Tier-2 TC/TK Equivalence Data Requirements and Decision Criteria, Sections 3.1 & 3.2

Introductory Notes

The JMPS, in its 15th Closed Meeting in Tokyo, reconsidered the data requirements for Tier-2 equivalence as laid down in the Manual, 3rd revision of the 1st edition (March 2016). The following issues were discussed and evaluated:

- The current Tier-2 data requirements (FAO/WHO Manual, 3rd rev. 1st edition, 2016) include a total of six acute toxicity studies (Section A.9.1) and, in cases where equivalence cannot be established, may also include sub-chronic and chronic toxicity studies (Section A.9.2).
  The Meeting noted that, taking the experience of the last 6 years of Tier-2 evaluations into account, the outcome of acute oral, inhalation and dermal toxicity studies were not instrumental to decide on equivalence or non-equivalence.
  This is not really a surprise - the more recent Guidelines like the OECD 425 (Acute Oral Toxicity – Up-and-Down-Procedure (UDP)) and OECD 403 (Acute Inhalation Toxicity) are i.a. intended to allow classification of a chemical according to the Globally harmonized system (GHS) with a minimum use of test animals. The outcome are rather limits than actual numbers and were therefore found not useful and could not be used for comparison purposes.
  As an example, a pyrethroid insecticide evaluated by JMPS, when tested using the OECD 401 Guideline (Acute Oral Toxicity), yielded a LD_{50} of 87 mg/kg bw for the reference product; in an equivalence assessment, the TC of the second manufacturer reported a LD_{50} range of >50 – 300 mg/kg, after a test following the currently recommended OECD Guideline 423, "Acute Oral Toxicity - Acute Toxic Class Method".

- The OECD Guideline 402 of 1987 (Acute Dermal Toxicity) may in principle provide a LD_{50} with a confidence interval, however fewer and fewer pesticide active ingredients show a more pronounced dermal toxicity, so the result is often expressed as a limit (e.g. > 2000 mg/kg). For this reason, the acute dermal toxicity has not been used in equivalence comparison for many years, even though the study summaries had been submitted.
  The criterion as set in the Manual for comparison of M1 and M2 hazard properties - not more than a factor of 2 more hazardous for acute oral, inhalation and dermal toxicity - can therefore not be used, as limits cannot be directly compared.

- For some recent evaluations of reference and second proposers however, some impurities had been identified in certain technical materials that would have been overlooked in the present Tier-2 equivalence evaluation. This is due to the fact that certain impurities meeting the criteria for relevance do not produce observable effects in acute, short term toxicity test protocols. Such an example is fluazinam TC that has a potentially relevant impurity ("impurity 5") that causes adverse effects in the central nervous system. Such effects would only become apparent in repeated dose (eg. 28 or 90 days) study.

- On the other hand, no decision criteria whatsoever had been established for requiring and comparison of repeated dose studies, that might be requested in cases where outcome of the acute toxicity studies would not allow to confirm or

reject a proposed equivalence of a technical material with the corresponding reference profile. This is not in agreement with the intention of openness and transparency in the JMPS decision process for equivalence of technical materials.

Based on the above findings and shortcomings, the Meeting recommended to modify the data requirements for acute toxicity studies as follows :

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- the acute oral, inhalation and dermal studies are no longer mandatory requirements from the second manufacturer equivalence for his TC. Nevertheless, if they are available, they should be submitted. This does not change of course the requirement of these studies from an initial manufacturer M1 for the establishment of the hazard profile of that compound. This is in agreement with the objective of Animal Health and Welfare, that is also well recognized by OECD and many national authorities.
- to amend the Tier-2 data requirements by a suitable additional toxicity study that helps to elucidate the suspected additional / more severe effect of a changed impurity profile in the second technical material not addressed by acute toxicity studies.
- (Q)SAR models may be used to provide information on impurities of unknown toxicity. They must be scientifically valid and in order to maximise the sensitivity and specificity of the prediction, at least two independent (Q)SAR models, where possible, (e.g. based on different training sets and/or algorithms as knowledge based and statistical-based models) should be applied[1].
- to clarify the acceptance criteria for the results derived from a repeated dose study.

Note: data requirements for subsequent proposer's specification are not considered as a subset of those for a new reference specification and should be covered in two separate subsections. Changed or new paragraphs are highlighted in yellow.

Existing data requirements for new specification (reference specification - with amended A.9.2 and new 10.3)

A.9 **Toxicological summaries** (including test conditions and results)
Recent studies are required to be GLP studies and to comply with established study guidelines.

A.9.1 Toxicological profile of the TC/TK based on acute oral, dermal and inhalation toxicity; skin and eye irritation, skin sensitization.

A.9.2 Toxicological profile of the TC/TK based on repeated administration (from sub-acute to chronic) with a description of dosage levels (mg/kg bw per d), NOAEL values and recapitulation of findings at the LOAEL dose, as well as studies on reproductive and developmental toxicity, genotoxicity, carcinogenicity, developmental and adult, neurotoxicity, etc.

A.9.3 Ecotoxicological profile of the TC/TK based on toxicity to aquatic and terrestrial organisms (e.g. fish, crustaceans, algae, birds, bees), as appropriate to the intended use, and information of persistence.

[1] EFSA Journal 2016;14(12):4549.

A.10 **Other information**

A.10.1 WHO classification by hazard where they exist

A.10.2 References to JMPR/JECFA evaluations for toxicology and environmental fate should be given, where these exist. The toxicological data supplied to the JMPR for evaluation should be cross-referenced to the batch analysis data of the technical materials used in those studies.

A.10.3 On request by JMPS: A certificate of registration for a formulated product and the active ingredient(s) issued by a national registration authority with a certified translation into English, in case the language of the certificate is other than English.

At the request of FAO/WHO, the proposer may provide, a letter of authorization (see Appendix I) granting competent FAO/WHO and registration authorities access to registration data on behalf of FAO/WHO. This is to enable FAO/WHO to assess whether or not:

(i) the technical material for which an FAO/WHO specification is proposed is equivalent to that registered by the authority, as assessed by a comparison between the data submitted to FAO/WHO and those submitted for registration; or

(ii) a decision that technical materials from different manufacturers are equivalent was based on data similar to those provided to FAO/WHO.

If the data are known to differ from those submitted by the proposer for registration, explain the relevance of the data provided to FAO/WHO.

At the request of FAO/WHO, the proposer may provide a written undertaking that the data submitted to FAO/WHO are identical to those submitted for registration to a specified national authority. Any deviations between the two data sets must be described in detail.

A.10.4 Statements to identify the links between purity/impurity data and the hazard information and risk assessments.

(i) Normally, the data provided are expected to have been generated from the proposer's material. Identify which, if any, of the hazard data were not generated from the proposer's technical grade active ingredient and formulated products, state the source of the information and explain the relevance of the data.

(ii) Identify any toxicological/ecotoxicological data generated from batches of material which were either specially purified, or in which the impurity concentrations exceeded the limits identified in paragraphs A.4, A.5 and A.6, above. Explain the relevance of the data.

(iii) Confirm that current production complies with the limits identified in paragraphs A.4, A.5 and A.6, above.

3.2 Minimum data requirements for extension of an existing specification to an additional manufacturer or a new manufacturing route.

E. Data requirements for the determination of equivalence (new)

E.1 Tier-1 data requirements for technical grade active ingredients include the information required in Section 3.1, paragraphs A.1, A2 (see also notes (i) to (v) above), A.3 to A.8, A.10.3, A.10.4(iii), and mutagenicity (bacteria *in vitro*) test data.

Tier-2 data requirements for technical grade active ingredients include the toxicological profile of the TC/TK based on skin and eye irritation[2], skin sensitization. Furthermore when deemed necessary by JMPS[3], additional toxicological studies, e.g. repeated dose 28 days or 90 days[4] studies in rodents are required as well as the information required in Section 3.1, paragraphs A.10.4(i) and A.10.4(ii).

E.2 Additional toxicological summaries
The following additional information may be required, in cases where the equivalence cannot be determined from the data required by paragraph E.1.

E.2.1 Studies on reproductive and developmental toxicity, genotoxicity other than that required at Tier 1, carcinogenicity, developmental and adult neurotoxicity, etc.

E.2.2 Ecotoxicological profile corresponding to that of section 3.1, paragraph A.9.3.

F.5.1 The toxicological profile will be considered equivalent to that of the reference profile, where the data required by paragraph E.1 above (referring to the requirements of section 3.1, paragraph A.9.1) do not differ by more than a factor of 2 compared to the reference profile (or by a factor greater than that of the appropriate dosage increments, if more than 2). There should be no change in the assessment in those studies which produce categorical results (e.g. category 1, 2, or 3 skin irritant, not a skin irritant).

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[2] Acute eye and skin irritation is required only in cases where the proposed minimum purity of the TC/TK is less than 990 g/kg and the hazard classification of the reference material is not Category 1 eye or skin irritant.

[3] Qualitative and quantitative differences in the second manufacturer's impurity profile may indicate additional or increased hazards in the TC/TK under consideration not covered by the acute toxicity studies. These suspected hazards need to be addressed by suitable toxicological studies.

[4] OECD Guideline for the testing of chemicals: Repeated Dose 28-Day Oral Toxicity Study in Rodents (OECD 407) and Repeated Dose 90-day Oral Toxicity Study in Rodents (OECD 408), respectively. The choice of study guideline is governed by the analogue study available for the reference material. When a novel study is performed for the equivalence determination, the animal species and strain shall be the same as in the study for the reference technical material. The dose spacing shall include the LOAEL, NOAEL, and NOAEL/$10^{-0.5}$ as established for the reference profile

a) Studies which produce categorical results (e.g. category 1, 2, or 3 skin irritant, not a skin irritant) do not lead to a more serious classification than the reference product.

b) No qualitatively new adverse effect is observed in the repeated dose studies (28 or 90 days repeated dose studies in rodents)

c) The “no observed adverse effect level” (NOAEL) or bench-mark dose for any toxicity end point is not more than a factor of $10^{-0.5}$ lower than that for the reference product.

2.7 **Conversion of specifications developed under "old procedure" and review of specifications**

2.7.1 Conversion of specifications developed under FAO "old procedure"

Note: this subsection is a temporary one and shall be removed, when all FAO specifications developed and published under old procedure are either converted into new procedure ones or withdrawn.

Specifications developed under the FAO "old procedure" (cf. Section " Background to FAO and WHO specifications for pesticides", pp. X onward) are reviewed at intervals based on suitable criteria like whether the compounds are still in use.

The information as outlined in Section 3.1 will apply for conversion of old procedure specifications into new ones. However, some particular aspects different than for the proposal of reference specifications for technical and formulated pesticides are considered by JMPS.

For the conversion process, the manufacturer providing the most complete hazard data package (see Section 3.1 A.9) supporting a recent purity and impurity profile of the technical material produced will be considered by JMPS as main data proposer and the specifications developed will be considered as reference specifications. In cases where such a firm link between a full hazard data and the purity and impurity profile of a technical material cannot be established by a manufacturer, JMPS will consider a proposal from a manufacturer submitting a data package similar as for an equivalence case (see Section 3.2, Minimum data requirements for extension of an existing specification to an additional manufacturer or a new manufacturing route, point E 1 for Tier-1). The Meeting will, in addition to the data submitted, consider the published subchronic, chronic, mutagenicity, neurotoxicity and reproduction toxicity studies on the active ingredient and their results that have been reviewed and evaluated by JMPR. A proposal for a TC or TK is deemed acceptable by JMPS provided that :

i) the technical material under evaluation does not produce a response in the *in-vitro* mutagenicity test worse than that for the material whose hazard profile has been evaluated by JMPR

i) no qualitatively new adverse effect is observed in the repeated dose studies (28 or 90 days repeated dose studies in rodents) and

ii) The “no observed adverse effect level” (NOAEL) or bench-mark dose for any toxicity end point is not more than a factor of $10^{-0.5}$ lower than that evaluated for the technical material evaluated and published by JMPR

2.7.2 Review of specifications developed under new procedure (same as in Manual 3rd revision)

Specifications will be reviewed at intervals, according to the priorities outlined in section 3.6 of this Manual. FAO and WHO will prepare a programme for review of all published specifications, which will be considered by the JMPS. As one of their responsibilities of product stewardship, and as a condition for maintaining an FAO or WHO specification, proposers must inform FAO/WHO of changes in the manufacturing process which have implications for the existing specification, and of changes in company name or address.

Specifications are published on the basis that information on the manufacturing process (confidential), impurity profiles (confidential), the hazard data available to FAO/WHO, and the manufacturer's name and address remain valid. Proposers have a responsibility to inform FAO/WHO of changes in this information. Where the validity of this information is in doubt, the specification(s) may be scheduled for review by the JMPS. The manufacturer of a product evaluated by WHOPES, and based upon which evaluation the WHO recommendations for use and specifications have been developed, should notify WHO of any changes to the manufacturing process, formulation characteristics and/or formulants that could require re-evaluation of the product and/or review of the specification. Proposers may also request review of specifications.

Specifications under review must be supported by the data indicated in Sections 3.1 or 3.2 of this Manual (as appropriate).

The JMPS will then:

(i) confirm that the existing specification is suitable, or
(ii) recommend an amended specification, or
(iii) recommend that the specification be withdrawn.

In cases where a specification serves as reference for equivalent products and needs revision, an amendment or modification of a clause may render the hitherto equivalent products non-equivalent. In such a situation, JMPS submits a draft version of the revised specification for consultation to those data proposers having equivalent products. Where new data to support the continued equivalence is needed, an appropriate deadline for submission of the data is conceded. The data is evaluated, discussed at the next Meeting if required and appropriate recommendations to FAO and/or WHO are made. (see Section 2.3, Meetings and functions of the JMPS).

Where national authorities find it necessary to adapt FAO or WHO specifications, FAO and WHO should be informed by the proposer, or the authority, of the changes made and the reasons for them. Such modified specifications cannot be considered to be FAO/WHO specifications but information supporting the changes will assist revisions of the specifications by the JMPS.

Comments and further information relating to specifications are welcomed by FAO and WHO. Proposals for modification of specifications should be supported by evidence to show that the change is pertinent to maintaining or improving the quality/performance, or to reducing the risks of the technical grade active ingredient or formulation.