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Safety of the Food Chain
Chemicals, contaminants, pesticides

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GUIDANCE DOCUMENT ON THE ASSESSMENT OF THE EQUIVALENCE OF TECHNICAL MATERIALS OF SUBSTANCES REGULATED UNDER Regulation (EC) No 1107/2009

This document has been conceived as a working document of the Commission Services, which was elaborated in co-operation with the Member States. It does not intend to produce legally binding effects and by its nature does not prejudice any measure taken by a Member State within the implementation prerogatives under Regulation (EC) No 1107/2009, nor any case law developed with regard to this provision. This document also does not preclude the possibility that the European Court of Justice may give one or another provision direct effect in Member States.

Revision history

When	What
Rev. 10.1 of 13.07.2012	Update of Appendix I containing the flow chart and time table on the procedure for the assessment of the equivalence of new sources of technical materials according to Article 38 of Regulation (EC) No 1107/2009.

Contents

1 Implementing schedule

This amended guidance document should be implemented as from 13 July 2012.

2 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 technical material. This document only addresses the hazard of technical materials. 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 whether plant protection products containing the new technical material will fulfil the safety requirements laid down in Article 4(2) and (3) of Regulation (EC) No 1107/2009.

This guidance document is intended to establish a harmonised procedure for assessing the equivalence of different sources of technical material versus the reference source according to the provisions stipulated in Article 38 of Regulation (EC) No 1107/2009.
Any change concerning the source of the technical material after the authorisation of a plant protection product is dealt with by Article 45 (2). The assessment of the change (e.g. new source, amended specification, amended manufacturing process, amended manufacturing location) has to be conducted according to the procedure stipulated in Article 38 and this guidance document.

The purpose is to apply harmonised hazard assessment criteria to a certain technical material which was not completely toxicologically and/or ecotoxicologically tested according to Annex II of Directive 91/414/EEC. By the comparison of the specification(s) which have been concluded and agreed on for the reference source(s) with the corresponding specifications for new sources or changes to those already assessed, technical materials can be considered as equivalent or not equivalent regarding their hazard potential or certain data gaps can be identified where further toxicological and ecotoxicological testing is needed.

This paper does not address:

- Technical materials that are micro-organisms
- Technical materials that are poorly-defined chemical compositions/mixtures, e.g. plant extracts, animal products and their derivatives

3 Legal basis

The legal basis for this guidance document is the Regulation (EC) No 1107/2009 as last amended. However, the guidance document can also be used for assessments that have to be conducted according to Directive 91/414/EEC. The given references to the requirements of Annex II and VI of 91/414/EEC have to be regarded as valid as long as the data requirements are not adopted as stipulated in Article 78, paragraph 1 (b) and (c) of Regulation (EC) No 1107/2009. If necessary the guidance document will be amended accordingly.

4 Approach

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

Tier I consists of the evaluation of points 1.1- 1.11 and 4.1 of Annex IIA of the Directive 91/414/EEC (evaluation of analytical data). If equivalence can be ascertained from these data the Tier II assessment is not necessary.

If equivalence cannot be established on the basis of the Tier I data, further mammalian toxicity/ecotoxicity consideration is necessary which will form the requirements of **Tier II**. A schematic representation of the approach proposed is found in Appendix Ib.

Evaluation Process

The processing of the evaluation has to be conducted according to Article 38 of the Regulation (EC) No 1107/2009. A flow chart and time table on the procedure for the assessment of the equivalence of new sources of technical materials according to Article 38 Regulation (EC) No 1107/2009 is given in Appendix I.

5 Definitions

Equivalence

If the new source has the same or less harmful effects within the meaning of Article 4(2) and (3) due to its impurities compared to the reference source, then the new source can be considered (eco)toxicologically equivalent to the reference source.

Reference source(s)

This is the source(s) on which the risk assessment in the Draft Assessment Report was based and for which a regulatory decision has been taken by the Commission. More than one reference source can exist if different applicants submit complete dossiers for Annex I inclusion. In cases where an active substance is included in Annex I without a harmonised reference specification, first of all a reference specification needs to be established according to SANCO/6075/2009.

There could be cases where an assessment of the equivalence before the decision on inclusion in Annex I is appropriate. For example, the same applicant used different plants and the RMS concludes that only one of the sources is the basis for the references specification.

In the context of this document **different sources** are intended to cover the following cases:

1. When technical material comes from a new/different manufacturer other than the applicant of the reference source.

2. When the production is switched from a pilot scale to a industrial scale commercial production, the latter is regarded as a different source.

3. When there is a change in the method of manufacture (e.g. process or quality of starting materials) and/or a change of the manufacturing location, and/or the addition of one or more alternative manufacturing locations (production sites).

Impurities

Any component other than the pure active substance and/or variant which is present in the technical material (including components originating from the manufacturing process or from degradation during storage) [Art. 3 (33) of Regulation (EC) No 1107/2009].

Significant impurities
Impurities that occur due to process variability[1] in quantities ≥ 1 g/kg in the active substance as manufactured, based on dry weight, are regarded as significant.

Relevant impurities
All impurities of toxicological and/or ecotoxicological or environmental concern[2] compared with the active substance, even if present in technical material at < 1 g/kg.

6 Evaluation of equivalence of technical materials (Tier I)

6.1 Data requirements

1. Technical material coming from a new/different manufacturer
The data under points 1.1.-1.11 and 4.1 of Annex IIA of the Directive 91/414/EEC must be provided.

2. Large scale production vs. pilot scale production.

The data under point 1.11 of Annex IIA of the Directive 91/414/EEC must be provided. For points 1.1-1.10 a statement from the applicant is sufficient if there are no changes.
The data under point 4.1 are required if there is a change to the impurity profile or if new analytical methods are used.

3. Change in the manufacturing process, and/or manufacturing location, and/or addition of one or more alternative manufacturing locations

The data under points 1.1.-1.11 of Annex IIA of the Directive 91/414/EEC must be provided.
The data under point 4.1 are required if there is a change to the impurity profile or if new analytical methods are used.

6.2 Evaluation process

For the evaluation of equivalence of different sources against the reference source, the following criteria should be considered in the Tier I approach.

The new source is deemed to be equivalent to the reference source if:

- the certified minimum purity is not lower than that of the reference source (taking into account the ratio of isomers, where appropriate),
- no new impurities are present
- the limits of relevant impurities, as certified for the reference source, are not increased and

[1] Significant impurities may be present as a direct result of the chemical synthesis process/conditions employed or may be present as a result of cross contamination within the production cycle.
[2] Considering the Regulation, the following definition is proposed for relevant impurities: such substances include, but are not limited to, substances meeting the criteria to be classified as hazardous in accordance with Regulation (EC) No. 1272/2008 [extract from Art. 3(4)] or the available information (e.g. (Q)SAR, genotoxicity) indicates that the impurity has a toxicological hazard. Relevant impurities have the inherent capacity to cause harmful/unacceptable effects within the meaning of Article 4(2) and (3). Compared to the active substance, relevant impurities show additional (or more severe) toxic properties (in the sense of the above given properties).

- the certified limits of all non-relevant impurities,[3] as certified for the reference source, are not exceeded by more than the following levels[4]:

Certified limits of non-relevant impurities in the reference technical specifications	Acceptable maximum increase[5]
≤ 6 g/kg	3 g/kg
> 6 g/kg	50% of the certified limit

In cases where there is more than one reference source listed in Annex I, the specification of the new source needs to be evaluated against the references sources individually. The new source is regarded as equivalent as long as the criteria given above are met for one of the reference sources.

6.3 Decision-making

On the basis of the above criteria the conclusions might be that:

- The new source is equivalent to the reference source, therefore no further consideration is needed
- Equivalence of the new source to the reference source cannot be established based on the Tier I criteria alone, therefore a Tier II evaluation is required in order to assess whether the impurity profile results in an unacceptable increase in the hazards of the material of the new source compared to those of the reference source.
- The new source is not equivalent to the reference source because the minimum purity is lower than that of the reference source. In this case an appropriate risk assessment must be conducted for the new source to determine whether plant protection products containing the technical material will fulfil the safety requirements laid down in Article 4(2) and (3) of Regulation 1107/2009.

6.4 Reporting

A report must be prepared in the format in Appendix VII. If an equivalence check is performed during the Annex I inclusion process, the confidential part of the assessment must be reported in Annex C (Volume 4) of the DAR.

7 Evaluation of equivalence of technical materials (Tier II)

7.1 Toxicity

7.1.1 Data requirements

Reliance should be placed on information that is already available. Only when there is definite concern that the hazard from the technical a.s. could have an adverse impact 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 a starting point for decision-making. Rigid adherence to guidance may not be appropriate in all cases.

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

[4] It should be noted that the intended purpose of these levels was to harmonise the comparisons of different specifications and not for setting a reference specification.

[5] These quantitative criteria are based on the*"Manual on Development and Use of FAO and WHO specifications for Pesticides (November 2010 - second revision of the First Edition, Rome)"*

7.1.2 Evaluation process

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

- any new impurities or/and
- increased levels of relevant impurities or/and
- increased levels of non-relevant impurities which exceed the limits mentioned in section 5.2

In the absence of appropriate test data for the new source, an unacceptable increase in toxicity, would generally be the case if, as a consequence, either reference values such as ADI, AOEL, or ARfD had to be lowered or a more severe hazard classification resulted. If appropriate data for the new source are available, the guidance at 6.1.3 should be followed.
If new or increased levels of impurities are present, the applicant must provide a case and/or data to show that the new source is not significantly more toxic than the reference source. If there is evidence that a new or increased level of an impurity will NOT have a significant adverse effect on the toxicity of the new source compared with the reference source, the new source is equivalent to the reference source. However, if there is evidence that a new or increased level of an impurity will have a significant adverse effect on the toxicity of the new source compared with the reference source; the new source is not equivalent to the reference source.

The upper limits specified for relevant impurities of toxicological concern in the reference source should not be exceeded. However, if this should be proposed, the applicant will need to provide a very strong case to support a) raising the upper limit concentration and b) equivalence to the reference source.

a) Assessment of the toxicity of impurities

For the assessment of the toxicity of impurities, the considerations described below should be followed. These considerations are also represented in the flow chart in Appendix Ib.

As a first step toxicologists consider the case provided by the applicant, any available data for the impurity (as a pure substance or present as an impurity - see Appendix II) and whether the impurity is a structure of toxicological concern (see Appendix III). Impurities of interest (because they are new or present at increased levels) can initially be 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 has to submit a reasoned case.

Impurities of known toxicological concern: (see examples in Appendix III, which is not necessarily exhaustive): if one of these impurities is present in the new source but not in the reference source, very good evidence would be needed to show that it 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 was 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 (>1g/kg) or increased levels of significant but non-relevant impurities: these impurities would elicit a further evaluation

Assuming suitable information is available, the competent authority considers whether the hazard of the new material is significantly increased 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 IV.

If worker/operator and consumer exposure to the impurity is below the threshold of concern (TTC, Kroes *et al.*, 2004 & 2005), it may be acceptable to waive the need to generate new data, but the applicant has to submit a reasoned case[7]. Basically it is a management decision, as to whether the TTC concept is sufficiently conservative to protect the population and to allow decision-making and whether the uncertainties due to the assumptions in this exposure estimation are acceptable.
The choice of an appropriate TTC value is a case-by-case decision, which takes into account *inter alia* the known/assumed properties of the impurity. Currently, further advice is needed to support the choice and harmonise the approaches between the MSs. The available open literature on the TTC concept as well as a recently submitted report by CRD could be visited to support such considerations (Applicability of thresholds of toxicological concern in the dietary risk assessment of metabolites, degradation and reaction products of pesticides; scientific / technical report submitted to EFSA prepared by Chemicals Regulation Directorate (CRD), UK, final report Sept. 2009).

b) Determination of an acceptable upper limit concentration for an impurity of toxicological concern

If an impurity of toxicological concern in the new source does not exceed an acceptable upper limit concentration, it may help to indicate that there is no increased hazard in the new source compared with the reference source.

Initially the following are examined:

- Consider case 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?

[6] It is conceivable 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.

[7] The maximum possible level of human exposure to the impurity can be calculated assuming that the impurity will be present at the maximum level specified in technical grade a.s, exposure to the a.s. will be at 100 % of the a.s. reference doses (AOEL, ADI, ARfD), and that the exposed person has a bw of 70 kg.

The following calculation can be applied:
Exposure [µg/person/d] = RfD for a.s. [mg/kg bw/d] * 70 kg bw * specified maximum amount of impurity in the a.s. [g/kg=µg/mg].

This approach makes some assumptions that may not always be met: e. g. (1) as the AOEL is a systemic value, it is presumed that dermal, oral and inhalation absorption is comparable to the a.s.; (2) the behaviour as a residue is comparable to the a.s.

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 IV and V.

Note: the limit for a relevant impurity may be set at a level less than 1 g/kg (<0.1%) for an exceptionally hazardous impurity, e.g. dioxins.

7.1.3 Decision-making

In taking a decision the options available are:

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

- The new source contains one or more impurities of uncertain (eco)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.

Where data are available for the new source, its toxicological profile will be considered equivalent to that of the reference source where the toxicological data provided on the technical a.s. (based on acute oral, dermal and inhalation toxicity, skin and eye irritation, skin sensitisation) do not differ[8] by more than a factor of 2[9] 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[10] 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[11] is one that could have implications for setting reference doses (ADI, ARfD or AOEL).

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

[9] 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.

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

[11] 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.

Irrespective of the above three paragraphs, if a more severe hazard classification is necessary for the new source compared to the reference source, equivalence can not be stated.

7.1.4 Reporting

A report must be prepared in the currently available format (see Appendix VII)

7.2 Ecotoxicity

7.2.1 Data requirements and evaluation process

In analogy to the toxicity evaluation process, the objective is to identify whether there is an unacceptable increase in the ecotoxicity of the new source caused by new impurities and/or significantly increased levels of impurities already present in the reference substance (compare chapter 6.1.2).

If new or increased levels of impurities are present, the applicant must provide a case and/or data to show that the new source is not significantly more ecotoxic than the reference source. If there is evidence that a new or increased level of an impurity will NOT have a significant adverse effect on the ecotoxicity of the new source compared with the reference source, the new source is equivalent to the reference source. However, if there is evidence that a new or increased level of an impurity will have a significant adverse effect on the ecotoxicity of the new source compared with the reference source, the new source is not equivalent to the reference source.

The assessment of the ecotoxicity of impurities should, in principle, address all organism taxa and endpoints given in Directive 91/414/EEC, Annex II chapter 8 (i.e., a change in the composition of the active substance should not lead to a higher hazard to any species in the environment) and thereupon follow similar considerations as described for the toxicology assessment in chapter 6.1.2 a) and b). However, the existing differences in assessment strategies between toxicology and ecotoxicology imply a different weighting of possible approaches for performing assessments in situations with few available experimental data on ecotoxicity. In particular, the use of SAR or QSAR approaches is limited by the lower availability of reliable models for the whole spectrum of taxonomic groups occurring in the environment.

a) Prediction of the expected increase in toxicity for assessing the ecotoxicological representativeness

A generic approach based on the pharmacological reference concept of concentration additivity (Loewe & Muischnek, 1926; Finney, 1971; Kortenkamp et al.., 2010) is suggested as the preferred choice in cases where experimental ecotoxicity data on the new source or specific impurities are lacking. This concept postulates a strictly similar mode-of-action (on the molecular scale) of the mixture component, whereas the individual potency (efficacy) can vary. For a multi-component system of n compounds, the concept allows a prediction of mixture effect concentrations based on single-compound effect concentrations according to the following equation.

$$\mathrm{EC_x(mix)} = \left(\sum_{i}^{n} \frac{\mathrm{p}(i)}{\mathrm{EC_x}(i)} \right)^{-1} \qquad (1)$$

with:

n	=	number of mixture components
i	=	index from 1…n, assigns the mixture components
mix	=	mixture
EC_x	=	concentration causing x % effect
p(i)	=	relative fraction of the i-th component in the mixture

Application for a binary mixture AB

The scenario refers to a binary mixture AB consisting of the impurity to be assessed, A at an amount of p(A) and the active substance, B (in this context: sum of all other mixture components) at an amount of p(B) = 1 – p(A). If it is assumed that the toxicity of the impurity compound A is higher by a factor of f than the active-substance compound B, the following equation can be derived.

$$\mathrm{EC_x(AB)} = \frac{f \times \mathrm{EC_x(A)}}{(f-1) \times \mathrm{p(A)} + 1} \qquad (2)$$

If a value is known for the toxicity of the impurity compound A, this can be used for calculating the factor f based on the also already known value for the overall toxicity of the mixture AB as follows.

$$f = \frac{\mathrm{EC_x(B)}}{\mathrm{EC_x(A)}} = \frac{\mathrm{EC_x(AB)} - \mathrm{p(A)} \times \mathrm{EC_x(AB)}}{\mathrm{EC_x(A)} - \mathrm{p(A)} \times \mathrm{EC_x(AB)}} \qquad (3)$$

Care must be taken that the effect concentrations of all individual compounds for an endpoint of interest are obtained under identical or at least largely similar test conditions (species, test duration, type of exposure, etc.), in order to allow the equation to be used. If such experimental values for effect concentrations do not exist, it is possible as an alternative option to estimate the order of magnitude of unknown effect concentrations using a validated QSAR model. The applicability of a certain model for the concrete case must always be substantiated.

Prediction of the toxicity of a binary mixture AB_{new} in relation to a mixture AB_{old}

On the same foundations, a comparison of predicted effect values for overall toxicity depending on the content of the impurity component A is possible (even without knowledge on the actual toxicity of all mixture components).

$$\frac{EC_x(AB_{old})}{EC_x(AB_{new})} = \frac{(f-1)\times p_{new}(A)+1}{(f-1)\times p_{old}(A)+1} \qquad (4)$$

The result of this calculation depends, on the one hand, on the respective content of the impurity component A in the "old" and the "new" mixture (i.e. reference and new source) and, on the other hand, on the factor *f*, by which the impurity component A is more toxic (or is assumed to be more toxic) than the active-substance component B.

Assessment of the relevance of impurities

For all ecotoxicological assessment areas, where the new source is different from the batches used in ecotoxicological testing according to the Tier I assessment, the predicted increase in ecotoxicity of the new source must be calculated based on its actual composition (equation 4), unless a comparison of ecotoxicity is possible based on experimental data (see below). The following cases are distinguished with regard to the selection of a value for the factor *f*.

- A factor $f = 100$ is applied by default. This reflects a conservative approach in cases where the toxic action of the technical active substance against the organism considered is not determined by the intended pesticidal mode-of-action (e.g., effects on fish through a herbicide) or another known specific mechanism. In such cases, a strong impact of an impurity compound on the overall toxicity of a technical active substance against the tested organism cannot be excluded with sufficient certainty.
- The factor may be lowered to $f = 10$ where it can be plausibly assumed that the toxic action of the technical active substance against the tested organism is determined by the intended pesticidal mode-of-action (e.g., effects of a herbicide on algae) or where existing knowledge (e.g., typical toxicity profiles of classes of active substances) confirms that a specific toxic mechanism of the active substance against the tested organism may be assumed.

b) Assessment of bridging studies in order to prove ecotoxicological representativeness

If studies exist that allow a direct comparison of the ecotoxicity of a new source against the ecotoxicity of a reference batch, the results from these studies should be used for assessing the equivalence of a new source and reference batch. As a prerequisite for such an assessment, both studies must be carried out according to the same testing methodology, under identical exposure conditions (e.g., static, flow-through) and with the same test species.

Furthermore, bridging is only possible between groups of organisms where it can be assumed that the effects of the test substance in both groups are caused by the same mode-of-action. In the case, e.g., of a herbicidal active substance, bridging is usually only possible between aquatic plants, but not from aquatic plants to invertebrates.

Bridging between acute and prolonged testing is in principle possible. If a study indicates that the acute toxicity of the new source mixture is determined by the pure active substance, it is considered unlikely that effect levels on the prolonged time scale will be determined by the impurity.

Bridging across different media (e.g., from aquatic to terrestrial insects) is possible based on a case-by-case decision, if the comparability of effect characteristics (mode-of-action and uptake) is plausibly founded.

Limit tests may be appropriate for bridging purposes when it can be ensured that the uncertainty around the measured effect level fully lies within the range of the acceptable deviation (see 6.2.2) from the effect level in the corresponding test with the reference source.

7.2.2 Decision making

The generic approach under 6.2.1 a) should be applied in all cases where no experimental ecotoxicity data or reliable modelled ecotoxicity values are available for the new source. As a result of such an assessment, an impurity must be considered relevant and hence the new source considered not equivalent when the increase of predicted ecotoxicity according to the calculation for the new source as compared to the reference specification for the respective organism group (birds, small mammals, aquatic organisms, non-target arthropods, soil organisms, terrestrial non-target plants) exceeds a factor of 2. To finally conclude on the relevance, bridging studies as described under 6.2.1 b) are then typically necessary. As long as the predicted increase in ecotoxicity remains smaller than a factor of 2, the impurity is considered not relevant and hence the new source considered equivalent. In this case, it can be assumed with sufficient certainty that the increased content of the impurity compound in the new source will not cause a serious increase in the ecotoxicity of this new source compared to the respective batches used in ecotoxicological testing for the assessment of the reference source.

Example calculations to illustrate the application of the generic approach are attached in Appendix VI.

Where experimental or reliable modelled data are available for the new source, the ecotoxicological profile will be considered equivalent to that of the reference profile where the ecotoxicological data provided on the technical a.s. do not differ by more than a factor of 3 compared to the reference (or by the appropriate spacing factor of the respective test system, if greater than 3), when determined using the same species. (Note: this factor is meant to account for the variability of ecotoxicological test results and must not be interpreted as if an actual difference in ecotoxicity with a factor < 3 was in principle irrelevant with regard to the risk assessment).

References

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 (Quantitaive) 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.

Tennant RW and Ashby 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.

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.

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.

Van den Berg, M., et al. (2006): The 2005 World Health Organisation reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicological Sciences, 93 (2), 223-241

WHO/FAO (2010) Manual on development and use of FAO and WHO specifications for pesticides. November 2010 – second revision of the First Edition, Prepared by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS), available only on the internet WHO and FAO, Rome

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Wurtzen G (2004) Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem Toxicol (42) 65-83

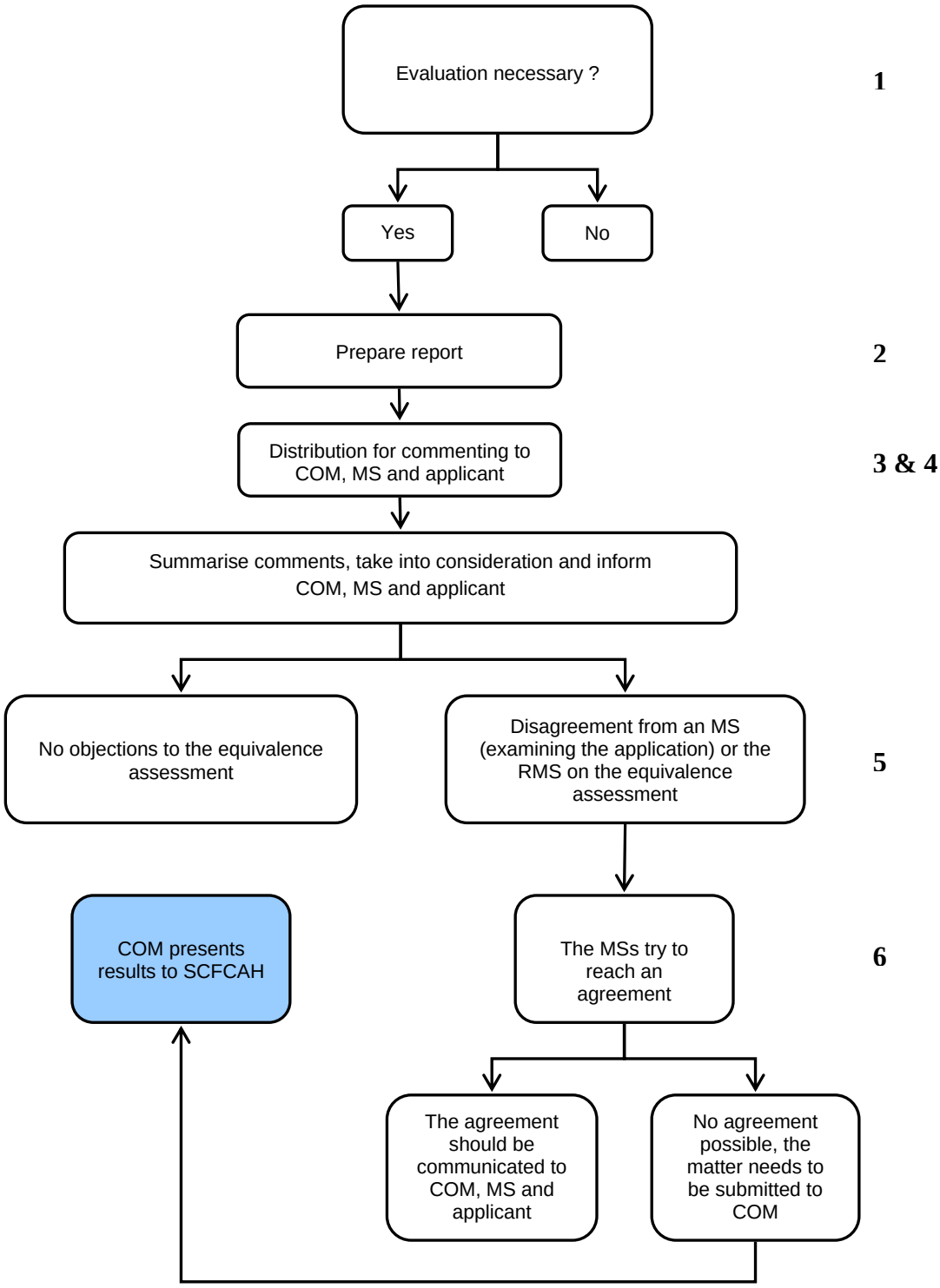
Kroes R, Kleiner J, Renwick A (2005) The threshold of toxicological concern concept in risk assessment. Toxicol Sci (86) 226-230

Finney, D.J. (1971): Probit Analysis, 3rd ed. Cambridge University Press, London.

Kortenkamp, A., Backhaus, T., Faust, M. (2010): State of the Art Report on Mixture Toxicity. Report for the European Commission, DG Environment, Study Contract Number 070307/2007/485103/ETU/D.1. Available online under
http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

Loewe, S, Muischnek, H. (1926). Über Kombinationswirkungen I. Mitteilung: Hilfsmittel der Fragestellung [On combined actions I., memorandum: an aid to posing questions]. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 114, 313–326.

Appendix I **Flow chart and time table on the procedure for the assessment of the equivalence of new sources of technical materials according to Article 38 Regulation (EC) No 1107/2009 (The numbering corresponds to the explanation given on the next page).**



1. Ascertainment of the necessity to conduct an assessment on the equivalence directly after receiving the application. It is of interest that the intention of a MS to conduct the equivalence assessment of a specific source appears in the table of '*equivalent sources and compliance checks*' on CIRCA. Therefore, as soon as a MS (Rapporteur Member State (RMS) or Designated Member State (DMS)) agrees to conduct an equivalence assessment, this should be communicated to the responsible contact point[12] and COM (in copy) by e-mail together with a 'completed row' (Excel file template) containing the relevant information on the application, in order to enable an update of the table. An up-to-date template can be found on CIRCA (https://circa.europa.eu/Members/irc/sanco/pest/library?l=/technical_evaluation/overview_tables/equivalence_templatexls/_EN_1.0_&a=d).
2. The RMS/DMS has to prepare the report on equivalence within 60 days from receiving the application (This should include the possibility for the applicant to submit comments).
3. The report has to be communicated to the COM, the other Member States and the applicant. The report is placed on CIRCA. This is communicated to relevant contact points by e-mail together with the deadline for comments. However, the confidentiality of business and trade secrets has to be guaranteed in cases where the applicant under consideration is differrent to the one of the references source.
4. Within 30 days the COM, the MS and the applicant should send their comments to the DMS/RMS.

5.1 In the case of a positive conclusion on equivalence and where no objection to this conclusion has been raised, the conclusion should be communicated within 10 days after the deadline (for commenting) to the COM and the Member States. If required, the initial report on CIRCA is replaced by a revised version that takes into account the comments received. For the report the following naming convention should be used when uploading on CIRCA: "*active substance* equivalence *Notifier Source (City) MS Date* "**draft**" resp. "**final**".

A reporting table that summarizes all comments on the equivalence report should be uploaded on CIRCA (in the same folder as the equivalence report). Each comment should be addressed by the RMS/DMS and non-adoption of comments should be properly justified.

[12] The e-mail should be sent to **equivalence@health.belgium.be**. Please be sure to use the proper template (see CIRCA).

The outcome of the peer-reviewed equivalence assessment should be communicated to the relevant contact points and the table of 'equivalent sources and compliance checks' on CIRCA should be updated accordingly[12].

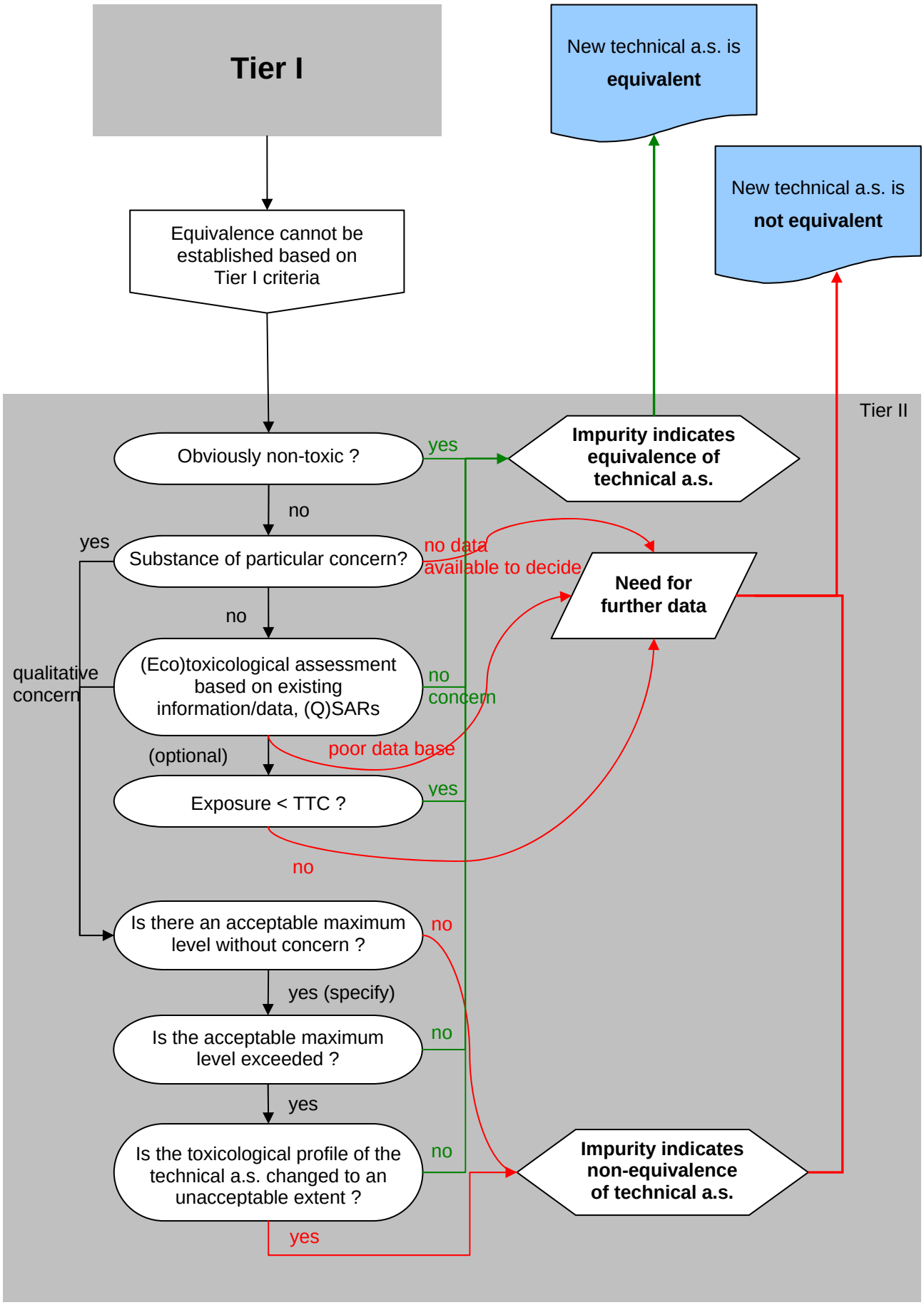
5.2 Where an MS examining the application does not agree with the conclusion of the rapporteur MS or vice versa, the RMS/DMS shall inform the applicant, the other MS and the Commission stating its reasons. A reporting table that summarizes all comments on the equivalence report should be uploaded on CIRCA (in the same folder as the equivalence report). Each comment should be addressed by the RMS/DMS and non-adoption of comments should be properly justified.

[It should be noted that disagreement on the assessment by another MS than the RMS or the MS examining the application does not necessarily lead to step 6. For the sake of feasibility though, all MS should express their concerns in step 4 and the DMS/RMS should take them into consideration even if this is not required according to Art. 38, paragraph 3.]

6. The MS concerned shall try to reach agreement on the assessment. They shall provide the applicant with an opportunity to submit comments. Where the MSs concerned do not reach agreement within 45 days, the MS assessing equivalence shall submit the matter to the COM. The COM shall present the results to the SCFCAH.

7. Before the COM adopts a decision according to the regulatory procedure referred to in Article 79, paragraph 3, the COM may ask the EFSA for an opinion, or for scientific or technical assistance.

Appendix Ib: Evaluation and decision making scheme in the perspective of toxicological assessment



Appendix II 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: applicant may have tested the impurity either in isolation or in a batch of the active substance.

Safety data sheets: if the impurity is a substance used in the manufacture of the pesticide or is a stabiliser, the applicant may have provided a safety data sheet for the substance (if not the applicant can be asked to provide one).

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

C and L: classification and labelling information may be available on the impurity, i.e. in Annex VI to regulation (EC) No 1272/2008 (which is updated from time to time by an ATP= Adaptation to Technical Progress) or in a draft ATP to this Directive.

Literature search: applicant may have conducted a literature search for toxicity data on the impurity

(Q)SAR: applicant may have conducted SAR analysis on the impurity using a recognised commercial database eg. DEREK. However, the limitations of SAR analysis should be recognised. For instance, with respect to the 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 action mechanisms 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 be 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. 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 JRC Institute for Health and Consumer Protection (Ex-ECB) at http://ecb.jrc.ec.europa.eu/qsar/.

Further information on QSAR and the OECD QSAR toolbox can be obtained at http://www.oecd.org/document/23/0,3746,en_2649_34377_33957015_1_1_1_1,00.html

Information on QSARs in REACH is also available from ECHA (http://guidance.echa.europa.eu/guidance_en.htm): especially chapters R.6 (QSARs and grouping of chemicals) and R.7 (Endpoint specific guidance) in the "Guidance on information requirements and chemical safety assessment" give details on non-testing approaches.

Chemical class of concern: does the impurity belong to a chemical class of well-known toxicological concern, such as nitrosamines, dioxins, oxygen analogues of organophosphates, etc? To answer this question, check the list of toxicologically significant impurities in

Appendix III, which is based on a list produced by the Australian Pesticides and Veterinary Medicines Authority.

Tennant and Ashby model: does the impurity contain a structural alert for DNA reactivity according to the model of Tennant and Ashby (1991)? This model indicates whether 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.

Rat metabolites: If the impurity is also a rat/mammalian metabolite of the a.s. and produced in significant amounts, then the toxicity of this impurity should have been assessed in toxicity studies with the a.s..

Similarity to a.s./metabolites: how similar is the structure of the impurity to the a.s and/or to mammalian metabolites of the a.s. produced in significant quantities? Close structural similarity might be used to support an argument of similar toxicity. A very different structure would indicate that the impurity might differ considerably in its toxicity to the parent and/or its mammalian metabolites e.g. impurities of an organophosphate a.s. that lack the AChE-reactive moiety would be expected to be less neurotoxic than the a.s.
However, in the absence of a generally accepted definition of 'structural similarity', such considerations have to be performed with great care. They should be limited to cases where the mode of (toxic) action of the substance to whose chemical structure of the impurity under question is compared, 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: can be requested on the impurity and/or on a batch of a.s. containing appropriate levels of the impurity. However a further study should only be requested if it is considered absolutely essential, especially if it involves animal testing.

Consider alternatives to experiments on mammals such as *in vitro* mechanistic studies (e.g. assay for anticholinesterase activity) or assays for pesticidal activity. Assays for pesticidal activity might be appropriate if the mechanism of pesticidal activity is considered relevant to critical toxic effects of the a.s. (in such an assay the pesticidal activity of the a.s. could be compared with that of the impurity of interest). An assay for pesticidal activity is likely to be most useful when the a.s. is an insecticide which 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 III Impurities of known toxicological concern

This listing, which is based on one produced by the Australian Pesticides and Veterinary Medicines Authority (APVMA), is not considered to be exhaustive. Impurities of particular concern are highlighted by bold text.

2,3-Diaminophenazine (DAP) and 2-amino-3-hydroxyphenazine (AHP)

Anilines and substituted anilines*

Dichlorodiphenyltrichloroethane (DDT) and DDT related impurities

Ethylene thiourea (ETU) and propylene thiourea

Halogenated dibenzodioxins and halogenated dibenzofurans

Hexachlorobenzene (HCB)

Methyl isocyanate (any isocyanate is of potential concern)

Nitrosamines

Oxygen analogues of organophosphates

Polychlorinated biphenyls (PCBs)

Hydrazine and substituted hydrazine

Tetrachloroazobenzene (TCAB) and tetrachloroazoxybenzene (TCAOB)

Tetraethyl dithiopyrophosphate (Sulfotep) and tetraethyl monothiopyrophosphate (O, S-TEPP)

Phenols and substituted phenols*

** This may be too broad a grouping, i.e. it may not always be of particular toxicological concern. For instance, in regulation (EC) 1272/2008 (Annex VI, Table 3.2) phenol is classified for acute and repeated dose toxicity, corrosion and mutagenicity.*

Acceptable maximum concentrations of nitrosamines

There are three types of nitrosamines: N-NO (N-nitrosamines), C-NO and O-NO. N-nitrosamines are known to be of particular toxicological concern because they can be activated to genotoxic carcinogens.

If analytical results indicate that total nitrosamine levels exceed 1 mg/kg in the technical material, the following toxicological requirements must be addressed:

i) A reasoned case primarily addressing the genotoxicity and carcinogenicity of the constituent nitrosamines (this is always required)

ii) Mutagenicity data relating to specific nitrosamines (N-nitroso compounds) present in the proposed technical material; this should include appropriately conducted *in vitro* mutagenicity

tests with information provided on the suitability of the exogenous metabolising fractions(s) used, and/or

iii) Toxicity data on batches of an active substance containing higher levels of the same nitrosamine(s) for which approval is being sought.

The overall objective is to reduce the total level of N-nitrosamines, which have the potential to be mutagenic, to below 1 mg/kg.

Acceptable maximum concentrations of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs):

2,3,7,8-Tetrachlordibenzo-p-dioxin (TCDD) is considered to be the most toxic dioxin. The toxicity of individual dioxin, furan and PCB impurities can be related to the toxicity of TCDD to produce individual 'TCDD toxic equivalents'. Toxic Equivalency Factors (TEFs) have been proposed for PCDDs, PCDFs and PCBs by WHO, see table below.

The concentration of each of these listed compounds present as an impurity is multiplied by the TEF to produce a TCDD toxic equivalent (TEQ). The sum of the TEQs can then be compared with the acceptable maximum concentration for TCDD.

It is considered that 10 ppb (0.01 mg/kg) is an acceptable impurity level for TCDD. The value of 10 ppb is based on the ADI set by the JMPR in 1981 for 2,4,5-T which contains TCDD as a trace impurity, i.e. 0-0.03 mg 2,4,5-T (containing not more than 0.01mg TCDD/kg) per kg bw.

Table1: WHO TEFs for human risk assessment

Congener	**TEF value**	
	Van den Berg et al., 1998	Van den Berg et al., 2006
Dibenzo-p-dioxins		
2,3,7,8-TCDD	1	1
1,2,3,7,8-PnCDD	1	1
1,2,3,4,7,8-HxCDD	0.1	0.1
1,2,3,6,7,8-HxCDD	0.1	0.1
1,2,3,7,8,9-HxCDD	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01
OCDD	0.0001	0.0003
Dibenzofurans		
2,3,7,8-TCDF	0.1	0.1
1,2,3,7,8-PnCDF	0.05	0.03
2,3,4,7,8-PnCDF	0.5	0.3
1,2,3,4,7,8-HxCDF	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1
1,2,3,7,8,9-HxCDF	0.1	0.1
2,3,4,6,7,8-HxCDF	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01
1,2,3,4,7,8,9-HpCDF	0.01	0.01
OCDF	0.0001	0.0003

non-ortho substituted PCBs		
PCB 77	0.0001	0.0001
PCB 81	0.0001	0.0003
PCB 126	0.1	0.1
PCB 169	0.01	0.03
mono-ortho substituted PCBs		
105	0.0001	0.00003
114	0.0005	0.00003
118	0.0001	0.00003
123	0.0001	0.00003
156	0.0005	0.00003
157	0.0005	0.00003
167	0.00001	0.00003
189	0.0001	0.00003

Note: the values from 1998 are still included in the table as they are quoted in the Regulation (EC) No 1881/2006 on setting maximum levels for certain contaminants in foodstuffs.

Acceptable maximum concentrations of certain solvents:

To determine whether the levels of selected solvents intended to be specified in the a.s. are toxicologically acceptable, certain ICH guidelines may be consulted (ICH Topic Q3C and VICH Topic GL18 [Impurities: residual solvents] and the annex to these): there "permitted daily exposures (PDE)" in "mg/day" for selected solvents are given. These might be compared to the potential exposure (calculated as described in section 6.1.2 a) for the TTC concept). Considering that these values are related to a different regulatory framework, which may take into account risk-benefit considerations for drugs, caution is advised. The applicant has to provide a reasoned case, that the protection levels needed for the evaluation of a.s and authorisation of PPP are reached.

ICH guidelines can be found at http://www.ich.org/ or http://www.ema.europa.eu/
VICH guidelines can be found at http://www.vichsec.org/ or http://www.ema.europa.eu/

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

Important notes:

a) 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 involves animal testing.

b) If there are new or increased levels of impurities (increased levels are defined in 5.2) in the new source compared with the reference source, additional toxicity data may be needed if the currently available information is insufficient. For large differences (e.g. 5-fold and above) in impurity levels between the reference source (or the material tested) and the new source, the need for a convincing case and/or data increases.

c) These guidelines are not intended to apply where the new source contains an increased level of a relevant impurity. The applicant will need to provide a very strong case to support this and it will require very careful case-by-case assessment.

d) The initial trigger for considering the need for further toxicity testing relates to a comparison of the technical specification of the new source with the technical specification of the reference source. However, ideally, a more refined assessment of the need for further testing should be based on a comparison of the technical specification of the new source with the technical specification of the material used in the relevant toxicity study(ies) to support the reference source. A more refined assessment such as this may not be possible if information on the technical specification of material tested in studies to support the reference source is not readily available.

The following approach is recommended for consideration of the need for additional toxicity information:

1. In all cases of new/increased levels of impurities, need:

- toxicology **(Q)**SAR analysis, if a reliable prediction is possible and can be supported scientifically. If there is an SAR alert for the impurity, it should be considered if this alert is also present in the active substance (and hence whether the potential concern is addressed by studies on the active substance). It might be considered appropriate to having a closer look at the alert and the structure triggering the alert or to investigate further to determine the validity of the alert in this particular case, e.g., by conducting a study.

2. For a new/increased impurity present at >0.1-< 1% in the technical specification for the new source, need:

- an Ames test either with technical material from the new source or the respective impurity, unless there are clear indications that another type of genotoxicity test might be a more appropriate (e.g. SAR evidence for an effect on the mitotic spindle). If the Ames (or other) test result is not clearly negative further *in vitro* genotoxicity testing is required.

  [No Ames study is needed if the impurity is present at a satisfactory level in all other genotoxicity studies with the a.s]

  If technical material from the new source is tested, the highest dose (micrograms technical material/plate) needs to be high enough to adequately investigate the

mutagenic potential of a low level of impurity. This should take into account the limit dose and the extent of toxicity at the highest dose tested.

3. For a new/increased impurity present at >1% in the technical specification for the new source, need:

- 3 *in vitro* genotoxicity assays with the technical material from the new source or the respective impurity (further genotoxicity testing *in vivo*, see data requirements for regulation 1107/2009, if the *in vitro* genotoxicity assays are not all clearly negative)

If technical material from the new source is tested, the highest dose (micrograms technical material/plate or mg technical material/mL medium) needs to be high enough to adequately investigate the mutagenic potential of a low level of impurity. This should take into account the limit doses for the tests and the extent of toxicity at the highest dose tested.

and consider[13] need for:

- acute oral study*
- and/or skin sensitisation study (local lymph node assay normally preferred)
- and/or 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)
- and/or neurotoxicity study (if there is a concern that the impurity could be more neurotoxic than the a.s.).

[*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 a.s.. To decide on this in the absence of data, assume an extreme worse case oral LD50 of 1 mg/kg bw for the impurity.]

4. Other information to be considered on a case-by-case basis for a new/increased impurity present at >5% in the technical specification for the new source, notably:

- A 28-day or 90-day bridging study (with technical material from the new source) for repeat-dose effects to assess ability of the available data to predict the toxicity of the technical specification for the new source.

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

[13] Inter alia, taking into account the predicted operator/worker and/or consumer exposure level

Appendix V 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 (see also Appendix III for nitrosamines, polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans):

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

- An acceptable upper limit may have already been agreed/proposed under 91/414/EC and/or 1107/2009 for this impurity in another active e.g. 2,3-Diaminophenazine (DAP) and 2-amino-3-hydroxyphenazine (AHP) in benomyl and carbendazim.

- 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.

- If the impurity is classified for adverse toxicological properties, the generic concentration limits applicable for impurities (0.1% or 1%, see Annex I to regulation (EC) 1272/2008) can be regarded as an acceptable upper limit unless a lower value is specified for the impurity in Annex VI to Regulation (EC) 1272/2008.

- If specific concentration limits are proposed for an impurity in Annex VI to regulation (EC) 1272/2008, as updated from time to time by way of an Adaptation to Technical Progress (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.

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 technical material to be marketed (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 technical material, some possible approaches are:

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

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

c) If a genotoxic impurity is present, the concentration should be kept “as low as reasonably achievable (ALARA)”: Kroes et al (2004) proposed a TTC of 0.15 µg/person/d for non-potent genotoxins. However, until now there has been no formal agreement within the EU of the TTC value that is applicable when genotoxicity is a concern for pesticide risk assessment. Additionally, the ALARA (“as low as reasonable achievable”) principle should

be followed for a genotoxic impurity. Hence if the ALARA level for a genotoxic impurity is below the TTC, the maximum specified level for the impurity should be the ALARA level (i.e., not to increase the specified level just because 0.15 µg/d have not yet been reached).

Appendix VI Example calculations for applying the generic approach for assessing ecotoxicological equivalence

Example A: The new source of a herbicidal active substance contains an impurity with a content of 5 %, which was contained in the batches for the algae test at an amount of 2 %.
With the parameters $f = 10$, $p_{old}(A) = 0.02$ und $p_{new}(A) = 0.05$, the relation of predicted toxicity to the known effect value is calculated as follows:

$$\frac{EC_x(mix_{old})}{EC_x(mix_{new})} = \frac{(f-1)\times p_{new}(A)+1}{(f-1)\times p_{old}(A)+1} = \frac{9\times 0.05+1}{9\times 0.02+1} = \frac{1.45}{1.18} = 1.23$$

The increase in toxicity is not serious (< 2); therefore, no further investigations are necessary for this area of risk assessment.

Example B: The specification of a herbicidal active substance contains an impurity with a content of 7 %, which was contained in the batches for the fish test at an amount of 1 %. The effect concentration (LC_{50}) in this study was determined as 2000 µg/L.

A specific action of the herbicidal active substance on fish cannot be assumed; hence, a factor $f = 100$ must be applied in the calculation.

$$\frac{EC_x(mix_{old})}{EC_x(mix_{new})} = \frac{(f-1)\times p_{new}(A)+1}{(f-1)\times p_{old}(A)+1} = \frac{99\times 0.07+1}{99\times 0.01+1} = \frac{7.93}{1.99} = 3.98$$

The toxicity predicted for the new source is seriously (> 2) higher than the known effect value for the tested batch. Thus, the representativeness of this source cannot be substantiated with sufficient certainty for the existing fish study; an appropriate bridging study is required to prove the ecotoxicological representativeness of the specification.

Example C: A measured effect value for an LC_{50} of 400 µg/L is known for the impurity in example B. Thus, the factor *f*, which describes the higher toxicity of the impurity as compared to the pure active substance, can be calculated and be used in the equation for estimating the extrapolated toxicity.

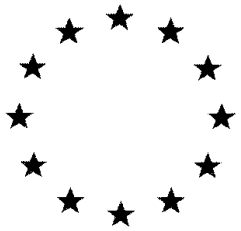
$$f = \frac{EC_x(B)}{EC_x(A)} = \frac{EC_x(mix_{old}) - p_{old}(A)\times EC_x(mix_{old})}{EC_x(A) - p_{old}(A)\times EC_x(mix_{old})} = \frac{2000 - 0.01\times 2000}{400 - 0.01\times 2000} = \frac{1980}{380} = 5.21$$

(i.e. an LC_{50} of $5.21 \times 400 = 2084$ µg/L is derived for the pure active substance)

$$\frac{EC_x(mix_{old})}{EC_x(mix_{new})} = \frac{(f-1)\times p_{new}(A)+1}{(f-1)\times p_{old}(A)+1} = \frac{4.21\times 0.07+1}{4.21\times 0.01+1} = \frac{1.29}{1.04} = 1.24$$

Taking into account the experimentally determined effect value for the impurity A, the increase in toxicity of the new source is not serious (< 2); hence, no further investigations are required in this area.

European Commission



Evaluation report on the equivalence of technical material for the active substance

XXXXXXXXXXX

RMS
date

TABLE OF CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THE REPORT WAS PREPARED

This report was prepared in accordance with the guidance document SANCO/10597/2003 rev. 9 (*Guidance document on the assessment of equivalence of technical materials of substances regulated under* ***Regulation (EC) No 1107/2009****).*

The rapporteur must indicate in the table below which case has been examined

Technical material from a new/different manufacturer	☐
Data from industrial scale production vs pilot scale production.	☐
Change in the manufacturing process, and/or manufacturing location.	☐

2. SUMMARY, EVALUATION AND ASSESSMENT OF DATA (Dossier Documents J, K-II and L-II)

SECTION A: IDENTITY OF THE ACTIVE SUBSTANCE (Annex IIA 1)

A.1 NAME AND ADDRESS OF APPLICANT(S) (ANNEX IIA 1.1)

Name of the person responsible for the submission of the dossier:

Contact:

Telephone:

Facsimile No:

E-mail:

A.2 COMMON NAME AND SYNONYMS (ANNEX IIA 1.3)

ISO :

A.3 CHEMICAL NAME (ANNEX IIA 1.4)

IUPAC:

CA:

A.4 MANUFACTURER'S DEVELOPMENT CODE NUMBER (ANNEX IIA 1.5)

XXXXX

A.5 CAS, EEC AND CIPAC NUMBERS (ANNEX IIA 1.6)

CAS:

EEC/EINECS No:

CIPAC No:

A.6 MOLECULAR AND STRUCTURAL FORMULAE, MOLECULAR MASS (ANNEX IIA 1.7)

Molecular formula:

Structural formula:

Molar mass:

A.7 MANUFACTURER OR MANUFACTURERS OF THE ACTIVE SUBSTANCE (ANNEX IIA 1.2)

XXXXXXX

Contact point:

Telephone:

Facsimile No:

E-mail:

Location of the plant for the active substance:

XXXX

A.8 METHOD OR METHODS OF MANUFACTURE (ANNEX IIA 1.8)

XXXXXXXXX

A.9 SPECIFICATION OF PURITY OF THE ACTIVE SUBSTANCE (ANNEX IIA 1.9)

Minimum purity:

A.10 IDENTITY OF ISOMERS, IMPURITIES AND ADDITIVES (ANNEX IIA 1.10)

XXXXXX

A.11 ANALYTICAL PROFILE OF BATCHES (ANNEX IIA 1.11)

XXXXXX

SECTION B: ANALYTICAL METHODS

B.1 ANALYTICAL METHODS FOR THE DETERMINATION OF PURE ACTIVE SUBSTANCE IN THE ACTIVE SUBSTANCE AS MANUFACTURED (ANNEX IIA 4.1.1)

Specificity:

XXXXXX

Linearity:

XXXXXX

Accuracy:

XXXXXX

Precision

XXXXXX

B.2 ANALYTICAL METHODS FOR THE DETERMINATION OF SIGNIFICANT AND/OR RELEVANT IMPURITIES IN THE ACTIVE SUBSTANCE AS MANUFACTURED (ANNEX IIA 4.1.2)

Specificity:

XXXXXX

Linearity:

XXXXXX

Accuracy:

XXXXXX

Precision

XXXXXX

3. TIER I: EVALUATION OF CHEMICAL EQUIVALENCE

1. ASSESSMENT OF CHEMICAL EQUIVALENCE

	Reference source (clearly defined, in cases where more than one exists)	**Different Source**	
	Certified values	**Certified values**	
Active substance			
			Variation
Impurity 1			
Impurity 2			
Impurity 3			
…			

2. CONCLUSIONS AND RECOMMENDATIONS

Include consideration of need for Tier II assessment.

4 TIER II: TOXICOLOGY & ECOTOXICOLOGY

1. ASSESSMENT OF EQUIVALENCE

2. CONCLUSIONS AND RECOMMENDATIONS

5. OVERALL CONCLUSION ON EQUIVALENCE

Give details of reference source, including location (e.g. DAR) and summary of TIER I and TIER II assessment

Technical material equivalent following Tier I assessment? ☐

Technical material equivalent following Tier II assessment? ☐

6. REFERENCES RELIED ON

A. IDENTITY (Annex IIA 1.1-1.11)

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant) Published or not	Owner

B. METHODS OF ANALYSIS (Annex IIA 4.1.1 & 4.1.2)

Author(s)	Annex point/ reference number	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant) Published or not	Owner

4.1. TOXICOLOGY AND METABOLISM (Annex IIA, Point 5)

Author(s)	Annex point/ reference number	Year	Title Source (where different from company), Report No GLP or GEP status (where relevant) Published or not	Owner

4.2. ECOTOXICOLOGY (Annex IIA, Point 8)

Author(s)	Annex point/ reference number	Year	Title Source (where different from company), Report No GLP or GEP status (where relevant) Published or not	Owner

SUMMARY OF THE TECHNICAL EQUIVALENCE

Technical note:
The compilation of the evaluated sources and the results of the assessment provide useful information for the Member States. In order to facilitate the data input in the existing table on CIRCA ("Equivalent sources and compliance checks"), the respective data should be provided in the Excel file template (https://circa.europa.eu/Members/irc/sanco/pest/library?l=/technical_evaluation/overview_tables/equivalence_templatexls/_EN_1.0_&a=d).