Equivalence of Pesticide TC and TK in the European Union

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Background

- Formerly based on Guideline 91/414 EC, Annex I: Positive List of pesticide a.i. to be used in formulations
- Similar process under Reg. 1107/2009
- “Old compounds” (off patent) and new compounds (mostly patent protected)
- Currently approx. 140 “existing” and 120 “new compounds” listed

Annex I Inclusion

- Each pesticide is included with minimum purity and relevant impurities published
- Summarized in published inclusion documents
- http://ec.europa.eu/food/plant/protection/evaluation/exist_subs_rep_en.htm

Evaluation of equivalence of technical materials according to the European Commission (DG Sanco)

Data from the manufacturer(s) are required in the following cases:

- Technical material from a new/different manufacturer
- Large scale production vs pilot scale production.
- Change in the manufacturing process, and/or quality of starting materials, and/or manufacturing location, and/or addition of one or more alternative manufacturing locations

Data Package for Assessment of Equivalence

Data from the manufacturer(s) shall include:

- Detailed information on starting materials, reagents and manufacturing process
- Data on composition of 5 typical batches including manufacturing specifications
- Properly validated analytical methods

European Union Equivalence Process – two tiered decision making GD 10597/2003 (2009) under revision

- Tier I: chemical equivalence: the new source is deemed to be equivalent to the reference source if:
- the minimum purity and impurity profile (relevant impurities) is in compliance with that published in FAO/(WHO) specification (where available) and
- the certified minimum purity is not lower than the reference source (taking into account the ratio of isomers, where appropriate) and
- no new impurities are present and

Chemical Equivalence, II

- the limits of relevant impurities, as certified for the reference source, are not increased and

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

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

Chemical Equivalence vs. Tox

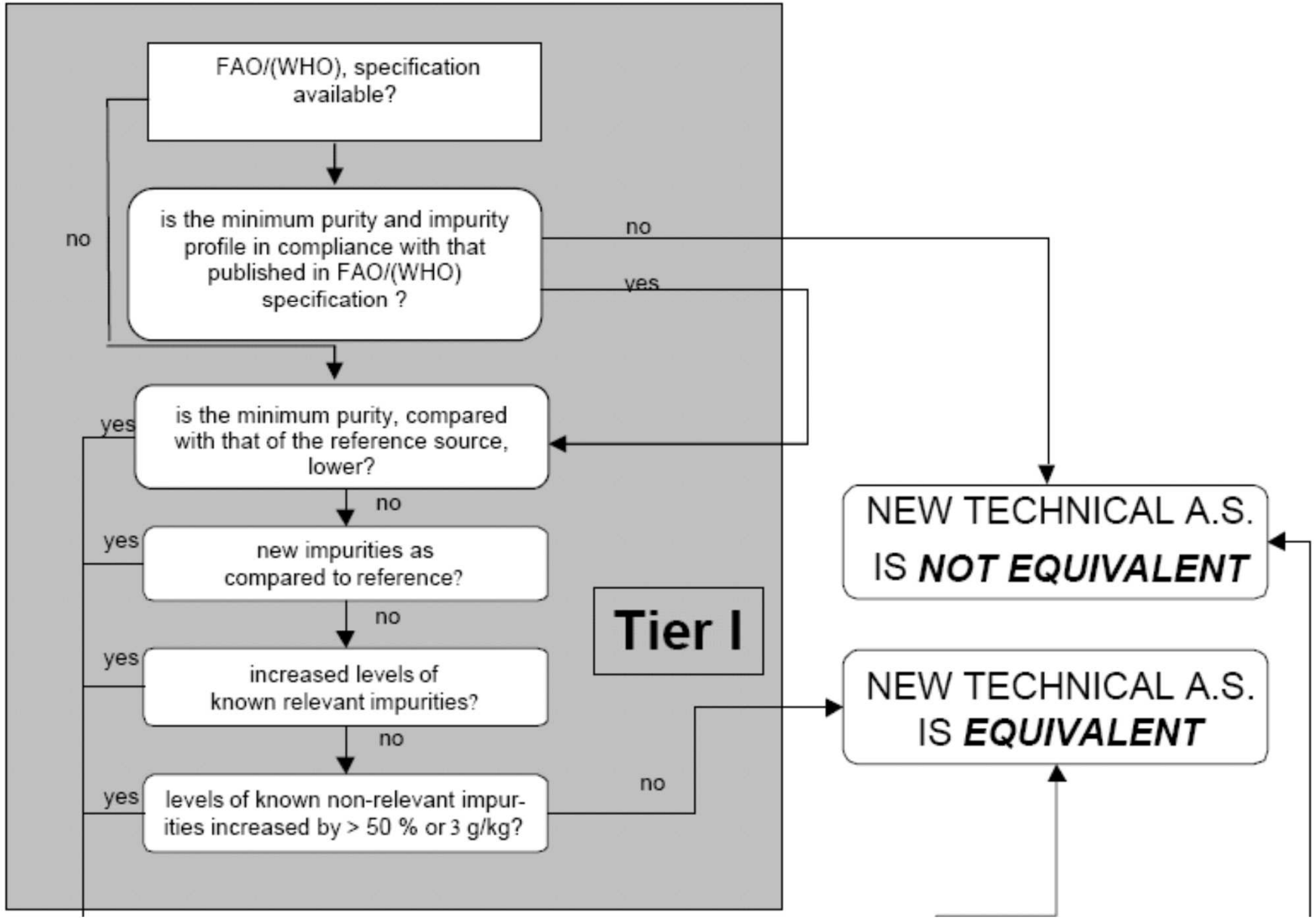
On the basis of the above criteria the conclusions might be that:

- The new source is equivalent → ok and data exchange
- The new source is not equivalent to the reference source because of non-compliance of minimum purity or impurity profile with that published in FAO (/WHO) specification or
- Equivalence of the new source to reference source cannot be established based on Tier I criteria alone, therefore Tier II evaluation is required in order to assess whether the altered minimum purity or impurity profile results in an unacceptable increase of hazard of the new source as compared to the reference source.

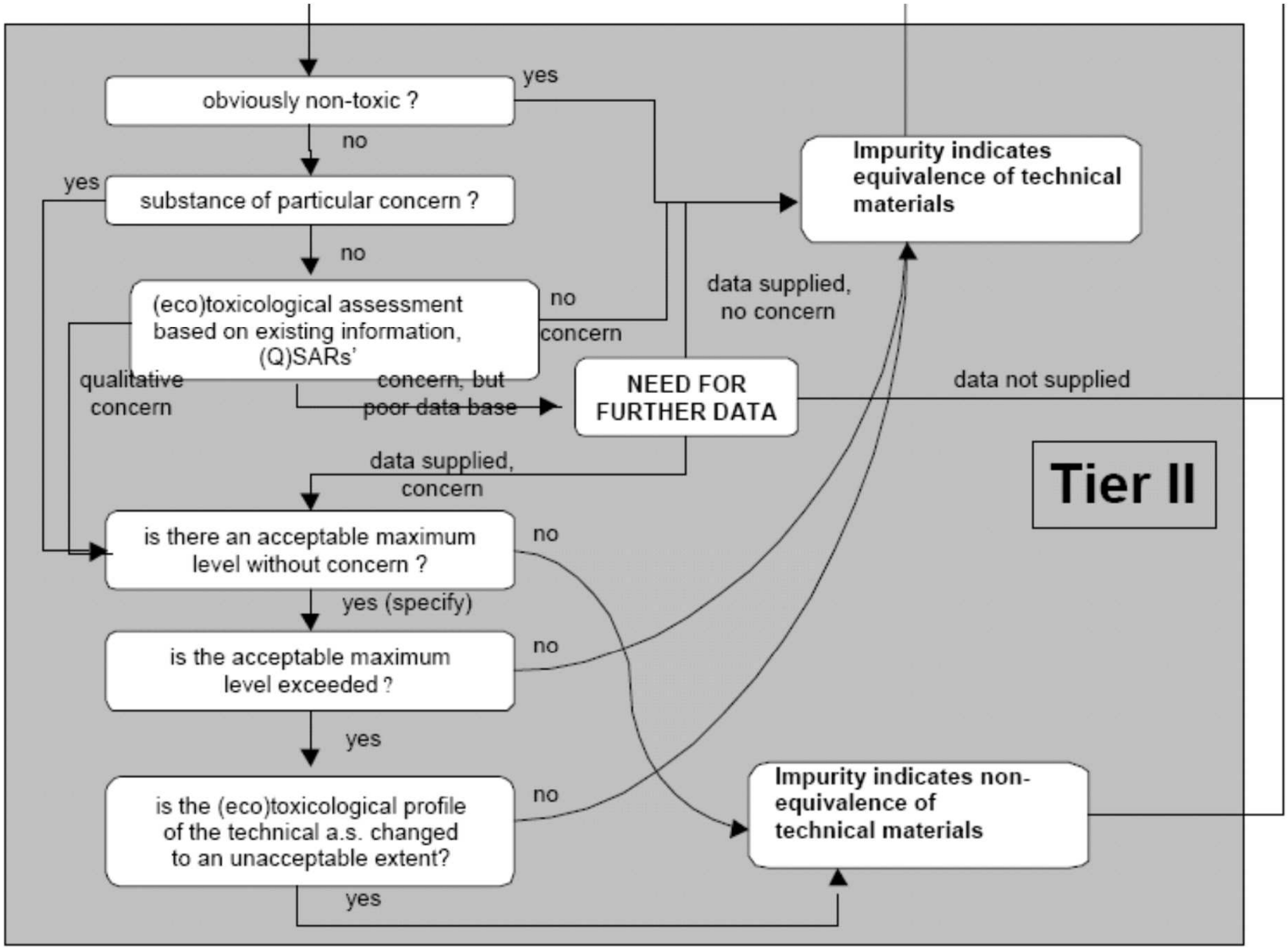
Evaluation of equivalence of technical materials (Tier II) for the EC

- **Toxicity**
- **Ecotoxicity**
- The objective of the evaluation is to identify whether there is an unacceptable increase in hazard for the new source as compared to the reference source as a result of:
  - any new impurities or/and
  - increased levels of relevant impurities or/and
  - increased levels of non-relevant impurities which exceed the limits mentioned before

Tier I: Chemical Equivalence Decision Tree (from GD equivalence)



Tier II: Tox/ecotox Decision Tree



Further Points on Equivalence Determination (Impurity data)

- A manufacturing process, however well-controlled, tends to be variable and manufacturing limits may change over time.
- A manufacturing process cannot be optimized for control of all impurities.
- What do the manufacturing limits represent?
- Are the 5-batch analysis data representative of current production? Are they representative of the materials used for testing hazards?

TC manufacturing specifications

	manufacturer A, g/kg
active ingredient, min	950
impurity 1 (relevant), max	0.001
impurity 2 (relevant)	1
impurity 3	31
impurity 4	10
Impurity 5	12
impurity 6	9
impurity 7	11
impurity 8	2
impurity 9	1
impurity 10	3
impurity 11	4
Unknowns	<1
acetone insolubles	<2

Equivalence of toxicity data

- Need to be assessed by toxicologists.
- Toxicity data are usually more variable than analytical data.
- Test animals, organisms and plants vary genetically, with age, conditions, etc. Test conditions, dosage rates and dosage vehicles often differ.
- Assessments of the data may differ.
- Detailed assessment of original study reports is often required.

Decisions on impurities

- Is a “new” impurity, or one which occurs at higher levels in the “new” TC/TK, important or possibly relevant?

- Decisions are made in the same way as for the “original” TC/TK.
  - (i) Chemical structures, product toxicity, product stability data, and so on, may provide clues.
  - (ii) If there is no evidence to show that an impurity is relevant, it is considered to be non-relevant.

List of Relevant Impurities identified so far available

- Containing approx. 40 pesticides and 60 rel. impurities and limits
- http://www.bvl.bund.de/nn_492022/DE/04__Pflanzenschutzmittel/09__Produktchemie/ListeRelevanterVerunreinigungen.html

Decisions on relevant impurities

- What if the levels of a relevant impurity in the “new” TC/TK exceed the limit agreed for the “original” TC/TK?
  - (i) The maximum acceptable limit represents an estimate of “negligible increase in hazard”, compared with the active ingredient.
  - (ii) As a precaution, actual limits are usually well below the maximum acceptable.
  - (iii) If the maximum acceptable limit is not exceeded and there is no evidence that hazards will be increased, the existing limit may be raised to encompass the “new” TC/TK.

Can equivalence be determined by analysis?

- Equivalence cannot be determined by analysis of either TC/TK or formulations.

- (i) Because equivalence is determined from manufacturing limits (using data from the whole population of batches), not from single batches.

- (ii) Because complete analysis of formulated products, to determine the impurity profile of the TC/TK used is virtually impossible in most cases.

Lack of information
(or the wrong information)

- Limitations in the data available are inevitable.
- Is the missing information critical to the assessment of equivalence? Or to the assessment of hazards, risks and performance?
- Additional data may be very costly, directly and indirectly, may take a long time to generate and may raise ethical questions. So additional data requirements must be justified.
- Sometimes “missing” data already exist, so it is worth asking if they are already available.

General Summary

- Equivalence is a simple concept but no two data sets are complete or directly comparable.
- Access to experts in chemistry, analytical chemistry and toxicology/ecotoxicology is required.
- Experience has shown that different manufacturing processes seldom lead to equivalent TC or TK
- When chemical equivalence fails, tox is often too expensive for generic manufacturers