) can be initially divided into the following categories:

Impurities of no toxicological concern: compounds for which the toxicity is known to be low (certain non-critical inerts, mineral salts, water, etc.). An additional toxicological evaluation would generally not be required, but the applicant would have to submit a reasoned case.

Impurities of known toxicological concern: if one or several of such impurities are present in the new source but not in the reference source, very good evidence would be needed to show that they will not result in significantly increased toxicity compared with the reference source. If convincing evidence cannot be provided, the new source is regarded as not equivalent to the reference source. If an impurity of toxicological concern had been identified as a relevant impurity in the reference source, further assessment has to determine whether levels in the new source are still acceptable.

New impurities of unknown toxicological concern: These impurities would elicit a further evaluation

Assuming suitable information is available, the competent authority considers if the hazard of the new material is significantly increased as compared with that of the reference source by the presence of the impurity at the respective level[6].

If not enough information is submitted, further data should be generated as indicated in Appendix III.

6.1.2.2. Determination of an acceptable upper limit concentration for an impurity of toxicological concern (case-by-case)

If an impurity of toxicological concern in the new source does not exceed an acceptable limit concentration, it may help to indicate that there is no increased hazard for the new source when compared with the reference source. Initially the following should be considered:

- The reasoned case as presented by the applicant
- Was the impurity present in the test material used in critical toxicity studies and did the findings indicate that at this concentration the impurity was not having an effect of concern?
    - If the answer is yes, it might be appropriate to use the level of the impurity in the tested material as the acceptable upper limit concentration but expert judgement will be particularly important.
    - If the answer is no, consider the guidance in Appendix II and III.

6.1.3. Decision making (which is always a case-by-case decision)

When making a decision the following options are available:

- The new source presents no greater hazard hence is equivalent to the reference source.

[6] It could be imagined that the hazard of the new source is significantly increased by the sum of all new or increased impurities rather than by one impurity alone. In this case which is expected to occur only very seldomly, equivalence would also have to be denied.

- The new source contains one or more impurities of uncertain toxicological concern; hence more information is required to assess equivalence (there would need to be strong grounds for requiring new toxicity studies).

- The new source is not equivalent to the reference source because it presents a greater hazard.

The toxicological profile will be considered equivalent to that of the reference source where the toxicological data provided on the active substance (based on acute oral, dermal and inhalation toxicity, skin and eye irritation, skin sensitization) do not differ[7] by more than a factor of 2[8] compared to the reference profile (or by a factor greater than that of the appropriate dosage increments, if more than 2; this might apply where an acute NOAEL is determined) and a more severe hazard classification would not result. There should be no change in the assessment in those studies which produce either positive or negative results unless the new source is less hazardous.

Where necessary, additional toxicological data from repeated administration (sub-acute to chronic) and studies such as reproductive and developmental toxicity, genotoxicity, carcinogenicity etc. will also be assessed by these criteria provided that, where appropriate, the organs affected are the same. The "no observable effect levels" (NOELs) or "no observable adverse effect levels" (NOAELs) should not differ[9] by more than the differences in the dose levels used.

In cases where the effect determining a critical NOAEL differs between the two sources, equivalence cannot be stated without additional scientific argument. Judgement will be needed to assess whether effects are truly toxicologically different. A critical NOAEL[10] is one that could have implications for setting reference doses (ADI, ARfD or AOEL).

Irrespective of the above three paragraphs, if a more severe hazard classification is necessary for the new source compared to the reference source, the two sources cannot be considered equivalent.

6.2. Ecotoxicity[11]

6.2.1. Data requirements and evaluation process

In analogy to the toxicity evaluation process, the objective is to identify whether there is an unacceptable increase of ecotoxicity of the new source relative to the reference source caused by new relevant impurities and/or significantly increased levels of relevant impurities already present in the reference source.

If new or increased levels of relevant impurities occur, the applicant must provide a reasoned case and/or data to show that the new source is not significantly more eco-toxic than the reference source.

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[7] if the data indicate the new source is less hazardous than the reference source, the two sources can be considered equivalent.

[8] If alternative validated tests are used (e.g. OECD 420 instead of OECD 401 for acute oral toxicity), expert judgement should be used when comparing results.

[9] If the data indicate the new source is less hazardous than the reference source, the two sources can be considered equivalent.

[10] Differences in effects (e.g. different target organs) at doses that do not determine the NOAEL and do not lead to a different hazard classification do not automatically preclude the sources being considered equivalent.

[11] Ecotoxicity is meant to cover all environmental hazards, including the potential for bio-accumulation and persistence into the environment.

If there is evidence that such changes will not have a significant adverse effect on the ecotoxicity of the new source as compared with the reference source, the new source is equivalent to the reference source. However, if there is evidence that such changes will have a significant adverse effect on the ecotoxicity of the new source as compared with the reference source, the new source is not equivalent to the reference source.

In principle, the assessment of the ecotoxicity of impurities should follow the considerations on toxicity given in chapter 6.1.2.1 and 6.1.2.2. The assessment should be based on any available ecotoxicity information, including previously conducted studies or at least valid SAR or QSAR information, in order to assure that a minimum data set will be available in all cases. Irrespective of the data available, the organism taxa and endpoints given in Directive 98/8/EC have to be considered.

6.2.2. Decision-making

The eco-toxicological profile of the new source will be considered equivalent to that of the reference source if the data provided on the substance as marketed do not differ by more than a factor of 5 relative to the reference source (or by a factor more than that of the appropriate dosage increments, if greater than 2), when determined using the same species.

Irrespective of the above three paragraphs, if a more severe hazard classification is necessary for the new source compared to the reference source, the two sources cannot be considered equivalent.

References

Ashby J and Tennant RW (1991): Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. Mutation Research 257, 229-306.

ECETOC (2003): (Q)SARs: evaluation of the commercially available software for human health and environmental endpoints with respect to chemical management applications. Technical Report No. 89. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels.

ECB (2003): Use of (Quantitative) Structure Activity Relationships ((Q)SAR) in Risk Assessment, in: Technical Guidance Document on Risk Assessment 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, Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, Part III, Chapter 4, European Commission, Joint Research Centre, Institute for Health and Consumer Protection, European Chemicals Bureau.

ECHA (2007): Guidance for identification and naming of substances under REACH.

Tennant RW and Ahby J (1991): Classification according to chemical structure, mutagenicity to Salmonella and level of carcinogenicity of a further 39 chemicals tested for carcinogenicity by the US National Toxicology program. Mutation Research 257, 209-227.

Van den Berg, M., et al (1998): Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environmental Health Perspective, 106 (12), 775-792.

Appendix I

Aide-memoire for sources of information that can be used to assess the toxic HAZARD of impurities

This aide-memoire can be used when considering a case provided by the applicant

Test data

The applicant may have tested the impurity as contained within a batch of the substance.

Safety data sheets

If the impurity is used in the manufacture of the biocide or is an additive, the applicant may have provided a safety data sheet for the substance

Also consider if the impurity is structurally and/or metabolically related to a substance used in the manufacture of the biocide (a safety data sheet should then be available for that substance).

C and L

Classification and labelling information may be available for the impurity in Annex I to the Dangerous Substances Directive 67/548/EEC (which is updated from time to time by an Adaptation to Technical Progress (ATP)) or in a draft ATP to this Directive.

Literature search

The applicant may have conducted a literature search for toxicity data on the impurity.

(Q)SAR

The applicant may have conducted SAR analysis on the impurity using a recognised commercial database e.g. DEREK. However the limitations of SAR analysis should be recognised. For instance, with respect to hazard and risk assessment of chemicals, ECETOC (2003) concludes that "current commercially available (Q)SAR models are of limited to good applicability for *in vitro* mutagenicity, limited applicability for acute oral toxicity, skin and eye irritancy and skin sensitisation and very limited applicability for chronic toxicity, carcinogenicity and teratogenicity". ECETOC does however acknowledge that (Q)SARs can provide warnings/alerts and that they are more reliable for chemicals of high structural similarity, common mechanisms of actions or single mechanistic steps. In addition, it should be noted that at the present stage of their development, most (Q)SARs available are suitable only for predicting toxicity, but not for the absence of it.

Ideally, (Q)SARs which are used for toxicological reasoning in the context of this document would have been validated at the EU level and well-documented especially in terms of their applicability domain, and (in the case of quantitative relationships) the statistical method used for their development along with the associated statistical uncertainty. However, at the time this guidance document was written, no officially validated (Q)SAR was available in the EU. Further information on the use of (Q)SARs in the frame of risk assessment can be obtained from ECB (2003) and on the internet pages of the European Chemicals Bureau (ECB) at http://ecb.jrc.it/QSAR/.

Tennant and Ashby model

Does the impurity contain a structural alert for DNA reactivity according to the model of Tennant and Ashby (1991), which indicates if there are structures of genotoxic concern. However, the absence of structural alerts in an impurity should not be used in isolation to argue that the impurity is unlikely to be of genotoxic concern.

Similarity to active substance /metabolites

How similar is the structure of the impurity to the active substance and/or to mammalian metabolites of the active substance produced in significant quantities? Close structural similarity might be used to support an argument of similar toxicity, but a very different structure would indicate that the impurity might possess very different toxicity to the parent and/or its mammalian metabolites e.g. impurities of an organophosphate active substance that lack the AChE-reactive moiety would be expected to be less neurotoxic than the active substance However, in the absence of a generally accepted definition of 'structural similarity', such considerations have to be performed with great care and should be limited to cases where the mode of (toxic) action of the substance (to whose chemical structure the impurity under question is being compared to), is clearly linked to a certain structural fragment.

Metabolism/excretion

Consider the ease with which the impurity might be excreted (as reflected by its polarity/size) and/or metabolised. Ready excretion might be used as an argument for reducing toxicological concern (although not necessarily if the site of excretion is the expected site of toxicity).

Further toxicity data

These can be requested on the impurity and/or on a batch of active substance containing appropriate levels of the impurity. However a further study should only be requested if it is considered absolutely essential, especially if it would involve animal testing.

Consider alternatives to experiments on mammals such as *in vitro* mechanistic studies (e.g. assay for anticholinesterase activity) or assays for biocidal activity. Assays for biocidal activity might be appropriate if the mechanism of biocidal activity is considered relevant to critical toxic effects of the active substance (in such an assay the biocidal activity of the active substance could be compared with that of the impurity of interest). An assay for biocidal activity is likely to be most useful when the active substance is an insecticide that acts on the nervous system of the pest. Results should be interpreted using expert judgement, as another type of toxicity might be associated with the impurity.

Appendix II

Guideline triggers for consideration of the need for additional toxicity information to assess the equivalence of a new source compared to the reference source

Important notes

These guidelines indicate the need for additional consideration. They are not automatic triggers for conducting additional toxicity studies. A reasoned case may be acceptable in place of a further study, particularly if a further study would involve animal testing.

The following approach is recommended when considering the need for additional toxicity information:

- Where there are increases in existing impurity level or the presence of new impurities in the new source relative the reference source then there is always a need for a case-by-case-decision based on ecotoxicology/toxicology (Q)SAR analysis (if a reliable prediction is possible and can be supported scientifically).

- Where there are increases in the existing impurity level or the presence of new impurities in the new source relative to the reference source at ≥ 1 g/kg but < 10 g/kg in the specification, the following information may be required on a case-by-case basis:

    - An Ames test either with the new source or the impurity, unless there are good reasons for conducting another type of genotoxicity test (e.g. SAR evidence for an effect on the mitotic spindle). No Ames test would be needed if the impurity is present at a satisfactory level in all other genotoxicity studies with the active substance.

    - One test with the new source or the impurity on one species (e.g. invertebrates, algae, plants) representative for the aquatic and one representative for the terrestrial compartment shown already as most sensitive for the reference source.

- Where there are increases in the existing impurity level or the presence of new impurities in the new source relative to the reference source at ≥ 10 g/kg in the specification, the following information may be required on a case-by-case basis:

    - 3 in vitro genotoxicity assays conducted on the new source or the respective impurity (further genotoxicity tests in vivo, if the in vitro genotoxicity tests are not all clearly negative) (No mutagenicity would be needed if the impurity is present at a satisfactory level in all other mutagenicity tests with the active substance)

    - Acute oral study (acute toxicity data would only be required if the evidence suggests that the presence of the impurity could result in a more severe hazard label for the active substance. To decide on this in the absence of data, assume an extreme worse case oral LD_{50} of 1 mg/kg bw for the impurity)

    - Skin sensitisation study (lymph node assay normally preferred)

- Developmental toxicity study (typically an oral developmental toxicity study in one species should be sufficient. Alternatively OECD reproduction/developmental toxicity screening test may be appropriate)

- Tests on two further species within the ecotoxicological profile for the aquatic and the terrestrial compartments, each.

- Where there are increases in the existing impurity level or the presence of new impurities in the new source relative to the reference source at ≥ 50 g/kg in the specification, the following information may be required on a case-by-case basis:

  - A 28-day or 90-day bridging study for repeat-dose effects to assess ability of the available data to predict the toxicity of the new source.

  - In very special cases, other studies that are crucial for coming to a conclusion might be requested.

For certain impurities of known toxicological concern it might be relevant to provide additional toxicity information even when the impurity is present at a concentration <1 g/kg in the new source. This should be decided on a case-by-case basis using expert judgment.

Appendix III

How to judge what is an acceptable upper limit concentration for an impurity of toxicological concern

The following information can be taken into account when considering what is an appropriate upper limit for an impurity in an active substance.

- Other toxicity data may (occasionally) be available to establish a NOAEL for the impurity. Further toxicity data should only be requested if absolutely essential, especially if this would involve animal testing.

- If specific concentration limits are proposed for an impurity in Annex I of 67/548/EEC, as updated from time to time by way of an ATP, there may be more than one concentration limit (i.e. classification may vary according to the concentration). In such a case, expert judgement will be needed to select the most appropriate value.

- An acceptable upper limit may have already been agreed/proposed under 98/8/EC (or 91/414/EC) for this impurity in another active.

- An acceptable upper limit may have already been proposed for this impurity in the same or in a different active by another authority e.g. by FAO or APVMA.

Genotoxic impurities are a particular concern. This is because for most genotoxic substances there is uncertainty as to whether a scientifically supportable NOAEL can be established. As a general rule, genotoxic impurities should therefore not be present in the marketed substance (especially impurities considered to be genotoxic *in vivo* and/or to be genotoxic carcinogens). However, it is important to apply expert judgement and case-by-case consideration.

If there is concern over the possibility of a genotoxic impurity being present in the substance, some possible approaches are:

- To screen each batch using an appropriately sensitive assay (typically the Ames test). Any batch giving a positive result should not be marketed.

- It may be appropriate to relate an acceptable upper limit concentration for an impurity to background levels of human exposure to naturally occurring genotoxins (e.g. to the concentration of a relevant naturally-occurring genotoxin in the human diet). Acceptance of this approach would be facilitated by a negative carcinogenicity study using technical material containing the impurity at a concentration equal to or above the limit concentration being proposed.