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GUIDANCE DOCUMENT ON THE ASSESSMENT OF THE EQUIVALENCE OF TECHNICAL MATERIALS OF SUBSTANCES REGULATED UNDER COUNCIL DIRECTIVE 91/414/EEC

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 Annex II, III and VI of Council Directive 91/414/EEC, 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.

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 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 if plant protection products containing the technical material will fulfil the safety requirements laid down in Article 5(1) and (b) of Directive 91/414/EEC.

This guidance document is intended to establish a harmonised procedure for assessing the equivalence of different sources of technical material versus the reference source. It will be used by rapporteurs for assessing the equivalence of different sources during the evaluation for Annex I inclusion as well as by national authorities during the registration process.

This paper does not address:

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

2. Legal basis

The legal basis for this guidance document is Directive 91/414/EEC as last amended.

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

4. Definitions

Equivalence
Is the determination of the similarity of the chemical composition presented by different sources of technical materials. If the new source presents a similar, or lesser hazard, compared to the reference source the new source can be considered equivalent to the reference source.

Reference source(s)
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 or, in case the equivalence check is performed during the Annex I inclusion process, the source(s) for which a complete dossier was submitted.

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 main notifier.

2. When data from large-scale commercial production are available and must be compared with the data from a pilot scale (or laboratory scale) production originally evaluated.

3. When there is a change in the manufacturing process and/or quality of starting materials, and/or a change of the manufacturing location, and/or addition of one or more alternative manufacturing locations.

Impurities
Any component other than the pure active substance, which is present in the active substance as manufactured (including non-active isomers provided that they are not covered by the ISO name of the active substance) originating from the manufacturing process or from degradation during storage.

Significant impurities
Impurities that occur or potentially occur due to process variability[1] in quantities ≥ 1 g/kg in the active substance as manufactured are regarded as significant. These impurities should be chemically identified and included in the technical specification, with stated maximum concentrations. Significant impurities may be considered relevant or non-relevant depending in particular on known toxicological and ecotoxicological characteristics.

Relevant impurities
Those impurities of the manufacturing process or storage of an active substance which, **compared with the active substance,** are toxicologically significant to health or the environment, are phytotoxic to treated plants, cause taint in food crops, affect the stability of the active substance, or cause any other adverse effect[2].These impurities should be chemically identified and included in the technical specification, with stated maximum concentrations.

5. Evaluation of equivalence of technical materials (Tier I)

5.1 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 on the impurity profile or if new analytical methods are used.

3. Change in the manufacturing process, and/or quality of starting materials, 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.

[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] This is the WHO/FAO (2002) definition; it is more informative than the definition in Annex 11A part 4 of 91/414/EEC (see 96/46/EC). Relevant impurities are included in the technical specification of an a.s. and are listed in the endpoint sheet for the a.s. An impurity may be relevant even if present in technical material at <1 g/kg.

The data under point 4.1 are required if there is a change on the impurity profile or if new analytical methods are used.

5.2 Evaluation process

For the evaluation of equivalence of different sources vs. 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 minimum purity and impurity profile is in compliance with that published in FAO/(WHO) specification (where available) and
- the certified minimum purity is not lower than the reference source (taking into account the ratio of isomers, where appropriate) and
- no new impurities are present and
- the limits of relevant impurities, as certified for the reference source, are not increased and
- the certified limits of all non-relevant impurities,[3] as certified for the reference source, are not exceeded by more than the following levels:

Certified limits of non-relevant impurities in the reference technical specifications	Acceptable maximum increase[4]
≤ 6 g/kg	3 g/kg
> 6 g/kg	50 % of the certified limit

In any case, where relevant <u>at least</u> the FAO/(WHO) specifications should be met.

5.3 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 or
- The new source is not equivalent to the reference source because of non-compliance of minimum purity or impurity profile with that published in FAO (/WHO) specification or
- Equivalence of the new source to reference source cannot be established based on Tier I criteria alone, therefore Tier II evaluation is required in order 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.

5.4 Reporting

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

[4] These quantitative criteria are based on the*"Manual of Development and Use of FAO and WHO specifications for Pesticides (First edition, Rome 2002)"*

A report must be prepared in the format in Appendix VI. 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.

6. Evaluation of equivalence of technical materials (Tier II)

6.1 Toxicity

6.1.1 Data requirements

Reliance should be placed on information that is already available. Only when there are clear concerns that could impact adversely on the hazard of the technical a.s. 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. 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 increase in hazard 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 would have to be lowered or a more severe hazard classification would result. 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 as 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 as 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. If an exceedence is proposed, the applicant will need to provide a very strong case to support a) raising of 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 flow chart in Appendix I and the considerations described below should be followed.

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) 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 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 notifier have 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 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 (>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 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[5].

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

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?

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.

[5] 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.

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.

6.1.3: 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 sensitization) do not differ[6] by more than a factor of 2[7] 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[8] 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[9] 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, equivalence can not be stated.

6.1.4 Reporting

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

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

[7] 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.

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

[9] 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.

6.2 Ecotoxicity

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 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 as 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 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 a) and b). 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 91/414/EEC, Annex II chapter 8, have to be considered.

6.2.2 Decision making

Where 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 5 compared to the reference profile (or by a factor more than that of the appropriate dosage increments, if greater than 5), when determined using the same species[10].

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.

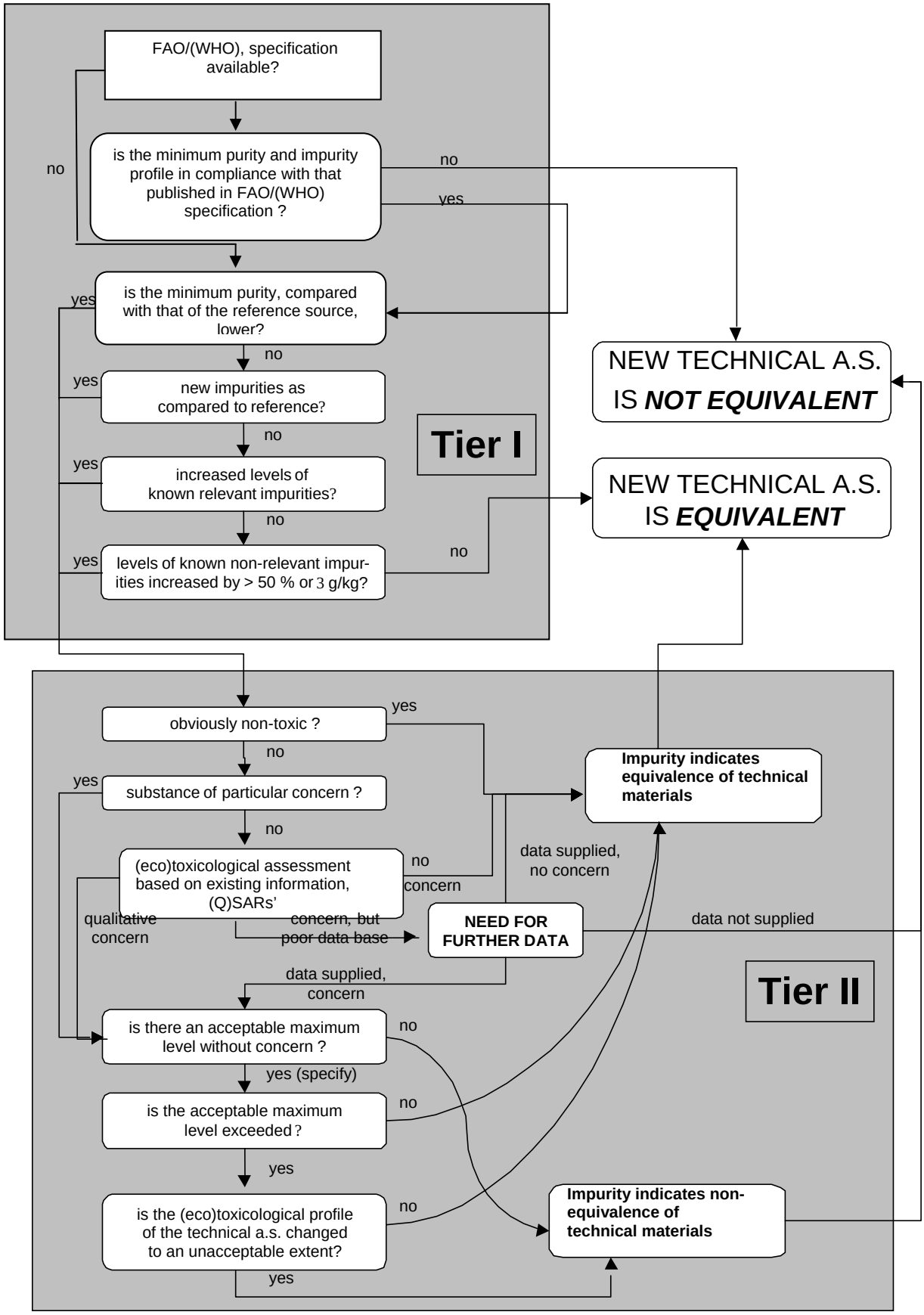
[10] This is consistent with FAO/(WHO) (2002) criteria

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.

WHO/FAO (2002) Manual on development and use of FAO and WHO specifications for pesticides. First edition, FAO Plant Production and Protection Paper 173. WHO and FAO, Rome

Appendix I: Evaluation and decision making scheme on the Equivalence of Technical Materials of Substances Regulated under Council Directive 91/414/EEC



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 if 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 1 to the Dangerous Substances Directive 67/548/EEC (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 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 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. 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/.

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 at 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 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 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 possess very different 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 and 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 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 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 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 analogs of organophosphates

Phenols and substituted phenols*

Hydrazine and substituted hydrazine

Tetrachloroazobenzene (TCAB) and tetrachloroazoxybenzene (TCAOB)

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

** This may be too broad a grouping, i.e. it may not always be of particular toxicological concern. For instance, in the Approved Supply List phenol is classified:*
at 5% and above: toxic following acute oral or dermal exposure, and corrosive
at >1% -<5%: harmful following acute oral or dermal exposure, and irritant to skin/eyes.

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) and polychlorinated dibenzofurans (PCDFs):

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

The concentration of each of these listed PCDDs and PCDFs 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, ie 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 (Van den Berg et al., 1998)

Congener	**TEF value**
Dibenzo-p-dioxins	
2,3,7,8-TCDD	1
1,2,3,7,8-PnCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0001
Dibenzofurans	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PnCDF	0.05
2,3,4,7,8-PnCDF	0.5
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OCDF	0.0001

Note: These values are considered to supersede earlier I-TEFs proposed by NATO/CCMS (1988.). See also discussion of TEFs at http://www.who.int/pcs/docs/dioxin-exec-sum/exe-sum-final.html
In addition, it should be noted that an EFSA Scientific Colloquium on Dioxins in June 2004 recommended a re-evaluation of the TEFs for dioxins. The colloquium was informed that WHO is coordinating a review of the current WHO-TEFs for dioxins, see *www.**efsa**.eu.int/science/**colloquium**_ series/no1_**dioxins**/599_en.html*

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

Important notes:

a) These guidelines indicate the need for additional consideration. They are <u>not</u> 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.

b) If there are new or increased levels of impurities (increased levels are defined at 5.2) in the new source compared with the reference source, additional toxicity data <u>may</u> 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 <u>not</u> 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. Such a more refined assessment 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

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

    - an Ames test either with the new source or the respective impurity, unless there are good indications that another type of genotoxicity test might be a more appropriate (e.g. SAR evidence for an effect on the mitotic spindle)
      [No Ames study would be needed if the impurity is present at a satisfactory level in all other genotoxicity studies with the a.s]

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

    - 3 *in vitro* genotoxicity assays (further genotoxicity testing *in vivo*, see 91/414/EEC, if the *in vitro* genotoxicity assays are not all clearly negative)

and consider 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).

[*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 for a new/increased impurity present at ≥5% in technical specification for the new source**, notably:

- 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 technical specification for the new source.

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

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 would involve animal testing.

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

- 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 VI of 67/548/EEC) can be regarded as an acceptable upper limit unless a lower value is specified for the impurity in Annex I of 67/548/EEC.

- 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 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:

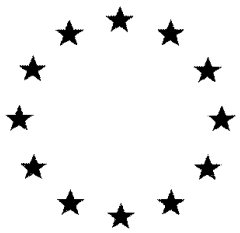
a) To screen each batch using an appropriately sensitive assay (typically the Ames test). Any batch giving an equivocal or positive result in this assay should not be marketed.

b) It may be appropriate to relate an acceptable upper limit concentration for an impurity to background levels of human exposure to 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 with technical material containing the impurity at a concentration equal to or above the limit concentration being proposed.

c) If a genotoxic impurity could be present, the concentration should be kept “as low as reasonably practicable (ALARP)”

APPENDIX VI

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 vers X (*Guidance document on the assessment of equivalence of technical materials of substances regulated under Council Directive 91/414/EEC).*

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

Technical material from a new/different manufacturer	☐
Data from large 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:

Molecular 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	**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 (eg DAR) and summary of TIER I and TIER II assessment

Technical material equivalent following Tier I assessment? ☐

Technical material equivalent following Tier II assessment? ☐

[1] I

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 TECHNICAL EQUIVALENCE

This section only to be sent via e mail to Maarten.Trybou@health.fgov.be and eva.fay@bvl.bund.de for copying to circa

1	Member State and contact details	
2	Active substance (ISO common name)	
3	CIPAC No	
4	Development code number	
5	Minimum purity of the a.s.	
6	Applicant	
7	Manufacturer and location of the plant	This should not be included if applicant has claimed as confidential.
8	Date of receipt of the information	
9	Remarks	State whether this was an evaluation of a new source from a new/different manufacturer, data from large scale production versus pilot scale production or a change in manufacturing process or site.
10	Conclusion	Technically equivalent according to SANCO 10597/2003 – rev 7