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GUIDANCE

Guidance on the Biocidal Products Regulation

Volume V, Guidance on applications for technical equivalence

Version 2.0
July 2018

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Guidance on the Biocidal Products Regulation: Volume V Guidance on applications for technical equivalence

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Document History

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Version 1.1	Corrigendum to add text and links on "Applicability of Guidance" and editorial format changes. The text has been revised as follows: • Preface: to add text and links on "Applicability of Guidance"; • The title and name of the document is aligned to Biocides Guidance standard format; • The "Introduction" is renamed "Preface" and moved to the front of the document; • The sub headings "Part I Procedural Guidance" and "Part II Technical Guidance" are removed as these "divisions" are not used in ECHA Biocides Guidance.	March 2017
Version 2.0	Full revision of the guidance to address a series of important issues necessary to reflect the current status of the scientific knowledge and assessment procedure. Obsolete information has been removed. The guidance structure has been revised. The update includes the following: • Section 1: Clarification added on the definition of reference source and assessment of technical equivalence per product type. • Section 2: List of definitions updated. • Section 3 on definition of the scope: Clarification of ○ eligibility; ○ description of possible scenarios where application for technical equivalence may be relevant; ○ recommendation on how to choose the assessment type; • Section 4 on overview of the process: Minor clarifications added to the steps of the procedure, particularly regarding information requests by the Agency. • Section 5 on Tier I: Subsection on information requirements moved from section 3; plus; ○ Additional explanation for information requirements; ○ clarification of Tier I assessment. • Section 6 on Tier II: Revision and further development of guidance on the Tier II information requirements and	July 2018

Version	Comment	Date
	the assessment of Tier II technical equivalence. • Addition of new Section 7 assessment of UVCB substances. • Deletion of Annex I "Template summary of Technical Equivalence".	

Preface

The Guidance on the Biocidal Products Regulation is to be applied to applications for active substance approval and product authorisation as submitted from 1 September 2013, the date of application of the Biocidal Product Regulation (the BPR).

This document is part of a series of documents which describe the BPR obligations and how to fulfil them.

Under the Biocidal Products Directive 98/8/EC (BPD), technical equivalence was assessed by the Member State competent authority (MSCA). Guidance on technical equivalence was available under the BPD in the form of a technical note for guidance (TNsG). The origin of the assessment of technical equivalence described in this guidance is this TNsG. Where considered relevant, the guidance is harmonised with the assessment of technical equivalence for plant protection products under Regulation (EC) No. 1107/2009 as described in SANCO/10597/2003-rev.10.1 of 13 July 2012 (DG SANCO, 2012).

Applicability of Guidance

Guidance on applicability of new guidance or guidance related documents for active substance approval is given in the published document "*Applicability time of new guidance and guidance-related documents in active substance approval*" available on the BPC Webpage[1] [https://echa.europa.eu/about-us/who-we-are/biocidal-products-committee] and for applicability of guidance for product authorisation, please see the CA-document CA-july2012-doc6.2d (final), available at https://echa.europa.eu/documents/10162/23036409/ca-july12-doc_6_2d_final_en.pdf.

[1] Link available under Working Procedures (right column).

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List of abbreviations

Standard term / Abbreviation	Explanation
AEL	Acceptable exposure level
AS-alternative	Active substance from the alternative source
AS-reference	Active substance from the reference source
BPD	Directive 98/8/EC of the European Parliament and of the Council on the placing on the market of biocidal products
BPD TNsG	Technical guidance note under Biocidal Products Directive
BPR	Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products
CA	Competent authority
CAR	Competent Authority Report
CAS	Chemical abstract (service or system)
CIPAC	Collaborative International Pesticides Analytical Council
C&L Inventory	Classification and Labelling Inventory
CLP	Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of Substances and Mixtures
EC50	Effect concentration. The test concentration at which 50% of the organisms is affected or at which 50% effect is measured for a specifically defined endpoint
ECHA	European Chemicals Agency
ED	Endocrine disruptor
EMA	European Medicines Agency
EPA	US Environment Protection Agency
EU OSHA	European Agency for Safety and Health at Work
FDA	US Food and Drugs Administration
FAO	Food and Agriculture Organization of the United Nations
g	Gram(s)
IARC	International Agency for Research on Cancer
IR	Infrared spectroscopy

Standard term / Abbreviation	Explanation
ISO	International Standards Organisation
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union for Pure and Applied Chemistry
kg	Kilogram(s)
LC50	Lethal Concentration. The concentration of the chemical that kills 50% of the test animals during the observation period.
LOAEL	Lowest observed adverse effect level
M-factor	Factor applied to the concentration of a substance classified as hazardous to the aquatic environment acute category 1 or chronic category 1, and used to derive by the summation method the classification of a mixture in which the substance is present.
MSCA	Member State competent authority
NMR	Nuclear magnetic resonance spectroscopy
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
QC data	Quality control data
(Q)SAR	(Quantitative) structure activity relationship
REACH	Regulation (EC No 1907/2006) on Registration, Evaluation, Authorisation and Restriction of Chemicals
R4BP 3	Register for Biocidal Products, version 3, established and maintained by ECHA
RI	Reliability Indicator
TAB	Technical Agreements for Biocides
TE	Technical equivalence
UV/VIS	Ultraviolet-visible
UVCB	Unknown or variable composition, complex reaction products or biological materials
UVCB-alternative	UVCB active substance from the alternative source

Standard term / Abbreviation	Explanation
UVCB-reference	UVCB active substance from the reference source
v/v	Volume per volume ratio
vPvB	Very persistent and very bioaccumulative
w/w	Weight per weight ratio
WHO	World Health Organisation

1. Introduction

1.1. Scope of the Guidance

The BPR provides a centralised provision for the assessment of technical equivalence between active substances. The legal basis is Article 54, which sets out the procedure for the assessment of technical equivalence applications, under the responsibility of the Agency.

This guidance document is intended to inform potential applicants about their obligations when they need to apply for an assessment of technical equivalence for an active substance and the procedural steps in making such an application. The guidance also informs potential applicants about the assessment conducted by the Agency and the approach used for assessing the technical equivalence of the alternative source of an active substance versus its reference source.

The guidance illustrates the tiered assessment approach established for the assessment of technical equivalence under the BPR. It provides details on the information requirements for both Tier I and II applications and on the criteria to be followed by applicants and the Agency in the assessment of technical equivalence.

This guidance does not address technical equivalence concerning:

- Active substances that are microorganisms;
- Active substances that are nanomaterials;
- Active substances generated in situ[2].

Note that additional information, which may be relevant for technical equivalence applicants, is contained also in the Technical Agreements for Biocides (TAB). This is an information document that intends to provide the agreements of the Working Groups of the Biocidal Products Committee (WGs) in a concise format. The TAB is intended to cover the technical and scientific WG agreements that have general relevance. The TAB is available on the Biocidal Products Committee section of the Agency website at https://echa.europa.eu/about-us/who-we-are/biocidal-products-committee/working-groups.

1.2. Structure of the document

The guidance is structured to present, after a general introduction and the definition of the basic elements and operators involved, the details of Tier I and Tier II assessment in separate sections. A final separate section addresses the elements to be considered when the assessment concerns UVCB[3] substances.

- Section 1 sets the scope of the document, its subject and defines the operators involved in the process described and therefore potentially interested in the Guidance.
- Section 2 lists the main terms relevant for this guidance and clarifies their definitions.
- Section 3 introduces the process of applying for technical equivalence, by defining potential applicants and possible scenarios when such an application could be required. The section also provides guidance on how the applicant can choose the appropriate assessment type.

[2] Please note, information on active substances generated in situ will be provided separately.
[3] UVCB is an acronym used for substances of **U**nkown or **V**ariable composition, **C**omplex reaction products or **B**iological materials.

- Section 4 provides an overview of the entire process and the role of the Agency.
- Section 5 addresses the Tier I assessment for mono- and multi-constituent substances, by clarifying information requirements and assessment procedure.
- Section 6 provides details on the Tier II assessment for mono- and multi-constituent substances. It explains the additional information requirements compared to Tier I and the possible options available for obtaining such information. The section also illustrates the assessment criteria applied in case the available data are on the active substance or its impurities.
- Section 7 describes the specific procedure for assessment of technical equivalence for UVCB substances. These substances are expected to require other types of information due to their complex nature.

1.3. Technical equivalence

Article 54 of the BPR sets the provisions for the assessment of technical equivalence by the European Chemicals Agency (ECHA). Technical equivalence is defined in the BPR in Article 3(1)(w): *"technical equivalence means similarity, as regards the chemical composition and hazard profile, of a substance produced either from a source different to the reference source, or from the reference source but following a change to the manufacturing process and/or manufacturing location, compared to the substance of the reference source in respect of which the initial risk assessment was carried out"*.

Technical equivalence under Article 54 of the BPR entails the assessment of the equivalence of the active substance from an alternative source with the active substance from a reference source for an active substance included in the Union list of approved active substances. The principle behind this assessment is to guarantee that for an active substance the level of hazard for human health and the environment is comparable regardless of the source of the active substance.

A reference source is defined by the following elements:
- the applicant,
- the manufacturer,
- the manufacturing location/plant location,
- the manufacturing process and
- the set reference specification[4].

The reference source is confirmed and/or established during the evaluation process of the active substance. The evaluation includes a verification that the test material used in the (eco)toxicological studies covers the specification. The reference source can be peer-reviewed by the member states and is agreed at a Working Group[5] meeting in the presence of the applicant.

Technical equivalence is assessed per active substance/product type combination. The definition of technical equivalence refers to the reference source "…. *in respect of which the*

[4] For a full list of definitions, refer to section 2 of this document.
[5] The Analytical Methods and Physico-chemical Properties Working Group of the Biocidal Products Committee.

initial risk assessment was carried out". This links the reference source to a specific risk assessment and thus to the product type or group of product types covered by this risk assessment. Therefore, applications for technical equivalence are considered specifically in relation to the product type or group of product types evaluated together and for which the reference specification has been established and the reference source(s) defined. This also means that applications for technical equivalence can only be submitted after the decision to approve an active substance/product type combination has been made. One application for technical equivalence can cover several product types, provided that the same reference specification was established for all those product types. On the receipt of the application, the Agency will confirm whether the indicated product types can be assessed together in one application.

1.4. Applications for assessment of technical equivalence

Any operator in the supply chain for the active substance or the corresponding biocidal product is eligible to apply for technical equivalence. This means that for example, the active substance manufacturer, an active substance supplier, or the formulator of the biocidal product are all eligible to submit applications to the Agency. A consultant representing the operator is also eligible to apply. A decision on technical equivalence may be shared between the actors in the supply chain by mutual agreement.

The following situations are foreseen when an applicant needs to apply for the assessment of technical equivalence, where the active substance manufactured or supplied or included in the biocidal product is either:

- from a different manufacturer than the one whose active substance has been assessed for the inclusion in the Union list of approved active substances, or
- from the same manufacturer whose substance has been assessed for inclusion in the Union list of approved active substances, following a change in the manufacturing process or the use of a different/additional manufacturing location. This includes also the change from a pilot plant to a full-scale plant.

In the above-mentioned situations, the active substance is considered as a substance from a "source different from the reference source". In this guidance document the term "alternative source" is used to refer to this situation.

In order to assess if the active substance from the alternative source is technically equivalent to the active substance from the reference source for the same product type, the applicant needs to request the Agency to establish technical equivalence. To do so, the applicant should submit a dossier containing information on the substance identification, analytical data (including five-batch analysis) and in some cases also all available information on the toxicological and ecotoxicological endpoints that are relevant for the evaluation. The information requirements are described in detail in section 5 and section 6 of this guidance.

Technical equivalence should be established before an application for authorisation of a product containing an active substance from the alternative source is submitted. The positive decision of the Agency on the assessment of technical equivalence should be included in the product authorisation application.

1.5. Assessment of technical equivalence by the Agency

The prerequisite for technical equivalence is that both the active substance from the alternative source and the one from the reference source have the same substance identity[6]. If this condition is not met, the assessment of technical equivalence cannot be conducted and the application will be concluded negatively. If the applicant is unsure of whether the substance identity is the same, they may contact the Agency via the helpdesk[7] prior to submitting an application.

Once the prerequisite is fulfilled, a tiered approach is followed to assess technical equivalence: **Tier I** consists of the comparison of the compositions of the active substances (analytical data). If technical equivalence can be established from these data, the application will be concluded positively. If technical equivalence cannot be established on the basis of analytical data, a **Tier II** assessment of toxicological and ecotoxicological data is required. The applicant can choose to either apply first for Tier I or apply directly for Tier II.

In general, one reference specification per active substance/product type combination is set during active substance approval. However, in cases of several review programme applicants with their own active substance dossier, it can occur that more than one reference specification (with different levels of purity of the active substance and/or different identities and concentration of impurities) is established for the same product type for an active substance included in the Union list of approved active substances. In such a case the active substance from the alternative source will be compared by the Agency to each reference specification. A positive decision will be taken by the Agency when the active substance from the alternative source proves to be technically equivalent to at least one of them.

2. Definitions

This section explains the key terms and definitions used in this guidance document.

Within the biocides framework under the BPR, the definition of 'substance' and the guidance for the identification and naming of substances under the REACH Regulation (EC) No 1907/2006, are applied. Consequently, certain definitions relevant for the assessment of technical equivalence are taken from REACH and the *Guidance for identification and naming of substances under REACH and CLP*. A list of relevant definitions and their sources is provided in the table below.

All ECHA guidance documents are available in the Support section of the ECHA website at: https://echa.europa.eu/guidance-documents/guidance-on-reach. Guidance documents relevant for each Regulation (BPR, REACH and CLP) are available under the respective tab.

Table 1: List of key terms with definition and their sources.

Term	Definition	Source
Technical equivalence	Similarity, as regards the chemical composition and hazard profile, of a substance produced either from a source different to the reference	BPR

[6] For more information on substance identity, see *Guidance for identification and naming of substances under REACH and CLP* available on the Support page at https://echa.europa.eu/guidance-documents/guidance-on-reach.
[7] ECHA helpdesk can be contacted using the contact web form at https://echa.europa.eu/contact.

Term	Definition	Source
	source, or from the reference source but following a change to the manufacturing process and/or manufacturing location, compared to the substance of the reference source in respect of which the initial risk assessment was carried out, as established in Article 54 of the BPR (Article 3(1)(w) of the BPR).	
Substance	A chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition (Article 3(1) of REACH).	REACH legislation
Active substance	A substance or microorganism that has an action on or against harmful organisms (Article 3(1)(c) of the BPR).	BPR
Specification	The specification is proposed by the applicants for active substance approval or technical equivalence and should in general be derived and/or confirmed by a 5-batch analysis. Quality control data might be used to refine or support the specification set by the applicant. In specific cases, it might be possible to refer to specifications set by other pieces of legislation e.g. the European Pharmacopeia or specifications set for food additives. Nevertheless, these specifications need to be supported by analytical data. Further information on the requirements for the specifications are provided in Guidance on BPR, Volume I, Part A.	*Guidance on applications for technical equivalence*
Reference specification	The reference specification is set during the active substance approval process. The reference specification is defined as the specification compared to the test substance used for the provided studies and adjusted by the experts of toxicology, ecotoxicology and chemistry taking into account the content of the different constituents in the (test) substance. Hence, it can be regarded as a scientific refinement of the specification. • The experts can narrow or expand the specification based on quality control data, the composition of the test material or expert judgement based on the physico-chemical, toxicological and ecotoxicological properties of the substance. A sound scientific justification should always be provided	*Guidance on applications for technical equivalence*

Term	Definition	Source
	when the reference specification deviates from the specification. • There should always be one reference specification for one active substance approval application. This also applies for an application which includes several applicants, e.g. task forces. In cases of several applicants with their own active substance dossier, the reference specification with the lowest purity is taken for the inclusion in the Union list.	
Source	A source is defined by the following information: • the applicant • the manufacturer • the manufacture location/plant location • the manufacturing process	*Guidance on applications for technical equivalence*
Reference source	A reference source is the combination of a source and the set reference specification considering the provided studies (including the composition of the test material). Each source listed in the active substance approval dossier is a reference source, when fulfilling the set reference specification.	*Guidance on applications for technical equivalence*
Alternative source	An alternative source is a source which is different from the reference source.	*Guidance on applications for technical equivalence*
Constituent	Any single species present in a substance that can be characterised by its unique chemical identity.	*Guidance for identification and naming of substances under REACH and CLP*
Main constituent	A constituent, not being an additive or impurity, in a substance that makes a significant part of that substance and is therefore used in substance naming and detailed substance identification.	*Guidance for identification and naming of substances under REACH and CLP*
Mono-constituent substance	As a general rule, a substance, defined by its composition, in which one main constituent is present to at least 80% (w/w).	*Guidance for identification and naming of substances under REACH and CLP*
Multi-constituent substance	As a general rule, a substance, defined by its composition, in which more than one main constituent is present in a concentration >10% (w/w) and <80% (w/w).	*Guidance for identification and naming of substances under REACH and CLP*
UVCB substance	Substances of unknown or variable composition, complex reaction products or biological materials, also called UVCBs are substances that cannot be sufficiently identified by their chemical composition, because: • The number of constituents is relatively large and/or • The composition is, to a significant part,	*Guidance for identification and naming of substances under REACH and CLP*

Term	Definition	Source
	unknown and/or • The variability of composition is relatively large or poorly predictable.	
Impurity	An unintended constituent present in a substance as manufactured. It may originate from the starting materials or be the result of secondary or incomplete reactions during the manufacture process. While it is present in the final substance, it was not intentionally added.	*Guidance for identification and naming of substances under REACH and CLP*
Significant impurity	An impurity is regarded as significant if it occurs or potentially occurs in a quantity ≥ 1 g/kg in the substance as manufactured. A significant impurity should be identified and quantified if technically possible and included in the substance specification, with stated maximum concentration. A significant impurity may be considered relevant or non-relevant depending, in particular, on its known toxicological and ecotoxicological properties.	*Guidance on the Biocidal Products Regulation, Volume I: Identity/physico-chemical properties/analytical methodology – Part A: Information Requirements*
Relevant impurity/ additive	An impurity/additive considered being of toxicological and/or ecotoxicological relevance. An impurity may be relevant even if it occurs in a quantity <1g/kg in the substance as manufactured (e.g. very toxic substances like dioxin). The relevant impurity should be identified and quantified if technically possible and included in the substance specification, with stated maximum concentration. Relevant impurities can be defined as (DG SANCO, 2012) constituents, including but not limited to, that meet the criteria to be classified as hazardous in accordance with CLP Regulation (EC) No. 1272/2008, or the available information indicates that the impurity has a toxicological and/or ecotoxicological hazard. Relevant impurities have the inherent capacity to cause harmful/unacceptable effects within the meaning of Article 19(1)(b) of the BPR. Compared to the active substance, relevant impurities show additional (comparable or more severe) toxic properties (in the sense of the definition above).	*Guidance on the Biocidal Products Regulation, Volume I: Identity/physico-chemical properties/analytical methodology – Part A: Information Requirements*

3. Application for assessment of technical equivalence

3.1. Who can apply for technical equivalence assessment?

Any operator (or a consultant representing the operator) in the supply chain of the active substance or the corresponding biocidal product is eligible to apply for technical equivalence assessment. In many cases however, the manufacturer of the active substance would be in the best position to apply, since they have direct access to information on the active substance and the manufacturing process. Applications for technical equivalence assessment should be submitted by one legal entity, whose name will appear on the technical equivalence decision. In the Register for Biocidal Products (R4BP 3) the owner of the regulatory decision is referred to as the 'asset owner', but the application may be submitted by a second legal entity referred to as the 'case owner', e.g. a consultant representing the asset owner[8]. Joint applications with several asset owners are not technically possible. However, the asset owner is free to share the decision with other legal entities by mutual agreement, on the condition that the active substance is obtained from the same alternative source (i.e. the substance is produced by the same manufacturing method at the same plant location, fulfilling the same specification). Therefore, a decision can be shared for example by different operators in the same supply chain.

3.2. When can applications for technical equivalence assessment be submitted?

Technical equivalence applications can only be submitted after the date of the Commission's decision to approve an active substance/product type combination. As part of the application for product authorisation, evidence has to be provided by the applicant that the active substance to be used in the biocidal product either comes from a reference source, or from an alternative source that is technically equivalent to the reference source. Therefore, applications for technical equivalence must be submitted to the Agency before product authorisation (both national or Union). Each technical equivalence application can include information for only one alternative source of the active substance. The alternative source refers to the specific manufacturing location of an active substance, a specific manufacturing plant for which the manufacturing process has been outlined.
Three scenarios are foreseen when an application for technical equivalence would be required. In all three scenarios, the applicant can be either the same applicant as for the reference source that was established during the evaluation process of the active substance, or a new applicant.

Scenario A: change in manufacturing location
The application relates to a change in location of the manufacturing plant, for a reference source or an alternative source for which the Agency has already established technical equivalence, without changing the manufacturing process or the starting materials.

Scenario B: change of manufacturing process
The application relates to a change of the manufacturing process of a reference source or an alternative source for which the Agency has already established technical equivalence.

The following elements should be considered when assessing a change in the manufacturing process:

- change in starting materials
- change in starting materials ratio
- change in process solvent

[8] See *Biocides Submission Manual: Technical equivalence and chemical similarity* for more information.

- change in the synthesis pathway
- change in processing steps (reaction or purification steps)
- change in process conditions

These are examples and should not be considered as an exhaustive list. The applicant has the best knowledge of the manufacturing process and will need to assess whether the effect that can be expected following a certain change will require technical equivalence assessment. Relevant to this assessment is the possible effect on the composition of the active substance. Not all changes in the manufacturing process will necessarily trigger an application for technical equivalence, for example in case of minor changes in the operational conditions. In case of doubt, the applicant may consult the Agency before submitting an application. A change from pilot-scale to large-scale production will always require technical equivalence assessment.

Scenario C: new source
In this scenario, the active substance to be used in the biocidal product is produced at a new source, i.e. a source which is not a reference source or an alternative source for which the Agency has established technical equivalence.

For all three scenarios, the positive decision of the Agency should be attached by the applicant or their downstream users to the authorisation applications after receiving confirmation of technical equivalence. This may be a first authorisation or a change to an already existing authorisation through an application for an administrative change under Implementing Regulation (EU) No 354/2013 (see item 5 of Section 1 of Title 1 of the BPR Annex). In case of a first authorisation, the applicant should assure that the technical equivalence application is submitted in sufficient time to obtain the decision before the submission of the related product authorisation application. When relevant, the applicant may need to inform downstream operators in the supply chain of the need to apply for an administrative change to product authorisation under Implementing Regulation (EU) No 354/2013 as a result of the technical equivalence assessment.

3.3. How can the applicant decide on the appropriate Tier?

The assessment of technical equivalence follows a tiered approach, where the different tiers, Tier I and Tier II, trigger different information requirements. The decision on the appropriate tier for an application should be made taking into account the composition and hazard profile of the active substance from the alternative source (hereinafter called the "AS-alternative") compared to active substance from the reference source (hereinafter called the "AS-reference"). Tier I and Tier II applications are different assessment types and are associated with separate fees (see section 4.1 of this guidance). The applicant can choose to either apply first for Tier I, or to apply for Tier II directly. If the applicant applies directly for Tier II, the Tier I assessment (analytical data) is also performed (as part of the assessment of the Tier II application) without an additional fee. If the applicant sends first a Tier I application and receives a negative decision, they will have to send a second application (in a new R4BP 3 case) for Tier II if they intend to continue with the assessment. The choice of which tier to apply for lies with the applicant and should result from the self-assessment of technical equivalence by the applicant. However, the possibility to carry out such an assessment depends on the level of information that the applicant has about the reference specification of the active substance.

If the technical equivalence applicant is either a Review Programme participant[9] who supported the active substance, an applicant who submitted the application for the active substance under Article 11 of Directive 98/8/EC (BPD), or an applicant who submitted the application for the active substance under Article 7 of the BPR, they have access to the reference specification that was set for the approval of the active substance. In this case, the applicant, by applying the principles described in section 5 (of this guidance) is in a position to make a self-assessment on whether the AS-alternative would be considered equivalent to the AS-reference in a Tier I assessment. Based on the outcome, the applicant can choose whether to apply for Tier I or Tier II.

If the applicant does not have access to the reference specification, they will know only the minimum purity of the active substance and the maximum concentrations of the relevant impurities (if any) and therefore may not be able to assess whether the AS-alternative could be considered equivalent in a Tier I assessment. The applicant can still choose to apply first for Tier I, but they should take into account the risk of receiving a negative decision from the Agency, which would lead to delays and an additional fee connected to submitting a new application for a Tier II assessment.

For Tier I applications, two assessment sub-types are available, with their respective fees as established by Annex III of the Implementing Regulation (EU) No 564/2013 (see section 4.1 of this guidance):

- The first sub-type, "*[…] when difference between the active substance sources is limited to a change in manufacturing location, and application is based solely on analytical data*" applies when the difference between the alternative source and the reference source is limited to a change in manufacturing location, i.e. there is no change of the manufacturing process and no change of the manufacturer. Furthermore, the definition of technical equivalence refers in part to similarity between the active substance of the reference source and the same active substance from the (same) reference source following a change of the manufacturing location. Hence, the first Tier I assessment sub-type described above will apply only when the application concerns a change in manufacturing location of a reference source.
- For the second sub-type "*[…] when the difference between the alternative source and the reference source goes beyond a change in manufacturing location*", i.e. when there is also a change of manufacturing process or a new manufacturer, "*and application is based solely on analytical data*", the higher Tier I fee would apply, provided that the applicant's self-assessment shows that the active substance is Tier I equivalent.

4. Technical equivalence process overview

4.1. Processing of the applications by the Agency

The processing of an application for technical equivalence by the Agency is depicted in Figure 1 below.
The procedure is as follows:

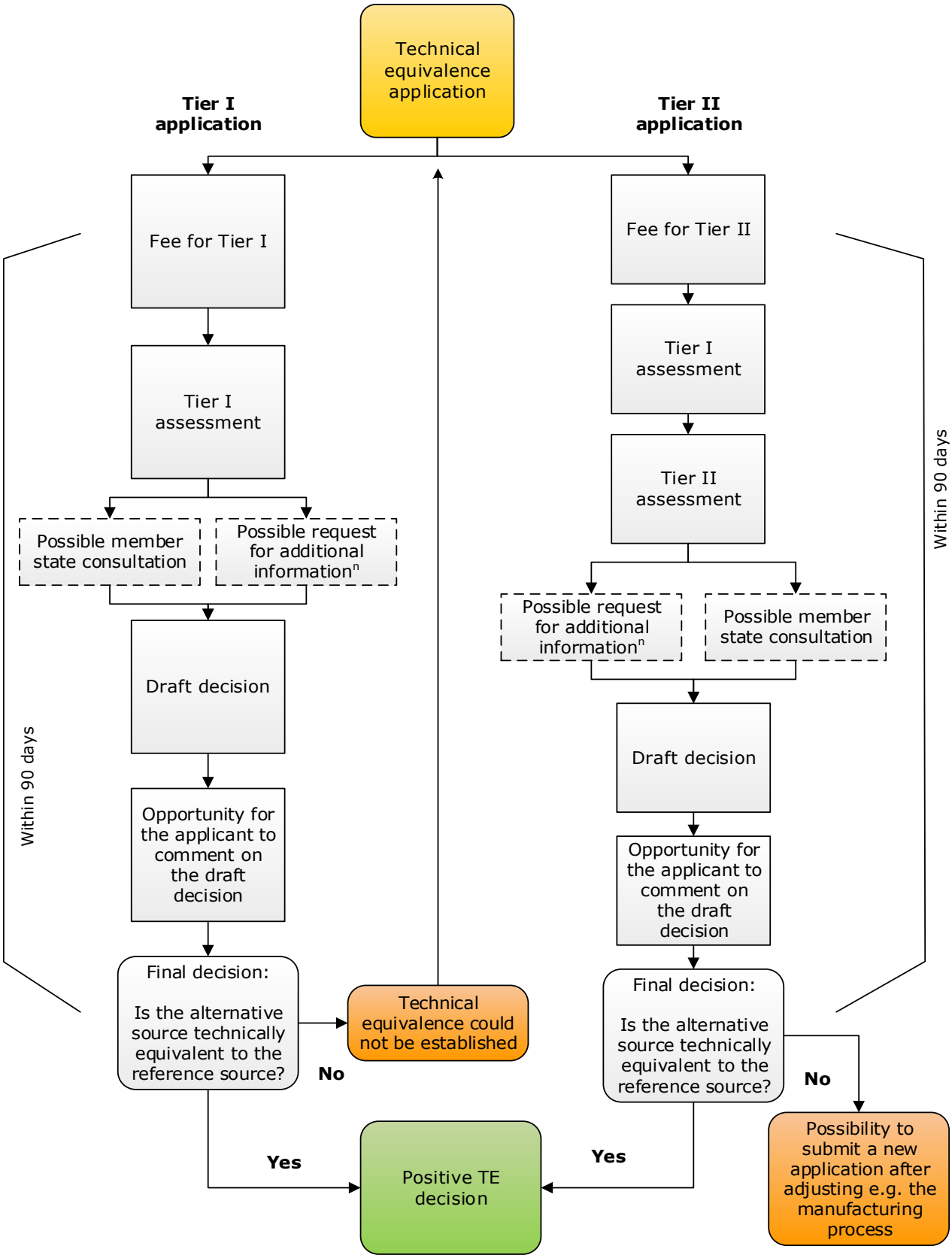
1. The applicant prepares the application according to the instructions given in this guidance

[9] A Review Programme participant is a person who has submitted an application for a substance/product-type combination included in the Review Programme. The Review Programme is the name commonly used for the work programme for the examination of existing biocidal active substances contained in biocidal products. Information on the Review Programme are available on the Agency website at: https://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/existing-active-substance.

and *Biocides Submission Manual: Technical equivalence and chemical similarity*. The application must contain a IUCLID dossier and must be submitted through R4BP 3. More detailed information on the compilation of the IUCLID dossier as well as information on R4BP 3 can be found in the submission manual that is available on the Agency website.

2. The Agency validates the application, checks the assessment type (defined by the applicant) and sends out the relevant invoice. The Implementing Regulation (EU) No 564/2013 foresees in Annex III three possible assessment types with different fees as follows:
    - *"Fee, when difference between the active substance sources is limited to a change in manufacturing location, and application is based solely on analytical data* (Tier I): EUR 5 000;
    - *Fee, when difference between the active substance sources goes beyond a change in manufacturing location, and application is based solely on analytical data* (Tier I): EUR 20 000.
    - *Fee when previous conditions are not met* (Tier II): EUR 40 000."

    For more information on how to select the appropriate assessment type, see section 3.3 of this guidance.
3. When the applicant has paid the fee, the scientific assessment of the application starts and the applicant is informed of this via R4BP 3. If the applicant does not pay the fee within 30 days, the Agency will not process the application and will inform the applicant of this via R4BP 3.
4. The Agency has 90 days to take a decision on technical equivalence. During the assessment, the Agency can ask for additional information from the applicant and request to submit it within a specified time limit. This time limit may not exceed 180 days except where justified by the nature of the data requested or in exceptional circumstances. The 90-day period within which the Agency must take its decision is suspended from the date of issue of the request until the information is received. If the applicant does not submit the additional information within the time limit specified by the Agency, the Agency may nevertheless proceed with the available information. The applicant needs to be aware that in such case the Agency will in most cases take a negative decision, on the grounds that there is insufficient information available to assess technical equivalence. The applicant will receive the request for additional information via R4BP 3 and the additional information must be submitted by updating the application (the IUCLID dossier). Several requests for additional information may be sent for the same case if considered necessary by the Agency, in this case the total time limit for all request may not exceed 180 days.
5. If necessary, the Agency can consult the competent authority that conducted the evaluation of the active substance. This is foreseen in cases where the Agency needs additional information on the established reference source(s).
6. The Agency prepares a draft decision and submits it to the applicant via R4BP 3 for commenting. The comments need to be provided to the Agency via R4BP 3 within a deadline specified by the Agency.
7. When preparing the final decision, the Agency takes into account comments made by the applicant (if any) and communicates the final decision to the applicant and the MSCAs via R4BP 3.
8. The applicant has the right to submit an appeal to the ECHA Board of Appeal according to Article 77 of the BPR within three months of the notification of the final decision.



[n] The 90-day deadline for the final decision is suspended from the date of the request until the information is received.

Figure 1: Processing of the application for assessment of technical equivalence

4.2. Outcome of the assessment of technical equivalence

The decision made by the Agency on technical equivalence can be positive (the AS-alternative is considered to be technically equivalent to the AS-reference) or negative (when the AS-alternative is not technically equivalent to the AS-reference or when, following a request for additional information, the information available is insufficient to assess technical equivalence).

Following a negative decision for a Tier I application (i.e. technical equivalence cannot be established based on the Tier I assessment), the applicant may submit a second application, for either Tier I or II, depending on the circumstances. In the case of a negative decision for Tier II, the applicant may adjust for example the manufacturing process or generate further information and submit a new application (either Tier I or Tier II) to the Agency.

5. Assessment of technical equivalence: Tier I

5.1. Information requirements for Tier I

The general information requirements for Tier I are described below in Table 2 and are applicable both to mono- and multi-constituent substances, and to UVCB substances (Substances of **U**nknown or **V**ariable composition, **C**omplex reaction products or **B**iological materials). For UVCB substances additional information requirements apply and are explained in section 7 of this guidance. For the definitions of mono-constituent, multi-constituent and UVCB substances please see section 2 of the current guidance; more information about the substance identification of the different types of substances can be found in the *Guidance for identification and naming of substances under REACH and CLP.*

Information required for a Tier I assessment is to be provided by the applicant also when applying for a Tier II assessment.

The first column of the table summarises the Tier I information that needs to be submitted in the technical equivalence application.

The second column of the table indicates for each Tier I requirement, the related information requirements under BPR for chemical substances, and also where further guidance on these requirements can be found (in parentheses the corresponding chapter and section of the *Guidance on the Biocidal Products Regulation, Volume I: Identity/physico-chemical properties/analytical methodology, Parts A+B+C: Information Requirements, Assessment and Evaluation*[10] (chapter II Dossier requirements for active substances)). The applicant needs to follow the requirements in the indicated sections of the aforementioned guidance document when preparing the technical equivalence application.

The third column of the table includes comments about the Tier I requirements that the applicant should take into account, in addition to the general requirements in the aforementioned guidance, when preparing the application.

Additional information of interest may be found in the Technical Agreements for Biocides (TAB)[11].

[10] Please note that update of Volume I is currently in progress and chapters and sections numbers may change. The references in table 2 will be updated accordingly.
[11] Available on the Biocidal Products Committee section of the Agency website at https://echa.europa.eu/about-us/who-we-are/biocidal-products-committee/working-groups.

Table 2. Tier I information requirements for technical equivalence applications.

Required Tier I information to be submitted in the technical equivalence application	Related requirements under BPR for chemical substances; for each requirement the specific chapter and section(s) in the *Guidance on the BPR*[12]	Comments
Applicant full name and address details	Applicant (Name and address); (Contact person) (chapter II sections 1.1 and 1.2)	
Manufacturer of the active substance: full name and address details (office address) Manufacturing plant location full name and address details	Active substance manufacturer (name, address and location of manufacturing plant(s)) (chapter II section 1.3)	Only one manufacturer and one plant location can be included in one technical equivalence application. The actual plant location address needs to be provided.
Manufacturing process description	Method of manufacture (synthesis pathway) of active substance including information on starting materials and solvents including suppliers, specifications and commercial availability (chapter II section 2.8)	Only one manufacturing process can be included in one technical equivalence application.
Identifiers for: active substance (main) constituents impurities additives	Common name proposed or accepted by ISO and synonyms (usual name, trade name, abbreviation) (chapter II section 2.1); Chemical name (IUPAC and CA nomenclature or other international chemical name(s)) (chapter II section 2.2); CAS number plus EC, INDEX and CIPAC numbers (if allocated) (chapter II section 2.4); Molecular and structural	In the context of technical equivalence, additive is considered as defined in the *Guidance for identification and naming of substances under REACH and CLP*: "A substance that has been intentionally added to stabilise the substance". Other substances with other functions, e.g. pH-regulators or colouring agents, are not considered as additives. The information available in the Competent Authority Report (CAR[13]) about additives (stabilisers) in the AS-reference is taken into account.

[12] *Guidance on the Biocidal Products Regulation, Volume I: Identity/physico-chemical properties/analytical methodology, Parts A+B+C: Information Requirements, Assessment and Evaluation.*
[13] The public Competent Authority Reports can be accessed via the Agency website https://echa.europa.eu/information-on-chemicals/biocidal-active-substances.

Required Tier I information to be submitted in the technical equivalence application	Related requirements under BPR for chemical substances; for each requirement the specific chapter and section(s) in the *Guidance on the BPR*[12]	Comments
	formula (including SMILES notation, if available and appropriate) (chapter II section 2.5); Molar mass (chapter II section 2.7)	
Proposed specification by the applicant for the minimum purity of the active substance and for the maximum concentrations of the impurities and additives	Specification of purity of the active substance as manufactured in g/kg, g/l or %w/w (v/v) as appropriate, providing inclusively the upper and lower limit (chapter II section 2.9); The identity of any impurities and additives including by-products of synthesis, optical isomers, degradation products (if the substance is unstable) unreacted and end-groups of polymers and unreacted starting materials of UVC-substances (chapter II section 2.10); Analytical profile of at least five representative batches (g/kg active substance) including information on content of the impurities referred to in section 2.10 (chapter II section 2.11)	Normally the specification is derived from the 5-batch analysis results by statistical calculations (mean±3×standard deviation). If applicable, quality control (QC) data can be used to support/refine the specifications, however, QC data cannot replace the 5-batch analysis. An explanation as to how the proposed specification has been derived must be provided. Any deviations from the normal approach need to be scientifically justified. Information on degradation products does not need to be provided unless they are considered as impurities in the active substance. According to the substance definition (see section 2 of this guidance), a solvent, which can be removed without affecting the stability of the substance or changing its composition, should not be considered for the active substance composition. Where the active substance is manufactured in the presence of solvents (e.g. directly as a product solution) then as well as a specification for the active substance as manufactured, a dry weight specification must be provided. The dry weight

Required Tier I information to be submitted in the technical equivalence application	Related requirements under BPR for chemical substances; for each requirement the specific chapter and section(s) in the *Guidance on the BPR*[12]	Comments
		specification[14] can be determined by calculation. In such case the reference specification of the AS-reference would be set according to the dry weight specification, and the solvent would not be considered for technical equivalence;
5-batch analysis	Analytical profile of at least five representative batches (g/kg active substance as manufactured) including information on content of the impurities referred to in section 2.10 (chapter II section 2.11); Information on optical activity and full details of any isomeric composition (if applicable and appropriate) (chapter II section 2.6); (see also chapter II sections 2.9 and 2.10)	The following information needs to be provided for the batches analysed in the 5-batch analysis: dates of manufacture, batch weights, justification for their representativeness (e.g. based on quality control (QC) data). In general, the age of the 5-batch analysis and the ages of the batches (dates of manufacture) shall not exceed 5 years. For batch analysis/batches older than 5 years, the applicant has to provide a justification to support the results of the 5-batch analysis, and to confirm that the batches are still representative for the manufacturing process. This would normally be done with QC data. If the assessment report for the approval of the active substance indicates limits for relevant impurities, then they must be addressed in the technical equivalence application. The normal requirements for 5-batch analysis of relevant impurities apply as well.
Method descriptions and validations for the analytical methods used	Methods of detection and identification (chapter II, section 5);	

[14] For more information on dry weight calculation please see document "Technical Agreements for Biocides" available on the Agency website https://echa.europa.eu/about-us/who-we-are/biocidal-products-committee/working-groups.

Required Tier I information to be submitted in the technical equivalence application	Related requirements under BPR for chemical substances; for each requirement the specific chapter and section(s) in the *Guidance on the BPR*[12]	Comments
in the 5-batch analysis	Analytical methods including validation parameters for the determination of active substance as manufactured and where appropriate, for relevant residues, isomers and impurities of the active substance and additives (e.g. stabilisers) (chapter II, section 5.1)	
Quality control (QC) data		QC data can be submitted as supportive information, for example to modify the minimum purity or the maximum limit of some impurities from what is shown in the 5-batch analysis data. However, it must be noted that such data cannot replace the 5-batch analysis. QC data may be necessary to confirm the representativeness of the batches analysed in the 5-batch analysis, or e.g. if the 5-batch analysis is more than five years old.
Spectral data Optical activity	Absorption spectra data (UV/VIS, IR, NMR) and a mass spectrum, molar extinction coefficient at relevant wavelengths, where relevant for the purified active substance of stated specification (chapter II, section 3.6); Information on optical activity and full details of any isomeric composition (if applicable and appropriate) (chapter II section 2.6)	Normally for the TE application the spectral data is to be provided for the substance as manufactured. Purified active substance refers in this case to e.g. removal of solvents if the substance is manufactured directly as a product solution and the presence of the solvent prevents the identification of the substance. It is sufficient to provide the spectral data for one batch. This batch needs to be representative of the current production. For inorganic substances other methods may be more suitable, e.g. X-ray diffraction together with results of elemental analysis.
Other information		Other information may be needed

Required Tier I information to be submitted in the technical equivalence application	Related requirements under BPR for chemical substances; for each requirement the specific chapter and section(s) in the *Guidance on the BPR*[12]	Comments
depending on the case		for the assessment depending on the active substance (e.g. additional requirements indicated in the Competent Authority Report (CAR) for the approval of the active substance). If such information is needed, the Agency will request it from the applicant. For UVCB substances see section 7 of the current guidance.

The Tier I assessment covers only the comparison of compositional information based on analytical data. No Tier II assessment, i.e. no toxicological or ecotoxicological assessment is carried out within a Tier I application. Therefore, applicants do not need to include toxicological or ecotoxicological data or reasoning in an application for Tier I assessment.

5.2. Assessment of technical equivalence Tier I – mono- and multi-constituent substances

This section on the Tier I assessment describes the procedure followed for mono- and multi-constituent substances. The decision tree for assessing technical equivalence for these substances is depicted in Figure 2 below. The approach for UVCB substances is described in section 7 of this guidance.

The first step in the Tier I assessment is the confirmation of substance identity and verification that the AS-alternative has the same identity as the AS-reference. This assessment is done on the basis of the *Guidance for identification and naming of substances under REACH and CLP*, and on the basis of information included in the Competent Authority Report (CAR) for the approval of the specific active substance. If the Agency concludes during the technical equivalence assessment that the substance identities are different, the assessment will not proceed further and the application will be concluded negatively.

For the assessment of technical equivalence, the following criteria are used in the Tier I assessment of mono- and multi-constituent substances. If all of the conditions are met, the AS-alternative is considered to be technically equivalent to the AS-reference:

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

- The limit of each relevant impurity or additive is not exceeded,[15] and
- The limits of all significant but not relevant impurities are not exceeded by more than the levels indicated in Table 3 below.

Table 3: Levels of significant but not relevant impurities[16]

Limits of significant but not relevant impurities in the technical specifications of the reference source	Acceptable maximum increase in the alternative source[17]
≤6 g/kg	3 g/kg
>6 g/kg	50% of the certified limit

If one of these conditions is not met, the Tier I assessment cannot conclude that the active substances from the two sources are technically equivalent.

The minimum purity of the active substance and the relevant impurities and their maximum limits for the AS-reference are available in the public version of the CAR and the BPC opinions.

[15] This criterion applies to the relevant impurities and additives present in the active substance from the reference source, which are indicated with their maximum limits in the CAR. No toxicological or ecotoxicological assessment is carried out during the assessment of a Tier I application.
[16] The criteria in Table 3 are applicable only if the impurity was included in the reference specification of the approved active substance as a significant impurity, they do not relate to new impurities.
[17] These quantitative criteria are based on the FAO manual (2016) available at http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/manual/en/.

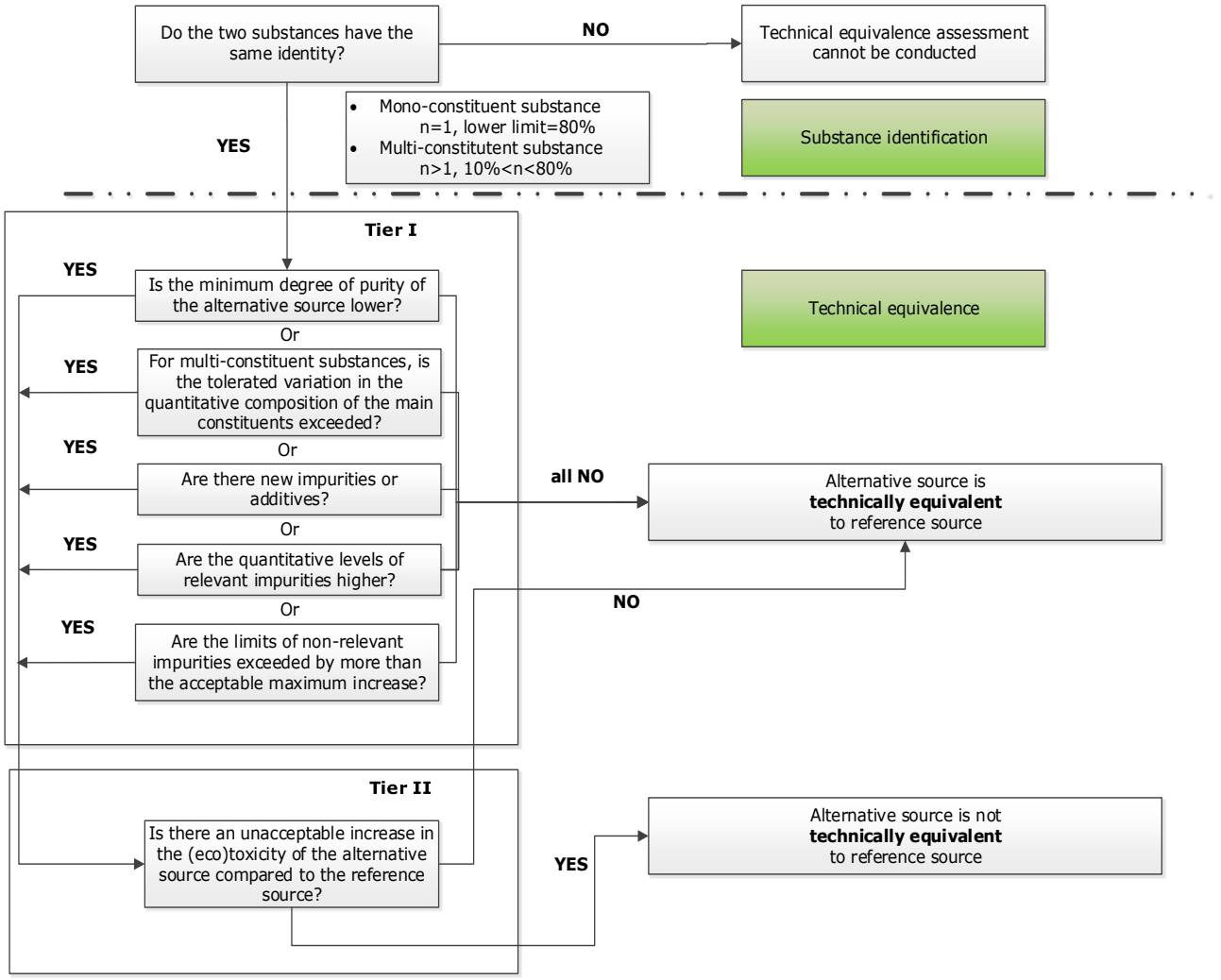


Figure 2 : Assessment of technical equivalence for mono- and multi-constituent substances (same identity would mean that the AS-reference and the AS-alternative have the same substance identity according to the principles explained in *Guidance for identification and naming of substances under REACH and CLP,* n = number of main constituents)

6. Assessment of technical equivalence: Tier II

6.1. General considerations

This section on the Tier II assessment applies to mono-constituent and multi-constituent substances. The approach followed for UVCB substances is described in section 7 of this guidance.

A dossier for a Tier II application should contain a technical equivalence assessment conducted by the applicant. A template for providing the applicant's self-assessment is available on the Agency website and should be included as an attachment in the IUCLID dossier. The decision on technical equivalence is made on the basis of a scientific evaluation performed by the Agency.

The principles for the assessment by the applicant and the evaluation by the Agency are the same. However, the Agency has access to information concerning the AS-reference which the applicant may not have. The additional information to which only the Agency has access can be information in the confidential part of the CAR (reference specification and composition of tested batches). Furthermore, the Agency may consult the responsible evaluating competent authority for the AS-reference when necessary. Therefore, the Tier II evaluation by the Agency may include additional elements to that of the applicant. The evaluation by the Agency will be based on the information provided by the applicant and on the information regarding the AS-reference. Any necessary information regarding the assessment of the AS-alternative needs to be provided by the applicant and the Agency will evaluate whether all required and relevant information has been provided to support the case. Some of the information may be covered by proprietary rights and it is the responsibility of the applicant to obtain the appropriate rights in order to use this information to support their case.

In this section, the steps and elements of the Tier II are described, specifying the relevant tasks in the assessment by the applicant and in the evaluation by the Agency. The guidance aims to help applicants when preparing their dossier and to reduce the need for the Agency to request additional information from the applicant. The applicant is encouraged to present all the information available and to describe the assessment methods in a clear and transparent way in order to reduce the need for an information request.

6.1.1. Objective of Tier II assessment

The objective of the Tier II assessment is to determine whether there is an unacceptable change in hazard profile of the AS-alternative compared to the AS-reference as a result of a change in the composition. The Tier II assessment is based on hazards only and neither exposure nor risk assessment is considered.

In the applicant's Tier II assessment, a reasoned case must be provided to show that the AS-alternative does not have more severe toxicity or ecotoxicity hazard properties (including bioaccumulation and persistence) than the AS-reference.

The AS-alternative is considered technically equivalent to the AS-reference if there is evidence to show that the changes in the composition will not result in an unacceptable change of the hazard profile of the AS-alternative compared to the AS-reference.

6.1.2. Overview of Tier II assessment

Figure 3 depicts a flowchart identifying the main steps of the Tier II assessment. The flowchart is valid both for the applicant when preparing the technical equivalence assessment as part of their dossier and for the Agency when processing the Tier II application. A short description of each step is given below. In the flowchart, reference is provided to the relevant section of the guidance where further information can be found.

Step 1) Identification of Tier II impurities

Tier II assessment is required if the result of the Tier I assessment shows:

1. **Presence of new impurities or additives** in the AS-alternative that were not present in the AS-reference, and/or
2. **Increased levels of relevant impurities or additives** in the AS-alternative already present in the AS-reference, **which exceed the limit** set in the reference specification, and/or
3. **Increased levels of significant but non-relevant impurities** in the AS-alternative, already present in the AS-reference, **which exceed the limits** given in Table 3 in section 5.2 of this guidance.

Any impurity or additive that triggers the Tier II assessment is referred to as a "Tier II impurity" in this guidance. If the applicant does not have access to the reference specification of the AS-reference, it may not be possible to identify which impurities need to be considered in the Tier II assessment. In this case, the applicant is recommended to cover all impurities in their Tier II assessment (even if they occur at a concentration < 0.1 %). It is noted that the level of the necessary information depends on the nature of the impurity (see Section 6.3.3). During the evaluation, the Agency focuses on the impurities that have triggered the Tier II evaluation (Tier II impurities).

Step 2) Collect and review available information

The applicant needs to cover each of the Tier II information requirements in their application (see Tables 4-5 in section 6.2.1 of this guidance). The information requirements can be fulfilled by providing study reports on the AS-alternative and/or by providing information for the Tier II impurities. The applicant should provide all available information in the application. Any waiving of information should be supported by a reasoned justification.

Step 3) Confirm all Tier II information requirements are fulfilled

If a data gap is identified by the Agency during evaluation, a request for additional information will be sent to the applicant. If the applicant does not provide the information requested by the Agency or a reasonable justification, the Agency may conclude that the active substances from the two sources cannot be considered technically equivalent based on the available information.

Step 4) Generation of new information (if necessary)

If a data gap is to be filled by providing information for the Tier II impurity, several non-testing methods exist in addition to experimental testing. If, for example, due to the nature of the substance or the type of information needed, information has to be provided for the AS-alternative as a whole (and not an impurity), experimental testing may be the only possibility. It is emphasised that vertebrate testing for the purpose of the BPR must be undertaken only as a last resort (Article 62(1) of the BPR).

Step 5) Perform Tier II assessment

In the Tier II assessment, the differences between the AS-alternative and the AS-reference should be assessed with respect to classification, toxicity and ecotoxicity profile as well as the PBT/vPvB and ED properties.

Step 6) Decision-making

All available information will be taken into account and all the Tier II assessment elements (step 5) will be considered in the decision-making (weight of evidence approach).

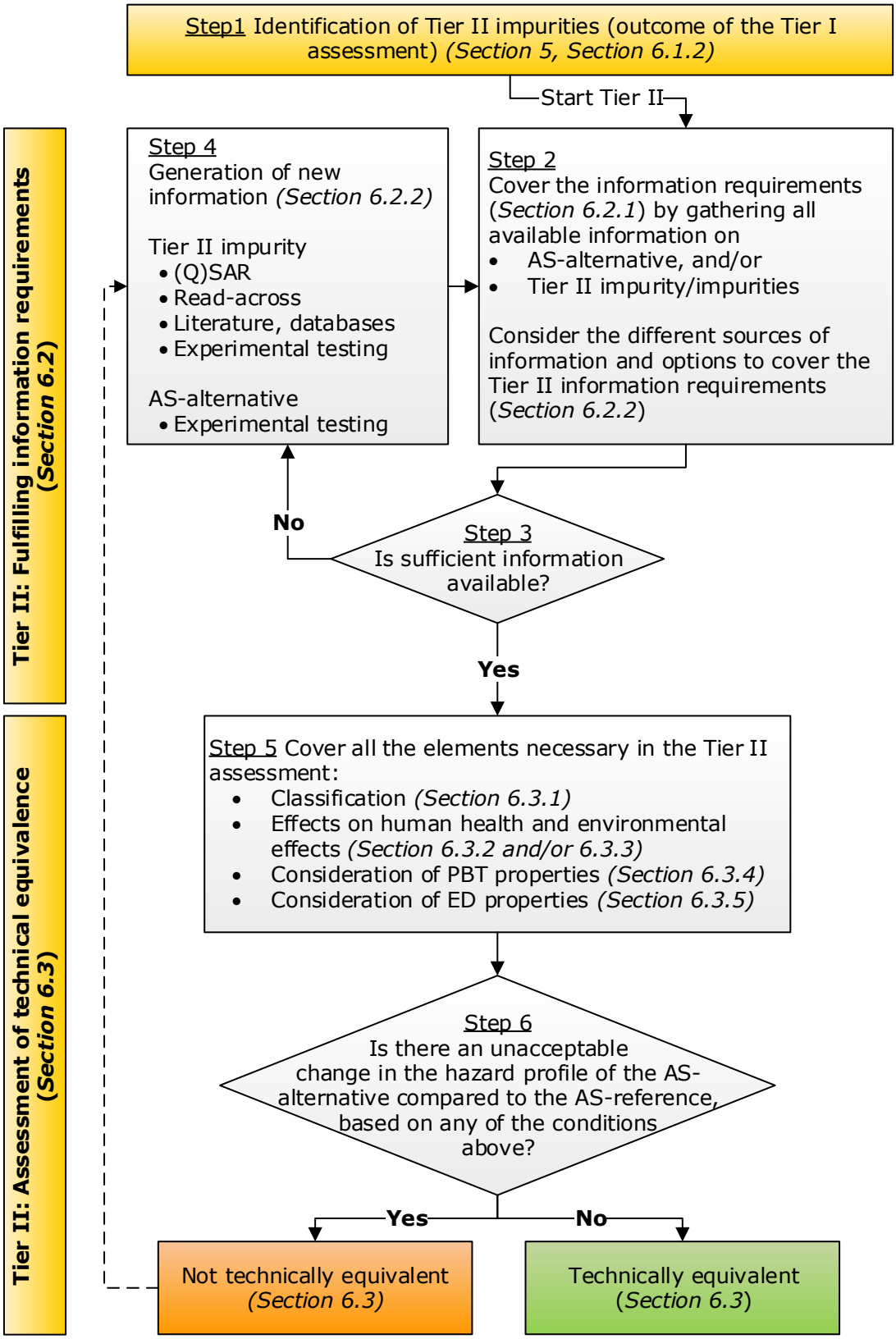


Figure 3: Overview of the technical equivalence Tier II assessment. For each step, reference is given to the corresponding section in the guidance.

6.2. Fulfilling the information requirements

The information requirements for a Tier II application are described in section 6.2.1 of this guidance. The information submitted should cover the effects on human health and the environmental effects[18]. The different sources and options that can be used to cover the information requirements are described in section 6.2.2 of this guidance.

Note: to cover an information requirement any of the provided options can be followed when adequate. It is not always necessary to provide experimental study results for each endpoint (see Tables 4 and 5 in section 6.2.1 below), but an information requirement could also be covered by non-testing information or by providing a waiving justification. As mentioned elsewhere in this guidance, a waiving statement could be provided to cover all information requirements of a certain Tier II impurity, for which the hazard is known to be low. In addition, if sufficient information for a Tier II impurity cannot be obtained, calculation methods can be applied to estimate impact on (eco)toxicity in some cases (see section 6.3.3).

The applicant should submit all available information they consider relevant, and the applicant needs to ensure that the information is sufficient for the Tier II application. If, after the first screening of the available information, it is concluded that data gaps exist, the applicant would need to make further effort to fulfil the remaining information requirements or provide a waiving statement where applicable.

The need for additional information can also be identified by the Agency when processing the application for technical equivalence. Consequently, a request for additional information would be sent to the applicant. The scope of the information request is defined by the nature of the problem identified and the relevance of the information with regard to the decision-making on the Tier II evaluation.

6.2.1. Information requirements for Tier II

The BPR does not specify the information requirements for a technical equivalence assessment by each data element but rather it is stated that all necessary information requested by the Agency should be provided by the applicant (BPR Article 54(2)). In this section of the guidance, it is described which endpoints are considered essential by the Agency in order to reach a conclusion on technical equivalence (referred to as "Tier II information requirements"). The Tier II information requirements are given in Tables 4 and 5 below. It should be noted that other information may be necessary and requested by the Agency depending on the case. For example, information on respiratory sensitisation and neurotoxicity might be necessary for certain cases only.

Covering the Tier II information requirements would normally be sufficient for assessing and deciding on technical equivalence. Other information should be submitted by the applicant if available.

[18] Depending on the type of information that is submitted, it may be sufficient to provide only a summary of the Tier II assessment to report the required information (Tier II self-assessment report as an attachment in IUCLID Section 13). For instance, information from literature search or databases can be summarised in the Tier II self-assessment report. (Q)SAR prediction reports from the (Q)SAR tools can be provided as a separate attachment in IUCLID Section 13. However, when the applicant provides study reports from experimental tests, robust study summaries for the corresponding IUCLID endpoints should be prepared.

Table 4: Tier II information requirements for the effects on human health.

Information requirement according to data elements in Annex II to BPR	Tier II information requirement
Toxicokinetics and metabolism studies in mammals	No[a]
Acute toxicity by oral route	**Yes**
Acute toxicity by dermal route	**Yes**
Acute toxicity by inhalation	**Yes**
Skin irritation or skin corrosion	**Yes**
Eye irritation (and serious eye damage)	**Yes**
Respiratory sensitisation	No[a]
Skin sensitisation	**Yes**
Repeated dose toxicity	**Yes**
Mutagenicity	**Yes**
Carcinogenicity	**Yes**
Reproductive toxicity - fertility	**Yes**
Reproductive toxicity - development	**Yes**
Toxicity of metabolites and degradation products	No[a]
Neurotoxicity	No[a]
Endocrine disruption	No[a]
Immunotoxicity	No[a]

Note to the table:
[a] The need to provide this information will be assessed case by case.

Table 5: Tier II information requirements for the environmental effects.

Information requirements according to data elements in Annex II to BPR	Tier II information requirement
Ecotoxicity	
Short-term toxicity testing on fish	**Yes**

Information requirements according to data elements in Annex II to BPR	Tier II information requirement
Short-term toxicity testing on aquatic invertebrates	**Yes**
Growth inhibition study on algae	**Yes**
Inhibition of microbial activity	No[b]
Long term toxicity testing on fish	**Yes**[c]
Long term toxicity testing on invertebrates	**Yes**[c]
Bioconcentration, aquatic organisms (BCF)	**Yes**
Bioaccumulation, aquatic	No
Studies on sediment-dwelling organisms	No
Effects on aquatic macrophytes	No
Terrestrial toxicity (micro-organisms, earthworms, plants)	No
Effects on birds	No
Effects on arthropods (honeybees, other non-target terrestrial arthropods)	No
Terrestrial bioconcentration or bioaccumulation	No
Effects on mammals	No
Identification of endocrine activity[a]	No
Fate and behaviour in the environment[d]	
Partition coefficient (n-octanol/water)	**Yes**
Degradation in water and sediment, Biotic (Ready biodegradability)	**Yes**
Degradation in water and sediment, Abiotic (Hydrolysis, Phototransformation)	**Yes**
Adsorption/desorption (Koc)	**Yes**
Other studies for fate and behaviour in water and sediment (e.g. STP simulation,	No

Information requirements according to data elements in Annex II to BPR	Tier II information requirement
anaerobic, biodegradation in freshwater/ sea water/ manure storage)	
Fate and behaviour in soil	No
Fate and behaviour in air (estimation method)	**Yes**
Monitoring data	No

Notes to the table:

[a] The need to provide this information will be assessed case by case.

[b] While this information is part of the BPR core data set, the Agency does not consider that it is required for all cases of technical equivalence Tier II assessment.

[c] This information is not part of the BPR core data set. Nevertheless, the Agency considers that when this data is available for the AS-reference, it is necessary for the comparison of aquatic toxicity. For the Tier II assessment, the information is requested as part of the data package whenever it can be obtained by (Q)SARs, read-across or from a database or literature or the applicant has such studies, that are available at the time of the technical equivalence dossier preparation.

[d] Usually information requirements related to physicochemical and environmental fate properties can only refer to individual compounds (e.g. impurities or constituents of the active substance). Environmental fate and behaviour related Tier II information is in general only needed for constituents, impurities or additives present at a concentration of ≥ 0.1 % (w/w). However, in specific cases information could be requested also for impurities at lower concentrations (e.g. in case of close structural similarity of individual constituents which are expected to have similar persistence and bioaccumulation properties, even though for individual impurities the concentration is <0.1 % (w/w)).

6.2.2. Options to fulfil the information requirements

The applicant can fulfil the information requirements (and consequently, perform the Tier II assessment) by any of the following means:

- providing (eco)toxicity test data on the AS-alternative (and by comparing the test results with those of the AS-reference);
- providing information on the Tier II impurities present in the AS-alternative, (and by assessing whether there could be an unacceptable change in the hazard profile of the AS-alternative compared to the AS-reference due to the presence of these impurities);
- a combination of the two options above, e.g. if study reports on the AS-alternative are available for certain information requirements, the remaining information requirements can be covered by information on the Tier II impurities.

The possible sources of information and options to fulfil the information requirements include existing experimental studies (carried out by the applicant), information from experimental studies available in public literature or databases, (Q)SAR, read-across and weight-of-evidence approach. In addition, an information requirement can be waived if sufficient justification is provided by the applicant. New experimental testing, especially animal tests, should be performed only as the last resort.

Providing (eco)toxicity test data is normally the only possible option when an information requirement is covered by providing information on the AS-alternative (including impurities and additives). In general, this option is recommended when the applicant has existing experimental studies on the AS-alternative available at the time of the application preparation. It is often possible to conclude on technical equivalence based on the existing experimental information and/or using non-testing methods to provide information on the Tier II impurities. Therefore, conducting new experimental testing for the purpose of technical equivalence assessment can be considered exceptional.

If the information requirements are fulfilled by providing information on the Tier II impurities, one or several of the alternatives to experimental testing can be applied, and different options can be used for the different information requirements or different Tier II impurities. For instance, for a certain Tier II impurity, sufficient information could be obtained from an existing assessment under a different regulatory framework while the information requirements for another Tier II impurity could be covered by using (Q)SAR.

Existing experimental studies
When study reports of experimental tests with the AS-alternative are available to the applicant and used for the Tier II case, the studies should be evaluated and given a reliability indicator (e.g. Klimisch score)[19]. Studies with a low reliability (e.g. Klimisch score of 3 or 4), should normally be used only as supportive information. Further information on the evaluation of studies is available in *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.4.*

In all tests conducted with the AS-alternative, the study report should include the batch number of the test material used and a certificate of analysis where the concentration of each impurity or additive is specified. If the test material used in the (eco)toxicity test is from one of the batches used in the five-batch analysis or quality control samples, this should be specified by the applicant. If information on the composition of the test material is not provided as part of the dossier, the Agency will evaluate on a case-by-case basis whether the results of the study can be taken into account in the decision-making.

If study reports of experimental tests with any of the Tier II impurities are available to the applicant, these should also be assessed for their quality, and reliable studies can be used for the assessment of the Tier II case.

Public literature and databases
Relevant and reliable information available in public literature and databases can be used when considered adequate for the Tier II assessment. Information on the hazard properties of the Tier II impurities may be obtained from public literature (e.g. literature reviews, PubMed, TOXNET) or existing data under other regulatory frameworks (e.g. from a plant protection product assessment). Information on harmonised classifications and self-classifications on Tier II impurities may be obtained for instance from the ECHA C&L Inventory (please note that it is the applicant's responsibility to build their case and decide how to determine the classification of the impurity in the absence of harmonised classification). Relevant information may also be obtained from a number of other specialised databases and portals. Examples are listed below:

- eCHEM portal (http://www.echemportal.org/echemportal/propertysearch/treeselect_input.action?queryID=PROQdre)

[19] If the available experimental study has already been evaluated under an existing regulatory framework there is no need to re-assess the quality.

- DAR (http://dar.efsa.europa.eu/dar-web/provision) – EFSA's database of Rapporteur Member State assessment reports submitted for the EU peer review of active substances used in plant protection products
- JMPR /FAO (http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmpr/jmpr-rep/en/)– Joint FAO/WHO Meeting on Pesticide Residues
- FDA (https://www.fda.gov/Food/IngredientsPackagingLabeling/)– US Food and Drugs Administration
- IPCS/INCHEM (http://www.inchem.org/) - Chemical Safety Information from Intergovernmental Organizations
- EPA Integrated Risk Information System (IRIS) (https://www.epa.gov/iris) – US Environmental Protection Agency
- IARC (http://monographs.iarc.fr/search.php#gsc.tab=0) – International Agency for Research on Cancer Monographs on the evaluation of carcinogenic risks to humans
- OECD QSAR Toolbox (https://www.qsartoolbox.org/)
- WHO (http://search.who.int/search?site=default_collection&client=default_frontend&output=xml_no_dtd&proxystylesheet=default_frontend&proxycustom=<HOME/>) – World Health Organisation
- ECHA dissemination website (https://echa.europa.eu/information-on-chemicals/registered-substances)- Database of registered substances under REACH
- ECHA Candidate list of substances of very high concern (https://echa.europa.eu/candidate-list-table)
- Cosmetic databases (https://ec.europa.eu/health/scientific_committees/consumer_safety/opinions_en#fragment2)
- EU OSHA Community workplace exposure limits (https://osha.europa.eu/en/legislation/directives/commission-directive-2009-161-eu-indicative-occupational-exposure-limit-values) – European Agency for Safety and Health at Work
- EMA Scientific guidelines (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000431.jsp&mid=WC0b01ac0580029593) – European Medicines Agency
- ECHA C&L inventory (for harmonised classifications the only legal source is the Official Journal)
- ECHA Annex III inventory (https://echa.europa.eu/information-on-chemicals/annex-iii-inventory)
- EMA document on impurities: guideline for residual solvents in pharmaceuticals (http://www.ich.org/products/guidelines/quality/quality-single/article/impurities-guideline-for-residual-solvents.html)
- Safety Data Sheet (SDS) documents
- EFSA OpenFoodTox https://www.efsa.europa.eu/en/data/chemical-hazards-data
- Database specific for the pesticide active substance and their metabolites, comprising the main genotoxicity endpoints https://data.europa.eu/euodp/en/data/dataset/database-pesticide-genotoxicity-endpoints/resource/a370f4ba-cfa5-4731-9af2-4af20a373cb1

(Quantitative) Structure-Activity Relationship ((Q)SAR)

Toxicological, ecotoxicological or environmental fate properties of a substance can be

estimated with (Quantitative) Structure-Activity Relationship ((Q)SAR) models. According to the BPR, the results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence, but not the absence of a given dangerous property. It is recommended to assess the same endpoints using the same (Q)SAR tools for the Tier II impurities and the active ingredient of the active substance. The following stepwise approach can be followed when (Q)SAR information is used to fulfil the information requirements in technical equivalence assessment:

1) Check if there is any information available about the Tier II impurity on the ECHA dissemination website (substance brief profile)[20],
2) Check if the Tier II impurity is in the Annex III inventory[21]. This inventory has been compiled by ECHA to identify substances likely to meet the criteria of Annex III to the REACH Regulation. The inventory shows indications for human health or environmental concerns. Although this inventory has been compiled for another purpose, it can still be used to support the assessment of a Tier II impurity.
3) Run the (Q)SAR model(s) available to the applicant (freely and commercially available models are indicated in Appendix 1 of the REACH Practical Guide How to use and report (Q)SARs)[22]. The assessment can be supported by running more that one (Q)SAR tool for the same endpoint. In general, in-silico programs can be grouped into rule-based expert systems and quantitative structure activity relationship systems (QSAR-systems). It is recommended to combine the use of both systems to minimize the number of false positive or false negative predictions[20].
4) Additional information on the Tier II impurity can be gathered from the OECD QSAR Toolbox (available at https://www.qsartoolbox.org/) and/or from the other databases/portals mentioned in the previous section.
5) Compare the collected Tier II impurity information with the available information on the active substance.

Examples of freely available (Q)SAR tools which may be used:

- Danish QSAR database (http://qsar.food.dtu.dk/)
- ECOSAR (https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model)
- OECD QSAR Toolbox (http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm)
- VEGA (https://www.vegahub.eu/portfolio-item/vega-qsar/)

The applicant should submit the complete (Q)SAR prediction report from the (Q)SAR tools (prediction specific QPRF). In order to facilitate the processing of applications involving (Q)SAR analyses, the applicant should provide detailed information on the (Q)SAR software applications (e.g. software version used and any alterations which have been made to the default settings) as well as information on the identity of the active ingredient and Tier II impurity (e.g. chemical structure, SMILES, CAS number, EC number).

For more information see *REACH Guidance on information requirements and chemical safety assessment, Chapter R.6: QSARs and grouping of chemicals* or Practical Guide How to use and report (Q)SARs.

Read-across
Read-across is an approach for predicting endpoint information for one substance ("target

[20] https://echa.europa.eu/information-on-chemicals
[21] https://echa.europa.eu/information-on-chemicals/annex-iii-inventory
[22] ECHA Practical Guides are available at https://echa.europa.eu/practical-guides.

substance") by using data from the same endpoint from (an)other substance(s) ("source substance"). The underlying assumption is that as a result of structural similarity the physicochemical, toxicological and ecotoxicological properties of the source substance and target substance are likely to be similar or follow a regular pattern. It should be noted that structural similarity alone is not sufficient to justify the possibility to predict properties of the target substance by read-across. The differences in structure should also be explained, i.e. why structural differences, or variations within the group, would not be expected to affect the property being predicted.

For a Tier II assessment, read-across can be used to provide information on the Tier II impurities. The Read-Across Assessment Framework (RAAF) developed by the Agency can be used to assess and report read-across[23].

Weight of evidence
In the context of fulfilling information requirements, the weight of evidence (WoE) approach refers to using evidence from several sources, where the information from each of the sources individually may be insufficient. The WoE approach by its nature requires scientific judgement, and therefore it is necessary to provide adequate and reliable documentation to justify the approach. It is important to document and explain how the WoE-based approach was used. A template and further guidance with examples on using WoE is available at the ECHA website at: https://echa.europa.eu/support/guidance-on-reach-and-clp-implementation/formats. The WoE background document also includes guidance and examples for the assessment of quality of other type of evidence in addition to experimental studies. Additional guidance is also available in the REACH Practical guide *How to use alternatives to animal testing to fulfil your information requirements for REACH registration* and in a report on non-animal approaches (*Non-animal approaches - Current status of regulatory applicability under the REACH, CLP and Biocidal Products regulations* available at https://echa.europa.eu/publications/technical-scientific-reports).

For Tier II assessment, the WoE can be applied to cover a specific information requirement. For example, information of bioaccumulation potential could be fulfilled by providing a BCF value from literature and in addition (Q)SAR prediction for a log Kow and/or BCF value as supportive information. In addition, WoE can be applied in the decision making for the overall conclusion on the technical equivalence case (see section 6.3 of this guidance).

Waiving an information requirement
Some of the information requirements may be waived when sufficient and acceptable justification is provided. More information on waiving is provided in the BPR Guidance documents Vol III Part A and Vol IV Part A, and ECHA Practical guide 4: How to report data waiving. For instance, the inherent physical and chemical properties of the substance may justify waiving of some information requirements. As an example, information on bioconcentration could be waived if there is other available information to show that the substance has a low potential for bioconcentration (e.g. based on the log Kow value and/or other evidence). Additionally, providing information on biodegradation of a metal impurity would not be applicable.

A waiving statement could be provided to cover all information requirements of a certain Tier II impurity, for which the hazard is known to be low (see section 6.3.3 of this guidance).

New experimental testing
When additional information needs to be generated, as a first step non-testing methods should be considered (e.g. QSAR or read-across). New experimental testing should be performed only

[23] More information available on ECHA website at https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across.

as the last resort. This is especially relevant for vertebrate animal testing; please see Chapter I, section 1.2, point (8) in the ECHA *Guidance on Biocidal Products Regulation, Part A: Information Requirements*.

In considering the need for further testing, the guidance SANCO/10597/2003-rev.10.1 (DG SANCO, 2012) should be considered.

Where additional experimental testing is necessary for toxicity properties, in general testing of the whole active substance, including all impurities (at a sufficiently high level for the purpose of the testing), is preferred. However, testing of a certain Tier II impurity is not excluded and could be reasonable for instance if the same data can be used to support an assessment under another regulatory framework.

New experimental testing of AS-alternative (or a Tier II impurity) should only be considered if there are indications based on the available information that there could be an increased hazard for the AS-alternative due to the change in composition compared to the AS-reference.

The general principle is that before carrying out any tests on animals, according to BPR Article 62(2) the applicant needs to send an inquiry to ECHA to find out whether a test or study addressing the same information requirement has already been conducted and submitted. If such information exists, companies are required to share the data.

Furthermore, before performing new (eco)toxicological studies with the AS-alternative (or a Tier II impurity), even as a result of an information request from the Agency, the applicant should discuss the testing strategy and study protocol with the Agency. Among other things, it may need to be ensured that the composition of the test material is appropriate and that the method and study conditions are comparable to those for the AS-reference.

If new experimental testing is performed by the applicant, the study reports should be submitted as part of the technical equivalence dossier. As for any existing studies, the reports need to be evaluated and given a reliability indicator. Also, information on the test material has to be provided (batch number and composition).

6.3. Assessment of technical equivalence Tier II

As described above, the aim of the Tier II assessment is to conclude whether there is an unacceptable change in the hazard profile of the AS-alternative compared to the AS-reference due to the changes in the chemical composition. The elements of the assessment that need to be covered in Tier II are:

- classification; is the classification of the AS-alternative more severe compared to the AS-reference?

- effects on human health and the environment; is there an unacceptable increase in the toxicity or ecotoxicity of the AS-alternative compared to the AS-reference?

- PBT/vPvB properties; is there an unacceptable change in the PBT/vPvB properties of the AS-alternative compared to the AS-reference?

- ED properties; is there an unacceptable change in the ED properties of the AS-alternative compared to the AS-reference?

As there are different ways to compile the necessary information (see section 6.2.2 of this guidance), the approach chosen for the Tier II assessment will depend on the type of information available. The assessment methods are described separately for the option where

the required information is provided for the AS-alternative (section 6.3.2 of this guidance) and for the option where the information is provided on each Tier II impurity (section 6.3.3 of this guidance).

The different pieces of information may provide various lines of evidence to support an overall conclusion on technical equivalence. All lines of evidence should be considered in a weight of evidence (WoE) approach in order to conclude on the technical equivalence.

The following outcomes are possible for a Tier II technical equivalence assessment:

- The AS-alternative does not present a greater toxicological or ecotoxicological hazard than the AS-reference and hence the AS-alternative can be considered as technically equivalent;
- On the basis of the information available it is concluded, or it cannot be excluded, that the AS-alternative presents a greater hazard than the AS-reference; hence the AS-alternative cannot be considered technically equivalent to the AS-reference.

The decision is based on a comparison of the AS-reference and the AS-alternative regarding all the Tier II assessment elements. If any of these indicate that the AS-alternative is more hazardous or this cannot be excluded, the active substances from the two sources cannot be considered technically equivalent. For example, if there is insufficient information on a Tier II impurity that could be carcinogenic, it might not be possible to exclude that the AS-alternative presents a greater hazard.

6.3.1. Classification of the AS-alternative

The classification of a substance is decided based on the available hazard information of the substance and by comparing the information against the classification criteria in CLP. In this section, the principles are described for determining the classification of the AS-alternative as part of the technical equivalence assessment. Detailed instructions on determining classification of substances and mixtures are available in the *Guidance on the Application of the CLP Criteria* and in the CLP Regulation.

After gathering all required information (as described in section 6.2 of this guidance), it is recommended to start the Tier II assessment by checking the classification of the AS-alternative. The reason is that whenever a more severe classification is warranted for the AS-alternative (including the M-factor) compared to the AS-reference, the active substances from the two sources cannot be considered technically equivalent. In that case, no further Tier II assessment would be required.

If the available information would not warrant a more severe classification for the AS-alternative, the Tier II assessment needs to proceed to the effects on human health and the environmental effects (sections 6.3.2 and 6.3.3 of this guidance). Information on the classification only is not sufficient to cover the toxicological and ecotoxicological properties of the substance. Since the same hazard information may be used for concluding on the classification and comparing changes in the effects on human health and environmental effects, in practice it might be necessary to assess these Tier II elements in parallel.

When there are no experimental data available on the AS-alternative and the assessment is instead based on the information on the Tier II impurities, the classification is determined using available classification information on the impurities. In this case, the bridging principles or calculation methods as explained in the CLP guidance for each endpoint should be used. It is the obligation of the applicant to check if any of the Tier II impurities can have an influence on the classification of the active substance. If harmonised classification is not available for the impurities, information from other sources should be used. Self-classification notifications in the C&L inventory may provide indications of possible additional hazards.

The Agency verifies that the classification of the AS-alternative reported by the applicant is correct regarding both the Tier II impurities and the active substance. More detailed instructions and an example regarding health hazards are provided in section 6.3.3.1 of this guidance.

It is possible that in some borderline cases the more severe classification of the AS-alternative is triggered due to a minimal difference in the reference values of the AS-alternative and the AS-reference. Such a situation would be evaluated on a case-by-case basis by the Agency in order to decide if other available information would justify considering the active substances from the two sources technically equivalent.

6.3.2. Effects on human health and the environment: Experimental studies on the AS-alternative

6.3.2.1. Comparison of toxicological hazard profiles

When toxicological test data are available for both the AS-reference and the AS-alternative, the results of the studies should be compared. If an unacceptable difference is observed, the conclusion on technical equivalence would be negative unless justification is provided which explains the difference and demonstrates that it does not lead to more severe hazards.

If the results for a particular endpoint show a similar level of hazard, the AS-alternative can be considered as not more hazardous than the AS-reference for this endpoint. For the comparison of the results of each endpoint, a 2-fold higher toxicity (when comparing e.g. NOAEL values) is considered as an indicative upper limit for a significant difference for the AS-alternative (SANCO/10597/2003-rev.10.1; DG SANCO, 2012). If experimental test data have been provided for all Tier II information requirements and they all show a similar level of hazard, it could be concluded that, overall, the active substances from the two sources are technically equivalent. Specific consideration is necessary to justify a study performed on a different species if there is information showing that it is not the most sensitive species.

Any difference of more than 2-fold would trigger the need to assess whether the difference can be attributed to a difference between the tests performed, such as the species/strain used, concentrations tested, dose spacing, test guideline/test method followed and the composition of the batches used in testing.

When performing this assessment, the whole data package should be taken into account in concluding whether this could be considered as an indication of a more severe hazard.

The effects in different studies should be seen in the same organs and in the same order of magnitude in order to conclude on similar hazards. Any additional or more severe effects on organs by the AS-alternative as compared to the AS-reference would lead to the AS-alternative not being technically equivalent with the AS-reference unless the difference can be justified.

If the studies performed with the AS-alternative are not directly comparable to the studies on the AS-reference, they may still be used in a weight-of-evidence approach. Any difference in the endpoint values would need to be justified and the applicant may need to provide further information to demonstrate that there is no increased hazard for that particular endpoint.

Where the studies provide no numerical value but either a positive or negative result (e.g. mutagenicity, corrosivity), and the AS-reference was negative, a positive result for the AS-alternative would lead to the AS-alternative not being technically equivalent to the AS-reference unless the difference can be justified. In Table 6, it is illustrated with an example how the different endpoints can be assessed.

Table 6: Examples of comparison of toxicological data on the AS-reference and the AS-alternative[a].

Information requirement	Toxicological data		<2?[b]	Acceptability
	AS-reference	AS-alternative		
Acute toxicity- dermal	NOAEL 30 mg/kg LD50 100 mg/kg	NOAEL 10 mg/kg LD50 40 mg/kg	No	Not acceptable because the difference in toxicity is more than two-fold and the classification of the substance has changed
Acute toxicity-inhalation	LOAEL 0.01 LC50 0.1 mg/L	LOAEL 0.001 LC50 0.04 mg/L	No	Not acceptable unless the difference is due to differences in study protocols (e.g. dose spacing)
Repeated dose toxicity	Lowest relevant oral NOAEL in dogs: 1 mg/kg bw/day	Lowest relevant oral NOAEL in rats: 2 mg/kg bw/day		Acceptable if the following conditions are met: - there is no information indicating that the dog (tested species for AS-reference) would be more sensitive than the rat (tested species for AS-alternative) for the substance and endpoint studied. - all the other evidence shows that TE Tier II is met

Notes to the example:

[a] The example is only to illustrate a potential way to address and report the specific part of technical equivalence assessment. Alternative approaches and formats are possible.

[b] Are the test results within 2-fold difference or dose spacing?

6.3.2.2. Comparison of ecotoxicological hazard profiles

When study reports from experimental tests with the AS-alternative are available, it is first necessary to assess whether the studies can be used to compare the ecotoxicity of the AS-alternative with the AS-reference. Usually detailed comparison can be performed only by the Agency, unless the applicant has access to the full study reports including information on the composition of the batches used in the tests with the AS-reference.

Differences in the study setups should be analysed in order to assess whether the two studies are directly comparable and/or if there are factors that could explain the differences in the results. As a starting point, information on the species/strain used, concentrations used (including dose spacing), test guideline/test method followed and the composition of the batches used in testing should be checked from the study reports of both the AS-reference and the AS-alternative. In addition, it should be specified the duration of the study and, for toxicity studies with aquatic organisms, whether the study endpoint is expressed in terms of nominal, mean measured or initial measured concentrations (since these factors can influence whether study endpoints are truly comparable).

If the studies performed with the AS-alternative are not directly comparable to the studies on the AS-reference, they may still be used in a weight-of-evidence approach. Any difference in the endpoint values would need to be justified and the applicant may need to provide further information to demonstrate that there is no increased hazard for that particular endpoint.

If the results for a particular endpoint show a similar level of hazard (within the agreed limits), the AS-alternative can be considered as not more hazardous than the AS-reference for this endpoint. If experimental test data have been provided for all Tier II information requirements and they all show a similar level of hazard, it could be concluded that, overall, the active substances from the two sources are technically equivalent. If an unacceptable difference is observed, the conclusion on technical equivalence would be negative unless justification is provided which explains the difference and demonstrates that it does not lead to more severe hazards.

For the comparison of the results, a difference of a factor higher than 5 between the endpoint values (or by a factor greater than that of the appropriate dosage increments, if greater than 5 in case of a NOEC) will be used as an indicative value for a significant difference. In other words, when comparing the test results for the AS-alternative and the AS-reference, the difference should be ≤ 5 in order to consider the active substances from the two sources as equivalent. Some illustrative examples are presented in Table 7.

All available information should be considered in concluding whether a difference greater than factor 5 in an endpoint must be considered as an indication of a more severe hazard (e.g. using WoE approach).

Regarding environmental fate studies (e.g. biodegradation, adsorption), the comparison between the AS-reference and the AS-alternative may be challenging since the test results (e.g. DT50 values) usually refer to the active ingredient. If environmental fate studies are available on the AS-alternative, these should nevertheless be evaluated and the results should be compared to the results on the AS-reference. Any major differences between the studies which could result in an unacceptable change in the PBT/vPvB properties or in the classification of the AS-alternative compared to the AS-reference should be identified and assessed. In order to overcome the difficulties when comparing the active substances, the environmental fate endpoints should be assessed for each Tier II impurity present at a concentration of≥0.1 %

w/w[24] in addition to the available results for the AS-alternative.

In general terms, the most critical aspect of the fate properties is to identify whether the overall conclusion on PBT/vPvB properties of the AS-alternative could differ from that of the AS-reference. Therefore, consideration of the PBT/vPvB properties of Tier II impurities (≥0.1 % w/w) is needed at least at screening level (see section 6.3.4 of this guidance).

Table 7: Examples of comparison of ecotoxicological and environmental fate data on the AS-reference and the AS-alternative[a]. (RI = Reliability indicator)

Information requirement	Ecotoxicological data		Acceptability of the observed difference	
	AS-reference	AS-alternative	<5%[b]	Overall acceptability and/or justification
Short-term toxicity testing on fish	96 h-LC50 (*O. mykiss*): 1.9 mg/L OECD 203, RI=1	96 h-LC50 (*O. mykiss*): 1.2 mg/L OECD 203, RI=2	Yes	Acceptable; same species, same study endpoint and guideline, within the 5-fold difference
Short-term toxicity testing on aquatic invertebrates	96 h-EC50 (*A. bahia*): 1.7 mg/L EPA OPPTS 850.1035, RI=2	48 h-EC50 (*D. magna*): 2.9 mg/L OECD 202, RI=2	Yes	Acceptable since within the 5-fold limit. However, possible impact from the different endpoint, guideline and species should be checked.
Growth inhibition study on algae	72 h-E_rC50 (*P. subcapitata*): 0.389 mg/L OECD 201, RI=2	72 h-E_rC50 (*P. subcapitata*): 0.064 mg/L OECD 201, RI=2	No (6.1)	Possibly acceptable with consideration - close to the 5-fold limit, additional information should be considered in a weight of evidence approach
Long term toxicity testing on fish	28 d NOEC (*O. mykiss*): 0.11 mg/L OECD 215 RI=1	No study available	-	Comparison not applicable (information may be provided for Tier II impurity)
Long term toxicity testing on invertebrates	No study available	No study available	-	Information not required since no data is available for the AS-reference. Information on Tier II impurity can be anyway provided as supportive evidence.

[24] In specific cases environmental fate information could be requested also for Tier II impurities at lower concentrations (e.g. in case of close structural similarity of individual constituents which are expected to have similar persistence and bioaccumulation properties, even though for individual impurities the concentration is <0.1 % w/w).

Bioconcentration	BCF = 420 (estimation method based on log Kow)	No study available.	-	Comparison not applicable. Additional argumentation was provided to justify the waiving.
Biodegradation	Readily biodegradable (OECD 301A, 78 % degradation)	Readily biodegradable (OECD 301C, 72 % degradation)	-	The available studies are not completely comparable. However, the results are consistent.
Hydrolysis	pH 5 stable pH 7 stable pH 9 stable (OECD 111)	No study available.	-	Comparison not applicable. (information to be provided for Tier II impurity)
Fate and behaviour in air (estimation method)	Half-life 4.6 h (estimation based on QSAR)	Half-life 4.6 h (estimation based on QSAR)	-	Endpoint predicted with the same QSAR model.

Notes to the example:

[a] The example is only to illustrate a potential way to address and report the specific part of technical equivalence assessment. Alternative approaches and formats are possible.

[b] Are the test results within 5-fold difference or dose spacing?

6.3.3. Effects on human health and the environment: Information on the Tier II impurities

When no experimental test data on the AS-alternative itself are available for a Tier II information requirement, it should be assessed whether the hazard properties and the concentration of the Tier II impurities in the AS-alternative could lead to an unacceptable change in the hazard profile of the AS-alternative compared to the AS-reference. Different methods are used for the assessment of toxicological and ecotoxicological hazards according to the current scientific knowledge and methodologies available (see sections 6.3.3.1 and 6.3.3.2 of this guidance).

Tier II impurities for which hazards are known to be low

As a starting point, the Tier II information requirements should be covered for each Tier II impurity. However, certain compounds for which the (eco)toxicity is known to be low (e.g. certain non-critical inert materials, mineral salts, and water) can be considered as an exception. For such impurities it would not be necessary to report all the toxicological and ecotoxicological properties according to the Tier II information requirements (section 6.2.1 of this guidance). A justification has to be included to explain why the information was not provided and why further assessment in Tier II is not considered necessary.

(Q)SAR alerts and predicted (eco)toxicity

When considering the alerts found in the SAR models for the Tier II impurities, it is appropriate to check whether similar alerts (i.e. for the same endpoints) are identified for the active ingredient using the same SAR tools. The limitations of (Q)SAR should be taken into account. If a SAR prediction shows no alerts, it can be used in contributing to the WoE to justify that there is no need for a further assessment of the Tier II impurity.

If a similar alert is found by the SAR model for the active ingredient and the Tier II impurity, a case-by-case analysis is needed. The alert for the impurity should not be discarded and should be followed up. For example, if there is an alert for genotoxicity for both the active ingredient and the Tier II impurity and for the active substance there are negative genotoxicity study

results, it should be assessed whether the alerts are due to the same structural feature.

It is possible that for a certain Tier II impurity a new alert is observed from a SAR prediction which is not observed for the active ingredient. In that case, assuming that the alert is correct, it should be assessed whether the concentration at which the impurity is present would cause a more severe toxicity or ecotoxicity profile of the active substance. The mode of action and the chemical group inducing the observed effect may need to be considered to determine if the impurity can have comparable or additional hazard compared to the active ingredient. If it is considered by the Agency that the impurity may significantly increase the overall (eco)toxicity of the active substance, the applicant may be requested to provide further information in order to refine the assessment and to justify technical equivalence.

6.3.3.1. Assessment of change in toxicity

The toxicological assessment for each Tier II impurity should cover all information requirements indicated in section 6.2.1 of this guidance. The impurities will be assessed based on all the information provided, including experimental studies, public literature, QSAR and/or read-across (illustrated in section 6.2.2).

The criteria and guidance for classification used in the CLP regulation may be used for evaluation purposes (e.g. information on the generic concentration limits, see section 6.3.2.1 of this guidance), together with the guidance for biocides hazard assessment (BPR Guidance Vol III and Vol IV).

For technical equivalence, two conditions need to be met: 1) the classification of the AS-alternative is not more severe than the AS-reference (see also section 6.3.1); and 2) the AS-alternative is not more than 2-fold more toxic for any given endpoint compared to the AS-reference. These conditions are further elaborated below.

Condition 1. Is there a change in classification?
Any constituent of unknown toxicity may be considered not to affect the classification of the substance if its concentration is lower than the generic concentration limits or cut off values specified in Regulation (EU) No 1272/2008 (CLP Regulation) and presented in Table 8 below. Based on this, if there is a Tier II impurity with unknown toxicity in the AS-alternative, the concentration limits indicated in the Table 8 are the criteria to decide whether the Tier II impurity may affect the classification of each endpoint. However, for those endpoints where additivity applies, i.e. acute toxicity and skin corrosion/irritation/serous eye damage/eye irritation, the calculation method should be used to assess whether classification can be changed considering all impurities classified for that endpoint.

All information has to be considered and in specific cases an impurity may have significant effects below the generic concentration limits. This would be the case for substances for which there is a specific concentration limit that is lower than the generic concentration limit, and for substances that are known to have significant effects at concentrations below the generic concentration limits (e.g. extreme sensitisers).

Table 8: Generic concentration limits or cut off values for human health endpoints (based on CLP Regulation EU No 1272/2008)

Health hazard endpoint	Generic concentration limit or a cut off value
Acute toxicity categories 1-3	0.1% (1 g/kg)
Acute toxicity category 4	1% (10 g/kg)
Skin corrosion/irritation/serous eye damage/eye irritation	1% (10 g/kg)

Health hazard endpoint	Generic concentration limit or a cut off value
Skin sensitisation 1A	0.1% (1 g/kg)
Mutagenicity 1A or 1B	0.1% (1 g/kg)
Carcinogenicity 1A or 1B	0.1% (1 g/kg)
Reproductive toxicity 1A or 1B	0.3% (3 g/kg)
Specific target organ toxicity (single and repeated exposure)	1% (10 g/kg)

Noting the possibility of effects below generic concentration limits, all available information, including a QSAR prediction, should be provided for impurities for which there is no experimental data available.

If, for an impurity that is present at a concentration below a general concentration limit or a cut off value, only a QSAR prediction showing an alert is available, case by case consideration is needed to conclude on whether further information is needed to demonstrate that the impurity will not affect the toxicity of the active substance (see Table 9 below; carcinogenicity and eye irritation examples).

Classification of the active substance should be taken into account in the assessment. For example, if the active substance is classified as Skin Sensitisation 1A, an impurity that is also a skin sensitiser would normally not affect the overall hazard on sensitisation unless it is an extreme sensitiser which would change the specific concentration limit.

Condition 2. Is the AS-alternative more than 2-fold more toxic?
For each endpoint, the AS-alternative should not have more than a 2-fold difference in the NOAEL compared to the corresponding NOAEL or other value used for deriving reference values in the AS-reference. Any exceedance of the 2-fold difference should be justified as explained in section 6.3.2.1 of this guidance. If the information is sufficient to derive a NOAEL for the Tier II impurity, the applicant should include an assessment of whether it could affect the overall NOAEL. An illustrative example is provided in Table 9.

If the endpoint and/or the effects are different (and not additive or synergistic), the following equation can be used to calculate whether an impurity may significantly affect the overall (lowest) NOAEL of the AS-alternative:

$$\text{Percentage of impurity that would not significantly affect the NOAEL of the active substance} = NOAEL_{impurity} / NOAEL_{active\ substance} \times 100$$

The above equation indicates whether there would be a possible impact on the NOAEL of the active substance due to the presence of the impurity i.e. a percentage of impurity that would affect the NOAEL of the active substance. The value obtained can be used in comparison whether the impurity (at the certain concentration) would increase more than 2-fold the toxicity of the active substance.

One option to show that there is no unacceptable increase in toxicity due to a Tier II impurity with unknown toxicological properties is to use the Threshold of Toxicological Concern (TTC) approach[25], especially for impurities for which genotoxicity alert is triggered. An example of applying the TTC approach is provided in Table 9.

[25] https://www.efsa.europa.eu/en/supporting/pub/1006e

If the impurity is present in the active substance from both sources, the possible effect of an increased concentration needs to be assessed. If the endpoint is the same and the effect is considered to be additive/synergistic, the risk based approach from Biocides Guidance vol III Parts B+C chapter 4.4 *Risk Characterisation for combined exposures* should be used.

Table 9: Example of an impurity assessed in Tier II for human health endpoints[a].

Impurity	Max. conc. in % (w/w) in the AS-reference	Max. conc. in % (w/w) in the AS-alternative	Summary of the toxicity for the critical endpoints	NOAELs and concentration limits (e.g. SCLs)	Conclusion
Impurity x	Not reported in the reference specification	0.1	(Q)SAR analysis of the impurity showed an alert in eye irritation, skin sensitisation and carcinogenicity. In a carcinogenicity study, the impurity was carcinogenic with a clear dose-response relationship (Cat 1B). In public literature, a mixture containing 0.05% of this impurity has been shown to cause skin sensitisation in humans with a high incidence in a large population in several epidemiological studies and case reports. Other substances in the mixture are not sensitisers.	NOAEL (carcinogenicity, thyroid tumours) for the reference substance is 100 mg/kg bw/day in mice. The substance is classified for Carc. 1B. NOAEL (carcinogenicity, testicular tumours) for the impurity is 1 mg/kg bw/day in rats. The SCL for skin sensitisation is 0.05% based on the CLP criteria.	Eye irritation is not of concern at a concentration of 0.1%. The NOAEL of the AS-reference is 100 times higher than that of the impurity. The concentration of the impurity is 1/1000 of the concentration of the a.s. Therefore, the concentration of the impurity does not affect the carcinogenicity NOAEL of the substance. The SCL of the impurity for skin sensitisation is 0.05, which means that the substance in the AS-alternative must be classified for Skin Sens 1A. Thus, the substance is not technically equivalent. Further information on skin sensitisation of the AS-alternative needs to be provided to support technical equivalence.
Impurity xx	Not reported in the reference specification	0.0003	No information is available on the impurity in the literature. The QSAR analysis shows an alert for genotoxicity. The active substance is not genotoxic. The	The TTC of 0.0025 µg/kg bw/day applies due to a genotoxicity alert. Maximum exposure to the impurity can be	The impurity may increase the hazard of this substance. Further information is needed to support technical equivalence.

Impurity	Max. conc. in % (w/w) in the AS-reference	Max. conc. in % (w/w) in the AS-alternative	Summary of the toxicity for the critical endpoints	NOAELs and concentration limits (e.g. SCLs)	Conclusion
			AEL of the active substance is 4 mg/kg bw/day. The TTC approach may be applied, using a threshold level which is compared to AEL.	calculated on the basis of the AEL of the active substance. This would be 0.000003 × 4 mg/kg bw/day = 0.012 µg/kg bw/day that is above the TTC.	

Note to the example:
[a] The example is only to illustrate a potential way to address and report the specific part of technical equivalence assessment. Alternative approaches and formats are possible.

6.3.3.2. Assessment of change in ecotoxicity

The required ecotoxicity information (e.g. EC50 and NOEC values) for each Tier II impurity should be collected in a summary table and the corresponding values for the active substance (e.g. from the assessment report of the AS-reference and/or QSAR prediction for the active ingredient) should be presented for comparison (see Table 10).

Table 10: Example of comparison of the ecotoxicological information for the AS-reference (and active ingredient) and the Tier II impurities[a].

Information requirement-Ecotoxicity	AS-reference (experimental)	Active ingredient (QSAR)	Impurity 1 in the AS-alternative (QSAR)	Impurity 2 in the AS-alternative (literature data)
Short-term toxicity on fish: Fish 96-hr LC50 (mg/L)	0.0014	0.033	$4.15*10^{-5}$	0.48
Short-term toxicity on aquatic invertebrates: Daphnia 48-hr LC50 (mg/L)	2.50	2.672	0.873	2.619
Growth inhibition study on algae: Algae 96-hr EC50 (mg/L)	0.67	0.144	0.00066	1.9
Long-term toxicity on fish: NOEC/chronic value (mg/L)	>0.0011 (90 days)	0.000548	$3.35*10^{-6}$	No information was found in literature and/or databases and reliable QSAR

				prediction not possible
Long-term toxicity on invertebrates: Daphnia – chronic (mg/L)	0.00062	0.00117	0.011	No information was found in literature and/or databases and reliable QSAR prediction not possible
Growth inhibition study on algae – EC10 (mg/L)	0.0047 (72 h)	0.015	$2.11*10^{-5}$	0.11

Note to the example:
[a] The example is only to illustrate a potential way to address and report the specific part of technical equivalence assessment. Alternative approaches and formats are possible.

When the available information indicates that there could be an increase in the ecotoxicity of the active substance due to Tier II impurity, a calculation method can be used to check whether the ecotoxicity endpoint values (e.g. EC50) of the AS-alternative are a factor of 5 greater than that of the AS-reference (as explained in section 6.3.2.2 of this guidance). For the calculation purposes, when QSAR information is used, the QSAR result (e.g. EC50) of the Tier II impurity should be compared with the QSAR result of the AS-reference. This is the recommended approach instead of comparing the QSAR result of the Tier II impurity with an experimental result on the AS-reference. The QSAR results of the AS-reference should be consistent with the experimental results of the AS-reference. Otherwise, the reliability and relevance of the QSAR should be checked and the use of the QSAR results for the AS-reference should be justified.

The calculation method can be used by the applicant if the concentration of the Tier II impurity is known in both the AS-reference and the AS-alternative. If the applicant does not have access to this information, ecotoxicological information should anyway be provided for the Tier II impurity and a comparison of the hazard properties without considering concentrations should be made to the AS-reference and/or active ingredient (e.g. if QSAR estimations available). When the applicant does not have access to the AS-reference impurity profile, the Agency will use the calculation method to assess the case, where relevant. When the calculation method is used by the applicant, detailed description of the values used in the calculation method should be presented in the technical equivalence assessment report to facilitate the evaluation by the Agency.

The calculation method is based on the well-accepted concept of concentration additivity applied in the assessment of mixture toxicity. The approach is based on the assumption of similar mode of action whereas the potency of the different components in the mixture may vary. The following equation (1) is applied for a mixture of n components with a relative fraction (p) and specific effect concentration (EC_x):

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

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

The different components relevant for the assessment of technical equivalence are the active substance itself (typically as the major constituent in a mono-constituent substance) and the Tier II impurities (typically present at low concentrations, e.g. 0.1 … 1 %). In the following, the Tier II impurity to be assessed is presented as "A" and the active substance is "B" (in this context: sum of all other constituents in the active substance). If the amount of "A" is p(A), the amount of "B" can be expressed as p(B) = 1 – p(A).

When the effect concentration of the impurity A is known (EC_x), a factor "f" can be calculated when the overall toxicity of the mixture AB is also known:

$$f = \frac{EC_x(B)}{EC_x(A)} = \frac{EC_x(AB) - p(A) \times EC_x(AB)}{EC_x(A) - p(A) \times EC_x(AB)} \quad (2)$$

The factor "f" is a parameter to indicate how much the impurity A is more toxic than the component B.

Prediction of the toxicity of a binary mixture AB_{alt} (AS-alternative) in relation to a mixture AB_{ref} (AS-reference)[26]

Based on the equations presented above, predicting the overall toxicity of the AS-alternative (with a different concentration of the impurity A than in the AS-reference) is possible even in the absence of toxicity information of all the mixture components:

$$\frac{EC_x(AB_{ref})}{EC_x(AB_{alt})} = \frac{(f-1) \times p_{alt}(A) + 1}{(f-1) \times p_{ref}(A) + 1} \quad (3)$$

Where,
EC_x = concentration causing x % effect
f = factor by which the impurity A is more toxic than the component B
$p_{alt}(A)$ = proportion of the impurity A in the AS-alternative
$p_{ref}(A)$ = proportion of the impurity A in the AS-reference

The difference in the toxicity of the active substances from the two sources (EC_x of the AS-reference compared to EC_x of the AS-alternative) depends on the concentration of the impurity (component A) in the AS-reference and in the AS-alternative as well as on the factor "f" which reflects the toxicity of impurity A in comparison to the toxicity of the active substance (component B).

If ecotoxicity information is available on the impurity as well as on the active substance, the factor f can be calculated, but in the absence of data, a default value can be assumed. The effect concentration of the active substance from the reference source (ECx(AB)) can be obtained from data available in the assessment report. If for example, literature data or QSAR estimations are available on the ecotoxicity of the impurity, equation 2 can be used for estimating the value for factor f.

[26] Example of the calculation method is provided in "Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (ec) no 1107/2009" (https://ec.europa.eu/food/plant/pesticides/authorisation_of_ppp/application_procedure_en)

For the purpose of the technical equivalence assessment, when no information is available on the ecotoxicity of the Tier II impurity (impurity A), a default factor f = 100 can be applied. This assumes that the impurity is 100 times more toxic than the active substance component. The factor can be lowered to a value f = 10, when there is sufficient information available on the toxicity of the impurity and based on expert judgement. This can be for instance information on the mode of action or ecotoxicity information on other endpoints or species.

If the AS-alternative contains multiple Tier II impurities which may increase the overall toxicity in comparison to the AS-reference, the sum of all these impurities should be taken into consideration.

In case there are several Tier II impurities having similar type of hazard properties (e.g. same mode of action) and the f factors are within the same order of magnitude (i.e. similar potency), the same calculation method could be used by summing up the concentrations of all impurities. In this case the highest (most conservative) f value shall be used. In cases where f is based on a default value (e.g. 10 or 100) for the different impurities, the concentrations could also be summed up and inserted in the equation as one single constituent.

In situations where the f factor from the different impurities differ from each other by a factor greater than 10, summing up the concentrations may result in an overestimation of the hazard. In this situation, a case-by-case assessment would be needed and it may be more relevant to consider each Tier II impurity separately (i.e. performing the calculation method for each impurity individually).

The presented calculation method forms the basis to decide on whether the ecotoxicity of the Tier II impurity has to be further assessed. When the result of equation 3 is greater than 5, it must be considered that the limit of increase of ecotoxicty has been exceeded and therefore the active substances from the two sources cannot be considered technically equivalent with the information available. If a difference greater than 5 is observed from the calculation method (by the applicant or from the evaluation by the Agency), the applicant may submit further information to refine the f value or ecotoxicty studies on the AS-alternative.

6.3.4. Consideration of PBT/vPvB properties

As mentioned earlier in this guidance (see section 6.2.1 and section 6.3.2.2), the environmental fate properties need to be considered per each constituent of the substance. Therefore, in the technical equivalence assessment information is normally needed for each Tier II impurity even in the case where experimental studies are available on the AS-alternative. Waiving of the information requirements can be accepted when sufficient justification is provided.

In the PBT/vPvB ECHA guidance (*Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11*), it is stated that the PBT/vPvB assessment should be performed on each relevant constituent, impurity and additive of the substance relevant for the PBT/vPvB assessment. Constituents, impurities and additives should normally be considered relevant for the PBT/vPvB assessment when they are present at a concentration of ≥ 0.1% (w/w). For the sake of proportionality of assessment efforts and the level of risk being considered, it is to be noted that the 0.1 % (w/w) threshold value could be elevated or reduced based on case-by-case considerations.

Regarding the technical equivalence Tier II assessment, changes in the PBT/vPvB properties of the AS-alternative compared to the AS-reference could result from increased levels of impurities or the presence of new impurities having PBT/vPvB properties. Therefore, the (potential) PBT/vPvB properties of Tier II impurities should be addressed at least based on screening level information (Table 11). The extent and content of the PBT assessment of the AS-reference should be taken into account when considering the necessary level of effort for

addressing the PBT/vPvB properties of Tier II impurities as well as the possible consequences.

Table 11: Example of environmental fate information of the Tier II impurities and consideration of PBT/vPvB properties[a].

Information requirement - fate and behaviour in the environment	Impurity 1 in the AS-alternative (QSAR)	Impurity 2 in the AS-alternative (information from literature and databases)
Partition coefficient (n-octanol/water)	Log Kow = 4.8	Log Kow = 1.6
Degradation in water and sediment, Biotic (Ready biodegradability)	Not readily biodegradable	Readily biodegradable
Degradation in water and sediment, Abiotic (Hydrolysis)	Not estimated	Stable to hydrolysis
Adsorption/desorption (Koc)	Koc = 8800	Koc = 170
Fate and behaviour in air (estimation method)	Half-life ~12 d	Half-life 2.6 h
Consideration of PBT/vPvB properties		
	High log Kow value is indicating potential for bioaccumulation, estimated BCF value should be provided. Based on the available screening information on biotic and abiotic degradation, persistence cannot be excluded. In addition, the Koc value is indicating that the substance could be adsorptive in soil or sediment. The (eco)toxicity and concentration of the impurity should be considered to assess if the impurity could have an impact on the PBT/vPvB properties of the AS-alternative.	The available information in literature is showing no concern regarding bioaccumulation or persistence (there is no indication of P or B properties).

Note to the example:

[a] The example is only to illustrate a potential way to address and report the specific part of technical equivalence assessment. Alternative approaches and formats are possible.

When assessing the Tier II impurities the following principles should be applied for the consideration of PBT/vPvB properties:

- Impurities with known PBT/vPvB properties (e.g. publicly available PBT assessment under BPR or other regulation): if there is a new impurity or increased level of an impurity with known PBT/vPvB properties in the AS-alternative and the concentration is >0.1%, the AS-alternative should be considered a PBT/vPvB substance. If the AS-reference is not PBT/vPvB, the active substances from the two sources cannot be considered equivalent unless it can be justified with case-by-case considerations.

- Consideration of PBT/vPvB properties of the Tier II impurities based on screening level information: if there is a new impurity or increased level of an impurity which is potentially a PBT/vPvB substance based on the screening information and the concentration is >0.1%, the applicant would need to provide more information to address the concern, whenever the AS-reference is not PBT/vPvB.

As stated in the same ECHA *Guidance R.11*, PBT and vPvB criteria are not applicable to inorganic substances. Nevertheless, for the assessment of technical equivalence such properties should be assessed as they may have an impact on the overall hazard properties of the AS-alternative when compared to the AS-reference. Therefore at least a qualitative assessment of environmental fate and behaviour and bioaccumulation properties should be provided in order to assess if the hazard profile of the AS-alternative could be affected due to the differences in the composition in comparison to AS-reference. In general, the presence of a new impurity or increased concentration of an impurity which is toxic, not removed from the environmental compartment (but remains bioavailable) and is bioaccumulative would be considered as an unacceptable change of the hazard properties in relation to the AS-reference. In this kind of case further considerations would be needed to conclude on the technical equivalence. Additional information on assessment on inorganic substances is available e.g. in the Guidance on information requirements and chemical safety assessment Appendix R.7.13-2: Environmental risk assessment for metals and metal compounds and guidance on the Application of the CLP Criteria (Annex IV METALS AND INORGANIC METAL COMPOUNDS).

6.3.5. Consideration of ED properties

In principle, consideration of the endocrine disrupting (ED) properties should be included as part of the technical equivalence Tier II application, assessing whether a more severe hazard is expected for the AS-alternative compared to the AS-reference. For the identification of endocrine disruptors, the criteria established in the Commission Delegated Regulation (EU) 2017/2100 and the available guidance should be followed (Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107 available on the EFSA Journal[27]).

However, for active substances assessed before the availability of the established criteria, an assessment of the ED properties is usually not available. Alternatively, if an assessment has been made it may not be easy to compare to an assessment performed using the criteria established in the Regulation. A comparison between the AS-alternative and the AS-reference may therefore not be straightforward.

A detailed assessment of ED properties following the guidance for each Tier II impurity is not expected, but any available information on the possible ED properties of the Tier II impurities

[27] https://efsa.onlinelibrary.wiley.com/journal/18314732. The Gudaince is expected to be published during the Summer 2018.

should be provided and taken into consideration.

If, as a result of these considerations, there is a higher concern with regard to the ED properties of the AS-alternative in comparison to the AS-reference, the active substances from the two sources cannot be considered technically equivalent. Case-by-case consideration should be taken into account regarding the issues explained above.

7. Technical equivalence assessment for UVCB substances: special considerations

7.1. Introduction

This section of the guidance describes the procedure for technical equivalence assessment of Substances of **U**nknown or **V**ariable composition, **C**omplex reaction products or **B**iological materials, also called UVCB substances.

UVCB substances cannot be sufficiently identified by their chemical composition, because:

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

As a consequence, UVCB substances require other types of information for their identification, in addition to what is known about their chemical composition. More information about the substance identification of UVCB substances can be found in the *Guidance for identification and naming of substances under REACH and CLP*. For UVCB substances, the whole substance as such is considered the active substance and the purity is normally indicated as 100%[28]. As an example, many of the biocidally active plant extracts would be identified as UVCB substances.

The technical equivalence assessment approach for UVCBs follows in principle the same approach as that of mono- and multi-constituent active substances, consisting of Tier I and Tier II assessments. Substance identity is assessed in the context of the Tier I assessment. The technical equivalence assessment criteria described in sections 5 and 6 of this guidance for mono- and multi-constituent substances, are not sufficient (alone) for UVCB substances. This is due to the nature of UVCB substances as they in general do not have a well-defined composition and may exhibit large compositional variations and part of the composition may be unknown. Due to e.g. analytical limitations it may also not be possible to identify and quantify all individual constituents in the active substance, and the composition might be presented in terms of blocks of constituents, rather than as specific individual constituents. Hence, there may be significant compositional differences for an active substance produced by different sources. Also, the reference specification of the approved active substance may include parameters which are not limited to compositional information of the active substance, but can be e.g. specifications of starting materials or physical-chemical characteristics of the active substance (e.g. viscosity). The unknown constituents, variation of concentrations (ranges for constituents/blocks of constituents in the specification) as well as the combined exposure of multiple constituents also add complexity to the assessment of toxicological and ecotoxicological properties in Tier II.

[28] Following the conventions in the *Guidance for identification and naming of substances under REACH and CLP.*

The approach and criteria for the technical equivalence assessment of a UVCB substance depend on the nature of the active substance, on the information available on the active substance from the reference source, and on how the reference specification has been set and described in the Competent Authority Report (CAR) for the approval of the active substance.

Due to the nature of UVCB substances, it is anticipated that it will often not be possible to conclude on technical equivalence only on the basis of chemical compositions (Tier I), without any toxicological and/or ecotoxicological considerations (Tier II). Therefore, an applicant for a UVCB substance is recommended to consider preparing and submitting directly a Tier II application instead of a Tier I application unless there are good reasons to expect that it is possible to conclude on technical equivalence on the basis of chemical compositions. In Tier II, different approaches can be taken for the assessment (see section 7.3 of this guidance).

Assessing or showing the technical equivalence of UVCB substances is normally difficult, and needs to be done on a case-by-case basis. It is not unlikely that the outcome of the assessment will be negative. Thus, this guidance - regarding the UVCB substances - has to be understood more as a possible way forward and general advice rather than fixed and generally accepted rules.

In the subparagraphs below, the following abbreviations are used:
- UVCB active substance from the reference source: UVCB-reference;
- UVCB active substance from the alternative source: UVCB-alternative.

7.2. Tier I assessment

7.2.1. Information requirements for Tier I

The general Tier I information requirements (see section 5.1 of this guidance) apply also to UVCB substances. The applicant is recommended to consult the Agency prior to submitting the application if proposing to deviate from these requirements (e.g. regarding how to carry out a 5-batch analysis or how to report the results).

In addition to the general requirements, the applicant should note the following for UVCB substances:

- For the proposed specification, the applicant should include concentration ranges for all constituents and blocks of constituents (derived e.g. by statistical calculation from the 5-batch analysis data). For blocks of constituents, it needs to be clear how the block was defined on the basis of the analytical information.
- The reference specification of UVCB active substances may include information not covered by the general technical equivalence information requirements, such as physical-chemical parameters (e.g. viscosity; for these parameters a range needs to be provided in the application), or starting material specifications. These are active substance specific, and the applicant needs to consult the public CAR to find whether information on such parameters needs to be submitted in the technical equivalence application. Some of the additional parameters may be available only in the confidential parts of the assessment report. In such cases the Agency will request further information from the applicant if the application does not include sufficient information.

7.2.2. Assessment of technical equivalence Tier I

7.2.2.1. Substance identity

As for mono- and multi-constituent substances, the first step in the Tier I assessment is the confirmation of substance identity and verifying that the substance from the alternative source has the same identity as that from the reference source. This assessment is based on the

Guidance for identification and naming of substances under REACH and CLP and on the information in the CAR.

Normally UVCB substances cannot be sufficiently identified by their chemical composition alone and other types of information are needed for the identification, in addition to what is known about the chemical composition. Therefore, the substance identity confirmation of a UVCB substance takes into consideration e.g. the following parameters:

- Chemical name (IUPAC name) of the substance derived according to the principles in the *Guidance for identification and naming of substances under REACH and CLP*
- Manufacturing process, including information on the identity of starting materials, their ratios, synthesis pathway, relevant steps taken during the process, process conditions, separation steps and conditions, etc. (for further information see, besides the *Guidance for identification and naming of substances under REACH and CLP* also *Guidance on the Biocidal Products Regulation, Volume I: Identity/physico-chemical properties/analytical methodology, Parts A+B+C: Information Requirements, Assessment and Evaluation*)
- Compositional information that verifies the substance identity
- Other substance specific parameters affecting substance identity, as described in the CAR.

The applicant is recommended to carry out a self-assessment of substance identity in comparison to the identity of the approved active substance, based on the information available and considering the above. If in doubt, the applicant may consult the Agency before submitting the application.

As an example, the UVCB substance "*margosa extract, cold-pressed oil of Azadirachta indica seeds without shells extracted with super-critical carbon dioxide*" does not have the same identity as the substance "*margosa extract from the kernels of Azadirachta indica extracted with water and further processed with organic solvents".* Here, even though both are plant extracts originating from *Azadirachta indica,* the manufacturing process steps are different and the resulting active substances have different identities.

7.2.2.2. Tier I assessment criteria

When the substance identity has been confirmed, the Tier I assessment proceeds to the comparison of the composition and other reference specification parameters defined for the active substance in the CAR.

It is foreseen that for the majority of UVCB substances, the focus of the Tier I assessment will be to determine the compositional differences between the active substance from the alternative source and that from the reference source, but it will not be possible to conclude on technical equivalence based only on Tier I.

For a positive technical equivalence outcome in Tier I, the Tier I information for both the active substance from the alternative source as well as that from the reference source need to fulfil preconditions including (but not limited to):

- Composition is fully accounted for (5-batch analysis up to 98% closure)
- The constituents of the UVCB substance are specific constituents with defined chemical identities (such as 2-methyldecane, instead of generic identity "C11 branched alkane")
- Composition does not include blocks of constituents (see section 7.3 of this guidance), unknown and/or unspecific constituents (individual constituents which cannot be identified specifically)
- Reference specification and the alternative source specification include defined concentration ranges for the specifically identified constituents and defined ranges for other specification parameters (such as viscosity, if applicable).

Deviations from these preconditions could be considered only in the case when it is clear from the CAR that the assessment of blocks of structurally similar constituents instead of specific constituents would not affect the hazard assessment, and it is clear how to group specifically identified constituents into blocks (see also section 7.3 of this guidance on Tier II assessment of UVCB substances).

In case the preconditions are met, the active substance from the alternative source is considered to be technically equivalent at Tier I if:

- no new constituents are present, and
- the compositional variability is within the reference specification.

Here, "constituents" include also any additives necessary to preserve the substance stability. In general for UVCB substances, no differentiation is made between (main) constituents and impurities. Furthermore, the purity is normally indicated as 100%.

If the reference specification includes parameters not based on active substance composition (e.g. starting material specifications, physical-chemical parameters), these will be considered separately based on the CAR. In general, the variability for the alternative source needs to be within the variability indicated in the reference specification.

7.3. Tier II assessment

7.3.1. Introduction

Although the Tier II information requirements and assessment methods described in section 6 of this guidance are intended for well-defined substances, the basic principles are expected to apply also to UVCBs. The overall workflow and elements of the assessment are the same as for well-defined substances (section 6.1.2, Figure 3 of this guidance). Furthermore, the same criteria apply in the decision-making, i.e. it needs to be assessed whether there is an unacceptable change of the hazard profile of the UVCB-alternative compared to the UVCB-reference.

Due to the nature of UVCBs, additional issues may need to be addressed in the Tier II assessment of these substances. For the same reasons, it is possible to present only general guidance and principles for the assessment. The aim of this guidance is to describe the key aspects while it is not possible to present an exhaustive description of Tier II assessment for all possible UVCB cases. Furthermore, more than one of the presented methods could be applied for a given case.

As for well-defined substances, the nature of the Tier II assessment of UVCBs is iterative. Therefore, it might be necessary to repeat the individual steps of the Tier II assessment either as part of the assessment by the applicant or as part of the evaluation by the Agency before the final conclusion can be taken.

The approach in the assessment of the UVCB-reference and knowledge of the hazard properties of the individual constituents and/or blocks have an impact on the assessment approach. Therefore, the approach of the Tier II assessment is connected to the information available on the UVCB-reference. This is further described in section 7.3.4 of this guidance.

7.3.2. Information requirements for Tier II

In principle, the information requirements for UVCBs are the same as for well-defined substances, i.e. all the Tier II information requirements should be covered (section 6.2.1 of this guidance). In addition to the human health and environmental effects related properties defined in the Tier II information requirements, information on the physical-chemical properties (e.g. volatility and water solubility) may be particularly important for the comparison of the UVCB substances in the Tier II assessment. The sources of information

presented in section 6.2.2 of this guidance should be used as far as possible.

As part of the evaluation by the Agency, it will be assessed whether the provided information is sufficient to establish technical equivalence, or if further information is needed. Due to the nature of UVCB substances and complexity of their assessment, it is acknowledged that Tier II assessment of a UVCB substance may require more (experimental) information than would be required for a well-defined substance. However, the level of information required depends on the type of the UVCB and the assessment approach followed.

For UVCB substances, special attention has to be given to the test material. This applies to any available information on the UVCB-reference and UVCB-alternative and any new information to be generated. If new testing will be performed for the purpose of Tier II assessment, the specific test and test material should be selected in a way that the results serve in the most efficient way the Tier II assessment with the chosen approach. In addition to testing the UVCB-alternative as manufactured (the whole substance containing all its constituents), the testing could also be targeted to a specific block or constituent of the substance that was recognised as critical in the assessment. More information on testing of UVCBs is available in the REACH guidance *Chapters R.7 Endpoint specific guidance and R.11: PBT/vPvB assessment*. Sectorial guidance for the environmental assessment of essential oils is provided by EFEO/IFRA (Guidelines on the Environmental Assessment of Natural Complex Substances (NCS)[29]).

It is acknowledged that experimental testing of a UVCB substance may be difficult or technically not possible for certain properties. Guidance on difficult substances is provided for instance in the OECD Guidance Document 23. Information is available also in the REACH guidance document *Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11*, section 11.4.2.2 Assessment of substances containing multiple constituents, impurities and/or additives.

7.3.3. Assessment approaches in Tier II

In this section, the different approaches for the Tier II assessment of a UVCB substance are described. The approach chosen by the applicant should be clearly described and justified in the technical equivalence application.

The choice of the assessment approach may depend on a number of issues such as (1) approach in the risk assessment of the UVCB-reference (assessment report of the UVCB-reference), (2) type of the UVCB substance and the available analytical methods to characterise the composition, (3) available information on the properties of the constituents and differences/similarity between them, (4) endpoint or property to be assessed, and (5) possibility to provide information by testing or non-testing methods. It is also possible to perform the assessment by a combination of approaches (see approaches i, ii and iii below). The different approaches can be applied at different stages of the assessment, for example, additional confirmatory information may be needed for a specific constituent of the UVCB after initial review of the available information.

The theoretical basis for each approach is described below[30]. Some illustrative examples are included in section 7.3.4 of this guidance.

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[29] Available on the IFRA guidelines webpage at http://www.ifraorg.org/en-us/library/s/Natural_Complex_Substances/t/21002/s0#.WovW88IqSUl.

[30] The approaches are described with a main focus in the effects assessment as part of the technical equivalence assessment. Similar approaches can be followed in the classification and PBT assessment of UVCBs. However, there may be differences with regards to the nomenclature and in the order of preference of the approaches.

(i) Known constituents approach
The assumption for this approach is that the individual constituents are identified and quantified and it is possible to perform the assessment constituent by constituent. In practise, however, it may not be technically feasible to identify and quantify all constituents in a UVCB substance and gather sufficient (eco)toxicity information for each constituent. Therefore, it is foreseen that the constituent-based approach can be used in combination with the other approaches or as a refinement option when it is necessary to improve the assessment. The constituent-based assessment follows in principle the same methods as the assessment of a well-defined substance. For each constituent to be assessed, sufficient (eco)toxicological information should be provided to describe the hazard properties and how each constituent may contribute to the overall hazard of the active substance.

Based on the available information on each constituent, it may be possible to identify constituents with the most significant toxicological and/or ecotoxicological contribution, either due to the high relative concentration and/or due to high toxicity (key constituents). Therefore, it might not be necessary to perform a full assessment for all the constituents but the Tier II assessment can focus on the comparison of these key constituents.

For human health, a certain threshold could be applied (e.g. TTC, Threshold of Toxicological Concern), below which the constituent would not be considered to affect the toxicity of the active substance.

(ii) Block/Fraction approach (grouping of constituents)
This approach is applied when it is not feasible to fully identify, assess or isolate single constituents but the substance can be divided into blocks (or fractions) in which the constituents are structurally similar and their (eco)toxicity properties can be expected to follow a regular pattern. Two options are possible for the block definition and for providing information: (1) the substance is divided into blocks and the necessary information is provided for each block, or (2) the substance is divided into blocks but the necessary information is provided for one or more representative constituent(s) within the block and then read-across is applied among the other constituents in the block.

This option can be considered as a way to reduce the analytical and/or experimental tests needed in comparison to constituent-based approach. The block approach can also provide a refined assessment in comparison to the whole substance approach (see below). It should be noted that the information provided for a given block should provide a reasonable worst-case estimation of that block in terms of the hazardous properties.

(iii) Whole substance approach
In this approach, the assessment is based on the substance as a whole for the purpose of the Tier II assessment. It may be the only option if it is technically not feasible to establish the exact identity of the constituents or blocks in the substance at the level needed.

Endpoint specific considerations may be required, since testing of the whole substance could be possible and/or relevant only for certain information requirement. The test results on the whole substance may be difficult to interpret or the level of detail may not be sufficient for certain properties.

If toxicity studies (information requirements for the effects on human health) need to be performed for UVCB substances, it may in general be advisable to test the whole UVCB (ensuring that the tested concentrations of constituents are representative) instead of testing individual constituents. This will provide the required information and eliminate the possible need to perform further studies with other constituents. If experimental testing of one or more individual constituents is however performed, a synthesis or extraction method is required for the test item.

Similarly, regarding ecotoxicity studies, testing of the whole substance may be more relevant as it provides the overall properties of the substance (i.e. mixture toxicity of multiple constituents and/or blocks). However, for some other properties, e.g. environmental fate properties, information is normally always needed per constituent or block and providing information on the whole substance is not sufficient (see e.g. R.11 guidance for further information).

7.3.4. Technical equivalence Tier II – hazard assessment

The focus of this section is the prediction of change in the human health and environmental effects of the UVCB-alternative in comparison to the UVCB-reference. The considerations are valid for both the applicant when preparing the technical equivalence assessment as part of their dossier and for the Agency when processing the Tier II application. Note that instructions for classification and assessment of PBT/vPvB properties are not included in this guidance. Detailed instructions on classification of UVCBs are given in *Guidance on the Application of the CLP Criteria*. Detailed instructions on PBT assessment of UVCBs are given in *Guidance on Information Requirements and Chemical Safety Assessment R.11: PBT/vPvB assessment*.

In comparison to Tier II assessment of a well-defined substance, the additional issues to be considered for UVCBs may include consideration of unknown constituents/blocks, variation of concentration ranges and combined exposure to multiple constituents (mixture toxicity). The scientific basis and concepts related to combined exposure to multiple constituents (mixture toxicity) are described in the in *Guidance on BPR, Vol III Human health - Assessment and Evaluation (Parts B+C)* and in *Vol IV Environmental - Assessment and Evaluation (Parts B+C)*.

A stepwise assessment, as for well-defined substance, can be followed in the technical equivalence Tier II assessment of UVCB substances:

1) Assessment based on available information: as a first step, the assessment should be based on information that is already available or that can be generated with non-testing methods (i.e. without performing new tests on the UVCB-alternative). Information on the individual constituents or blocks can be obtained for example, from literature, databases or by (Q)SAR prediction. In the Tier II assessment the constituent-based or block approach can be applied. If available, experimental data on the whole substance should be used in the assessment (however, information on the environmental fate properties is needed per constituent or block).

2) Performing new experimental tests on UVCB-alternative: if the available information in the first step is not sufficient to conclude on technical equivalence, experimental testing may be the only reliable option to fill the data gap with sufficient confidence. Testing can be performed with the whole substance or it can focus on specific constituent(s) or block(s) that are identified as critical for the assessment (key constituent). Testing of the (eco)toxicity of the whole substance is foreseen especially if there is a high proportion of unknown constituents, high variability of concentrations that hinders the calculation-based prediction of (eco)toxicity, or when synergistic effects are expected. The applicant is recommended to contact the agency before conducting any test (see section 6.2.2 of this guidance).

7.3.4.1. Known constituents and block/fraction approach

The constituent-based approach can be used when the composition of the UVCB is (sufficiently) known and there is (eco)toxicity information available for the individual constituents. The block approach can be used as such or for instance in conjunction with the constituent-based approach.

As for well-defined substances, the starting point of the assessment is a comparison of the compositions of the substances from the UVCB-alternative and the UVCB-reference. If the

applicant does not have access to the reference specification (and information on the composition of tested material of the UVCB-reference), it may not be possible for the applicant to make the comparison and to estimate if there could be an unacceptable change in the hazard properties. In any case, the applicant should cover the Tier II information requirements for each constituent and/or block. The Agency will then evaluate whether any differences in the composition of the UVCB-alternative in comparison to the UVCB-reference would significantly affect the overall (eco)toxicity of the active substance as presented in the assessment report for the UVCB-reference. If the applicant has access to the reference specification, they should perform the corresponding comparison and Tier II assessment where necessary.

The aim of the Tier II assessment is to ensure that the individual constituents or blocks (new or at a concentration outside the range in the reference specification) do not have an unacceptable impact on the overall hazard properties of the UVCB-alternative compared to UVCB-reference.

7.3.4.1.1. Example 1: constituent and block approach

In this illustrative example case, the UVCB substance is an organic substance that consists of two blocks (Blocks 1 and 2), and four identified constituents (A, B, C, and D). The compositions of UVCB-reference and UVCB-alternative are presented in Table 11.

Table 11 Illustrative example of comparison of compositional information on a UVCB substance.

Constituent/block	Concentration range in the reference specification of UVCB-reference (%)	Concentration range of UVCB-alternative (%)
Block 1	48 – 53	53 – 55
Block 2	20 – 26	2.5 – 4.5
Constituent A	3.5 - 4.5	4.0 – 4.5
Constituent B	20.5 – 26.5	30.5 – 36
Constituent C	0.02 - 0.07	0.1 – 0.2
Constituent D	Not present	1.5 – 1.9

Outcome of Tier I assessment: Technical equivalence of the UVCB-alternative compared to the UVCB-reference cannot be concluded in Tier I due to the significant compositional differences between the active substances. The following should be considered in Tier II:

1) both compositions include blocks
2) the concentration ranges in the UVCB-alternative for block 1 and block 2 are outside the concentration ranges specified for the UVCB-reference
3) the concentrations of constituents B and C are higher in the UVCB-alternative compared to UVCB-reference; and
4) constituent D of UVCB-alternative is not present in the UVCB-reference.

Considerations for Tier II assessment
In the Tier II assessment, the impact of the higher maximum concentration of block 1 and constituents B and C would need to be assessed. In addition, impact of the new constituent (D) should be assessed. The Tier II information requirements for the new constituent D could be covered as a first step by obtaining information from literature, (Q)SAR or by read-across.

The available information in the CAR of the UVCB-reference should be reviewed to check if one or more of the individual constituents and/or blocks are identified as the key constituents (e.g. high toxicity or PBT/vPvB properties). Also, if it is clearly stated in the CAR of the UVCB-reference that variations of the concentration ranges within a certain block or for a certain constituent do not affect the hazard properties, that information can be used to justify the scope and focus of the technical equivalence assessment.

For instance, if block 1 has low (eco)toxicity it could be concluded that there is no significant impact from the increased concentration and no further consideration of block 1 is needed in the Tier II assessment.

The following considerations are provided as a possible assessment approach and outcome of the Tier II assessment in this example case:

- Human health assessment: The composition of the test material used for toxicity testing should be compared with the reference specification and specification for the UVCB-alternative (comparison performed by the Agency when the applicant does not have access to the necessary information). The comparison can help identifying which blocks or constituents could need more careful consideration if they (or the maximum concentrations) are not covered by the available test data.

  According to the information in the CAR of UVCB-reference, the constituents A and B were grouped together for the purpose of toxicity assessment. The maximum concentrations of the sum of A and B in the UVCB-reference and UVCB-alternative can be compared. Since the maximum (theoretical) concentration is higher in the UVCB-alternative it needs to be assessed whether this may result in an unacceptable change in toxicity.

  Based on the available information in literature, it was concluded that the toxicity of constituent D is similar to the constituent C. Furthermore, a limit value for the sum of constituent C and D has been determined under another chemical regulatory framework. The maximum value for the sum of constituent C and D in the UVCB-alternative can be compared to this available limit value to conclude if the observed increase in comparison to the UVCB-reference can be considered acceptable.

- Environmental assessment: In the environmental assessment of the UVCB-reference it was concluded that block 1 and block 2 do not contribute to the risk assessment due to their low ecotoxicity and as they are not identified as PBT/vPvB substances. Furthermore, block 1 and 2 do not contribute to the environmental classification. Therefore, the higher maximum concentration of block 1 is not considered further in the technical equivalence assessment.

  The constituents A and B were identified as the key constituents in the UVCB-reference. Therefore, the increased concentration of B could have an impact on the overall toxicity of the active substance. The calculation method (presented in section 6.3.3.2 of this guidance) could be applied in order to estimate if the predicted increase in ecotoxicity is acceptable (below the 5-fold difference as an indicative value).

  In the PBT assessment of the UVCB-reference, it was concluded that constituents A and B are not PBT/vPvB substances. The observed increase in the maximum concentration of these constituents in UVCB-alternative would not change the overall PBT/vPvB properties. Therefore, there is no unacceptable change regarding the PBT properties of the UVCB-alternative compared to the UVCB-reference.

  Based on the information in the assessment report of the UVCB-reference, constituent C does not contribute to the ecotoxicity of the active substance. Based on the available

information in literature, the environmental effect properties of constituent D are similar to those of constituent C. Therefore, it can be concluded that no increase in the ecotoxicity of the UVCB-alternative compared to the UVCB-reference is expected due to the new constituent D. In addition, the PBT/vPvB properties of constituent D should be assessed in order to consider if there can be a change in the overall PBT properties of the active substance (concentration >0.1 %).

7.3.4.2. Whole substance approach

This approach may be applicable when there is a (high) fraction of unknown constituents, when there is insufficient information on the individual constituents and/or blocks, when the variability in concentrations is high, or when a constituent-based approach is not applicable due to a high number of individual constituents.

When a test is performed with the UVCB substance itself, it is important that the test material is representative (see section 7.3.2 of this guidance). Since the information is obtained by experimental testing of the whole substance, interactions (synergy or antagonism) accounting for the observed (eco)toxicity are reflected in the test results. Nevertheless, information on environmental fate properties is normally needed per constituent/block in order to perform the assessment with sufficient level of detail.

When experimental test results are available for the UVCB-reference and UVCB-alternative (from comparable studies), the endpoint values can be compared to assess if there is unacceptable increase in the hazard properties. The composition of the UVCB substance may vary and a combination of different constituents could affect the test systems in an unforeseen way, and therefore also the variability in the (eco)toxicity test results can be high. For example, the difference in (eco)toxicity could be above the 2/5-fold rule of well-defined substances (see section 6.3.2 of this guidance) even when the same UVCB-material is tested under similar conditions. Therefore, certain flexibility in the criteria set for well-defined substances could be allowed in the Tier II assessment of UVCBs based on case-by-case consideration.

7.3.4.2.1. Example 2: whole substance approach

In this example, the UVCB-reference and UVCB-alternative contain several constituents and blocks with variable concentrations and the variability in the concentrations is relatively high. For certain constituents and blocks in the UVCB-alternative there is an increase in the concentration and for others there is a decrease. Some of the constituents and blocks of the UVCB-reference are not present in the UVCB-alternative. Furthermore, the UVCB-alternative contains additional constituents and blocks in comparison to UVCB-reference (new constituents).

Table 12 Illustrative example on comparison of compositional information on a UVCB substance.

Constituent/block	Concentration range in the reference specification of UVCB-reference (%)	Composition of UVCB-alternative (%)
Block 1	20 – 40	10 – 30
Block 2	10 – 20	20 – 50
Block 3	-	1 – 5

Constituent A	-	1 – 5
Constituent B	35 – 65	20 – 40
Constituent C	< 10	-
Unknown 1	1 - 5	-
Unknown 2	0.5 – 1	-
Unknown 3	-	5 – 10
Unknown 4	-	0.8 – 1.5

Outcome of Tier I assessment
As the compositional differences between the active substances are extensive, the Tier I assessment focuses only on checking whether the 5-batch analysis has been carried out appropriately and on which are the differences between the compositions, as far as can be determined. In this case a larger part of the composition is unknown for UVCB-alternative than for UVCB-reference; no information is available on the chemical nature of the "unknowns", and it cannot be confirmed if the unknowns would be the same constituents (or blocks) in both the UVCB-reference and UVCB-alternative.

Considerations for Tier II assessment
In this example, it is assumed that experimental test results are available on the toxicity and ecotoxicity for the UVCB-reference but not for the UVCB-alternative. In Tier II, it would need to be assessed if it is possible to predict the specific hazard properties for the UVCB-alternative.

The high variability of concentrations leads to a very complex assessment scheme. In addition, there is a higher concentration of unknowns in UVCB-alternative. Therefore, on the basis of the information available conclusion on technical equivalence would not be possible and further information would be requested by the Agency. Consequently, testing of the UVCB-alternative for certain Tier II information requirements may be necessary (required testing would be decided case-by-case). Alternatively, the composition should be analysed in more detail and more information should be provided on the hazard properties of the individual constituents and/or blocks. For instance, if it is found out that constituents of Block 3 are not indicating (eco)toxicological concern, it could be concluded that this block does not impact negatively the overall hazard profile.

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