

What applicants need to know about technical equivalence and chemical similarity

Technical equivalence - Tier II

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Outline

- What does Tier II assessment cover?
- What information should be provided?
- How is the assessment carried out?

Tier II - Purpose

Comparing the alternative source to the reference source

No unacceptable change in toxicity profile

and/or

No unacceptable increase in the environmental hazard profile

Tier II - Criteria

Significant impurity

An impurity is regarded as significant if it occurs or potentially occurs in a quantity ≥ 1 g/kg

and

Relevant impurity/additive

An impurity/additive is considered being of toxicological and/or ecotoxicological relevance

An impurity may be relevant even if it is < 1 g/kg

Tier II - Criteria

Tier II is required if the result of the TE assessment of Tier I indicates:

- The presence of any **new impurities or additives** in the alternative source
- **Increased levels of relevant impurities or additives** present in both the alternative and reference source
- **Increased levels of non-relevant impurities** present in both the alternative and the reference source

Tier II - Criteria

Levels of significant but not relevant impurities

Limits of significant but not relevant impurities in the technical specifications of the reference source

Acceptable maximum increase in the alternative source

≤6 g/kg

3 g/kg

>6 g/kg

50% of the certified limit

Tier II - Criteria

If **new** or **increased** levels of **relevant impurities** occur, the applicant must provide a reasoned case and/or data to show that the alternative source **is not more toxic** and does not have **a more hazardous ecotoxicity profile**

What does Tier II assessment cover?

Tier II assessment includes the assessment of substance from the alternative source:

Identity and composition (Tier I)

+

Toxicity profile

+

Environmental hazard profile

Tier II Assessment of the impurity profile:

Identify whether there is any available data for an impurity of **toxicological/ecotoxicological concern**

Tier II - Toxicity

1. Impurities of **no toxicological concern**

Compounds for which the **toxicity is known to be low**

An additional toxicological evaluation is generally not required, **but the applicant needs to submit a justification**

Tier II - Toxicity

2. Impurities of **known toxicological concern**

If one or several of such impurities are present in the alternative source but not in the reference source, evidence is needed to **show that they do not result in a significantly increased toxicity** compared to the reference source

Tier II - Toxicity

3. New impurities of **unknown toxicological concern (>1 g/kg)** or increased levels of **significant but non-relevant impurities**

These impurities would elicit a **further evaluation**

If an impurity of toxicological concern is identified in the reference source, it has to be demonstrated that the levels in the alternative source will be acceptable

Tier II - Ecotoxicity

1. Impurities of **no ecotoxicological concern**

Compounds for which the **ecotoxicity is known to be low**

An additional ecotoxicological evaluation would generally not be required, **but the applicant would have to submit a justification**

Tier II - Ecotoxicity

2. Impurities of **known ecotoxicological concern**

If one or several such impurities are present in the alternative source but not in the reference source, evidence would be needed to **show that they will not result in a significantly increased ecotoxicity** compared to the reference source

If an impurity of ecotoxicological concern has been identified in the reference source, it has to be demonstrated that the levels in the alternative source are acceptable

Tier II - Ecotoxicity

3. New impurities of **unknown ecotoxicological concern (>1 g/kg)** or increased levels of **significant but non-relevant impurities**

These impurities would elicit a **further evaluation**

Decision making



- The alternative source **does not present a greater hazard**; hence, the source can be considered as technically equivalent to the reference source



- It is concluded or **it cannot be excluded** on the basis of the information available **that the alternative source presents a greater hazard**; hence, the source cannot be regarded as technically equivalent to the reference source

Decision making – toxicological profile

A difference of a **factor 2** (indicative) between the toxicological data on the active substance for the alternative source compared to the reference source

Based on...

acute oral, dermal and inhalation toxicity, skin and eye irritation, skin sensitisation

Decision making – toxicological profile

However...

The whole data package should be taken into account to conclude whether a difference greater than factor 2 in an individual study could be considered as an indication of a more severe hazard

Decision making – toxicological profile

In addition...

There should be no change in the assessment in those studies which produce either positive or negative results unless the alternative source is less hazardous, for example mutagenicity or corrosivity

Decision making – toxicological profile

Additional toxicological data...

From repeated administration (sub-acute to chronic) and studies such as reproductive and developmental toxicity, genotoxicity and carcinogenicity **will be assessed by these criteria** provided that, where appropriate, the organs affected are the same

Decision making –ecotoxicological profile

A difference of a **factor 5** (indicative)
between the endpoint of ecotoxicological data
on the active substance for the alternative
source compared to the reference source

Based on...

acute toxicity to the same aquatic and terrestrial
species

Decision making – ecotoxicological profile

However...

The whole data package should be taken into account to conclude whether a difference greater than factor 5 in an individual study could be considered as an indication of a more severe hazard

Decision making – ecotoxicological profile

In addition...

There should be no change in the assessment in those studies which produce either positive or negative results unless the alternative source is less hazardous, for example, the test for ready biodegradability

Decision making – ecotoxicological profile

Additional toxicological data...

From long-term studies on aquatic or terrestrial organisms tested for the reference substance, bioaccumulation and biodegradation studies in the relevant environmental compartment will be assessed by these criteria provided that, where appropriate, the tested species and environmental compartments are the same

Thank you

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