

## FAO/WHO SPECIFICATIONS FOR PESTICIDES

### Guidance notes for the completion of proposer's templates. Version: July 2009

#### Confidential data (Proposer's data entry template)

Where a specification is proposed jointly by manufacturers who produce separate technical materials (TC/TK), each manufacturer must submit a separate file of confidential data.

#### Non-confidential data (Proposer's data entry and specification templates)

Where a specification is proposed jointly, non-confidential data may also be submitted jointly but the source(s) of data or information must be attributed to the appropriate Proposer(s).

Where the **proposed specifications** deviate from the guidelines given in the FAO/WHO Manual<sup>1</sup>, or include a clause which requires justification, the Proposer must enter the supporting data and/or arguments in appropriate sections of the data entry template.

#### Tiered data submission for equivalence determination

Data for equivalence determination may be submitted in two tiers. Tier-1 is essentially the chemical + mutagenicity data and Tier-2 the toxicological. See FAO/WHO Manual<sup>1</sup>, revised Section 3.2 E (Included, for convenience, in the Annex of this document).

#### General

Entries should be made where indicated in [red]. Replace the template text given in red (presented as instructions or examples) with appropriate entries in red. The brackets and quotes, [ ] and “ ”, should be deleted but do not reformat the inserted text to black. Notes for information only are indicated in [blue]. Notes and any inappropriate text should be deleted before submission.

Template entries should be adapted or extended as required. Where an entry is not applicable, state “not applicable”. Where information is not available, state “not available”. Omission of data or information should be explained, briefly, by a note, in red, in the appropriate section.

It is not essential to adjust the pagination, this will be done by FAO/WHO before publication.

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<sup>1</sup> As detailed in the "Manual on development and use of FAO and WHO specifications for pesticides. February 2006 Revision of First Edition. FAO Plant Production and Protection Paper. Revised. [www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm](http://www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm) and [http://whqlibdoc.who.int/publications/2006/9251048576\\_eng\\_update2.pdf](http://whqlibdoc.who.int/publications/2006/9251048576_eng_update2.pdf)

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Proposer's data entry template. Version: July 2009  
SECTION 1. CONFIDENTIAL DATA ON [insert A.I.]

The information in this section is the property of [insert company name(s)] and must be kept secret

**Date of submission**

[Insert dd/mm/yyyy]

**Comparability of data with those submitted for registration**

**Either** The confidential data presented here are identical to those submitted for registration in [insert country/countries].

**Or** The confidential data presented here differ from those submitted for registration in [insert country/countries]. The differences are [insert differences]. The reasons for these differences are [rationalise the differences].

**Manufacturing process**

[Insert brief description, including starting materials (with % purity where critical) and their sources, stages and conditions, solvents, extraction and purification steps of the TC/TK.].

Include a flow diagram of the process.

Indicate the location(s) of the manufacturing plant(s).

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The information in this section is the property of [insert company name(s)] and must be kept secret

**Names, codes and structures of impurities and methods of analysis**

[Notes. (i) Insert additional rows for all impurities at or above 1 g/kg and additional rows for any impurities <1 g/kg (e.g. nitrosamines, dioxins) considered to be relevant<sup>2</sup>. (ii) Provide the method identification number as stated in the study on the batch analyses.]

Name	Code	Structure (Note)	Method of analysis
[insert name]	[insert code]	[insert structure]	[insert method identification number]
[insert name]	[insert code]	[insert structure]	[insert method identification number]
[insert name]	[insert code]	[insert structure]	[insert method identification number]

Note: Structure is not needed for water, sulphated ash, etc.

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<sup>2</sup> Relevant impurities are associated with manufacture or storage of the a.i. and comply with the requirements given on page 19 of the "Manual on development and use of FAO and WHO specifications for pesticides. February 2006 Revision of First Edition. FAO Plant Production and Protection Paper. Revised. [www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm](http://www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm) and [http://whqlibdoc.who.int/publications/2006/9251048576\\_eng\\_update2.pdf](http://whqlibdoc.who.int/publications/2006/9251048576_eng_update2.pdf)

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**5 batch analysis data**

[Notes. (i) Insert data in the same order as the table of names, codes and structures. (ii) Insert additional rows as required, insert additional columns for additional batch data. (iii) Do not insert "not detected", insert "< 1 g/kg" (or < LOD, if > 1 g/kg).]

Code or name	Batch 1 [insert date], g/kg	Batch 2 [insert date], g/kg	Batch 3 [insert date], g/kg	Batch 4 [insert date], g/kg	Batch 5 [insert date], g/kg	Manufacturing QC limit (technical specification), g/kg
[insert code]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]
[insert code]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]
[insert code]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]
[Insert "unknowns", if appropriate]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]
total, g/kg	[insert value]	[insert value]	[insert value]	[insert value]	[insert value]	

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**References Section 1. Confidential data** (sorted by study number)

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
XX-nnn	Analyst BD and Chemist EF	2003	Determination of active ingredient and impurities in technical grade xoo6. Study XX-nnn. Report XX-nnn.05. GLP. XYZ Contract Laboratories, XXland. Unpublished.

[Notes. Insert additional rows as required.]

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SECTION 2. NON-CONFIDENTIAL DATA ON [A.I.] (CIPAC number xxx)

**Explanation**

The data for [insert a.i.] were evaluated in support of [insert "new" or "review of existing"] FAO or WHO specifications [insert numbers and dates of existing specifications, if appropriate].

Either [insert a.i.] is under patent in [insert countries] until [insert date(s)]. Or [insert a.i.] is not under patent.

[Insert a.i.] [insert was/has not been] evaluated by the FAO/WHO JMPR and WHO/IPCS [insert dates]. [If appropriate, insert, "It was evaluated/reviewed by the European Commission/US EPA, etc., in [year] or is currently under evaluation/review by the European Commission/US EPA, etc"].

The draft specification and the supporting data were provided by [insert company or companies] in [insert year].

**Uses**

[Insert a.i.] is [insert, e.g., "an insecticide"], [insert mode of action, systemic activity, etc.]. It is used in [insert agriculture/horticulture/viticulture/forestry/public health, or list typical crops] against [insert list typical pests/diseases]. [Insert literature reference if appropriate].

**Identity of the active ingredient**

*ISO common name*

[insert a.i.] ([insert status of ISO name])

*Chemical name(s)*

IUPAC

[insert full name, with stereochemistry if appropriate]

CA

[insert full name, with stereochemistry if appropriate]

*Synonyms*

[insert synonyms or state "none"]

*Structural formula*

[Insert structural formula(e), with stereochemistry indicated if appropriate. If the a.i. consists of two or more isomers, insert a 3-column table of names, structures and proportions present]

*Molecular formula*

[Insert in the form, C<sub>n</sub>H<sub>n</sub>Cl<sub>n</sub>F<sub>n</sub>N<sub>n</sub>O<sub>n</sub> etc]

*Relative molecular mass*

[Insert MW to 1 decimal place]

*CAS Registry number*

[insert separate numbers for each isomer, if appropriate, identifying each]

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*CIPAC number*

[insert number]

[Insert any other internationally recognised system of numbering or coding]

[insert number/code]

*Identity tests*

[Insert, for example, GC/HPLC retention time, IR, etc]

[Insert identity tests for the counter-ion(s), ester(s), isomers (quote the method of determination of isomer ratios), etc., if appropriate.]

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**Table 1. Physico-chemical properties of pure [insert a.i]**

[In the table below, insert additional rows for other isomers, salts, esters, etc. or for other characteristics. Provide information on the composition of the pure compound if it is a mixture, e.g. information on isomer ratio.]

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number <sup>3 4</sup>
Vapour pressure	[n.n x 10-n] Pa at [nn] °C ([Insert if extrapolated])	[nn.n]	[Insert e.g. "OECD 104, by extrapolation", not internal report]	XX- <sup>nnn</sup>
Melting point.	[nn.n] °C	[nn.n]	[Insert e.g. "OECD 102", not internal report]	XX- <sup>nnn</sup>
Temperature of decomposition	[nn.n] °C [insert with gas evolution and pressure, if appropriate]	[nn.n]	[Insert e.g. "OECD 102", not internal report]	XX- <sup>nnn</sup>
Solubility in water	[nn x]g/l at [nn] °C [insert at pH n.n] [insert additional rows for other pH values, if appropriate]	[nn.n]	[Insert e.g. "EEC A6", not internal report]	XX- <sup>nnn</sup>
Octanol/water partition coefficient	log P <sub>OW</sub> = [n.n] at [nn] °C [insert at pH n.n, if appropriate] [insert additional rows for other pH values, if appropriate]	[nn.n]	[Insert e.g. "EEC A8", by extrapolation", not internal report]	XX- <sup>nnn</sup>
Hydrolysis characteristics	Half-life <sup>5</sup> = [n.n days etc.] at [nn] °C at pH [n.n] [insert additional rows for other pH values]	[nn.n]	[Insert e.g. "EPA CG5000", not internal report]	XX- <sup>nnn</sup>
Photolysis characteristics	[insert conditions and estimated half-life <sup>5</sup> at stated latitude and season]	[nn.n]	[Insert e.g. "EPA CG6000", not internal report]	XX- <sup>nnn</sup>
Dissociation characteristics	[pKa = n.n or state "Does not dissociate."] [insert additional rows for other pKa values]	[nn.n]	[Insert e.g. "OECD 112, titration method", not internal report]	XX- <sup>nnn</sup>
Solubility in organic solvents	[nn x]g/l [solvent name] at [nn] °C	[nn.n] <sup>6</sup>	[Insert e.g. "OECD nnn method", not internal report]	XX- <sup>nnn</sup>

[Insert any necessary additional information, brief conclusions or explanatory notes on the above data, if applicable.]

<sup>3</sup> Copies of the full studies should be provided for evaluation.

<sup>4</sup> Study numbers appearing in the data tables must match study numbers in the references section at the end of the document.

<sup>5</sup> If estimated half-life exceeds twice the period of data observation, state the percentage of the compound remaining at the end of the observation period as an alternative to estimated half-life.

<sup>6</sup> Available information should be provided on the solubility of pure active ingredient (Table 1) OR technical active ingredient (Table 2) in organic solvents.

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**Table 2. Chemical composition and properties of [insert a.i.] technical materials (TC and or TK)**

[Notes. (i) In the table below, insert additional rows for other salt, ester, etc., TCs or TKs. (ii) Unless the a.i. can exist only in one form, identify the form of a.i. to which the data refer. (iii) If isomer ratio is a key property, insert an additional row for the data.]

Manufacturing process, maximum limits for impurities $\geq 1$ g/kg, 5 batch analysis data		Confidential information supplied and held on file by FAO and or WHO. Mass balances were [nn.n – nnn.n] % and percentages of unknowns were [n.n – n.n] %.		
Declared minimum [a.i.] content		[nnn] g/kg		
Relevant impurities $\geq 1$ g/kg and maximum limits for them		[insert data or None, as appropriate].		
Relevant impurities $< 1$ g/kg and maximum limits for them:		[insert data and additional rows, or enter None, as appropriate].		
Stabilisers or other additives and maximum limits for them:		[insert data and additional rows, or enter None, as appropriate].		
Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC and/or TK	[nnn – nnn] °C [state whether decomposition or gas evolution occurs]	[nn.n]	[Insert e.g. "OECD 102"]	XX- nnn
Solubility in organic solvents	[nn x]g/l [solvent name] at [nn] °C	[nn.n] <sup>7</sup>	[Insert e.g. "OECD nnn method"]	XX- nnn

[Insert additional information, brief conclusions or explanatory notes on the above data, if applicable. Insert additional information and data in support of specification clauses for water in TC/TK or formulations, if required.]

<sup>7</sup> Available information should be provided on the solubility of pure active ingredient (Table 1) OR technical active ingredient (Table 2) in organic solvents..

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**Toxicological summaries**

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from [insert a.i.] having impurity profiles similar to those referred to in the table above. [If there are differences, briefly describe them.]

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

[(iii) State if the data relate to more than one form of the a.i. and whether the different forms have similar or dissimilar tox./ecotox. profiles.]

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Table 3. Toxicology profile of the *[insert a.i.]* technical material, based on acute toxicity, irritation and sensitization.

[Notes. (i) Only examples are given, insert additional rows for additional species and tests. (ii) Insert additional column(s) for different isomers, salts, esters, etc.]

Species	Test	Purity % Note <sup>8</sup>	Guideline, duration, doses and conditions	Result <i>[(isomer/form)]</i>	Study number <sup>4</sup>
<i>[insert species and sex]</i>	oral	<i>[nn.n]</i>	<i>[insert duration, etc]</i>	LD <sub>50</sub> = <i>[nnn – nnn]</i> mg/kg bw	XX- <i>nnn</i>
<i>[insert species and sex]</i>	dermal	<i>[nn.n]</i>	<i>[insert duration, etc]</i>	LD <sub>50</sub> = <i>[nnn – nnn]</i> mg/kg bw	XX- <i>nnn</i>
<i>[insert species and sex]</i>	inhalation	<i>[nn.n]</i>	<i>[insert duration, etc]</i>	LC <sub>50</sub> = <i>[nnn – nnn]</i> mg/m <sup>3</sup>	XX- <i>nnn</i>
<i>[insert species and sex]</i>	skin irritation	<i>[nn.n]</i>	<i>[insert duration, etc]</i>	<i>[insert assessment]</i>	XX- <i>nnn</i>
<i>[insert species and sex]</i>	eye irritation	<i>[nn.n]</i>	<i>[insert duration, etc]</i>	<i>[insert assessment]</i>	XX- <i>nnn</i>
<i>[insert species and sex]</i>	skin sensitisation	<i>[nn.n]</i>	<i>[insert duration, etc]</i>	<i>[insert assessment]</i>	XX- <i>nnn</i>

*[Insert any necessary explanation, additional information and brief conclusions or interpretations, if applicable.]*

<sup>8</sup> Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

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*Table 4. Toxicology profile of the technical material based on repeated administration (subacute to chronic)*

[Examples given, insert additional rows for additional species and tests. Insert additional column(s) for different isomers, salts, esters, etc.]

Species	Test	Purity % Note <sup>9</sup>	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number <sup>4</sup>
[insert species and sex]	[e.g. oral]	[nn.n]	[insert duration, etc]	NOAEL = [n] mg/kg bw/d LOEL = [n] mg/kg bw/d	XX- nnn
[insert species and sex]	[e.g. inhalation, if applicable]	[nn.n]	[insert duration, etc]	NOAEL = [n.n] mg/m <sup>3</sup> LOEL = [n.n] mg/m <sup>3</sup>	XX- nnn
[insert species and sex]	[e.g. feeding, carcinogenicity]	[nn.n]	[insert duration, etc]	[insert assessment]	XX- nnn
[insert species and sex]	[e.g. feeding, [n] generation reproduction]	[nn.n]	[insert duration, etc]	NOAEL = [nn] mg/kg bw/d LOEL = [nn] mg/kg bw/d	XX- nnn
[insert species and sex]	[e.g. teratogenicity and developmental toxicity]	[nn.n]	[insert duration, etc]	[insert assessments]	XX- nnn
[insert species and sex]	[e.g. sub-chronic delayed neurotoxicity, if appropriate]	[nn.n]	[insert duration, etc]	[insert assessment]	XX- nnn

[Insert any necessary explanation, additional information and brief conclusions or interpretations, if applicable.]

<sup>9</sup> Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

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*Table 5. Mutagenicity profile of the technical material based on in vitro and in vivo tests*

[Examples given, insert additional rows for additional species and tests. Insert additional column(s) for different isomers, salts, esters, etc.]

Species	Test	Purity % Note <sup>10</sup>	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number <sup>4</sup>
[Insert species and cells]	[insert test and define <i>in vitro</i> or <i>in vivo</i> ]	[nn.n]	[insert conditions]	[insert assessment]	XX- <i>nnn</i>

[Insert any necessary explanation, additional information and brief conclusions or interpretations, if applicable.]

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<sup>10</sup> Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

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Table 6. *Ecotoxicology profile of the technical material*

[Examples given, insert additional rows for additional species and tests. Insert additional column(s) for different isomers, salts, esters, etc.]

Species	Test	Purity % Note <sup>11</sup>	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number <sup>4</sup>
[insert species, e.g. <i>Daphnia magna</i> (water flea)]	[e.g. acute toxicity]	[nn.n]	[insert duration, temperature and other test conditions]	EC <sub>50</sub> = [n.n x]g/l	XX- nnn
[insert species, e.g. <i>Leuciscus idus melanotus</i> (golden orfe)]	[e.g. short-term toxicity, flow-through]	[nn.n]	[insert duration, temperature and other test conditions]	LC <sub>50</sub> = [n.n x]g/l	XX- nnn
[insert species, e.g. <i>Scenedesmus subspicatus</i> (green alga)]	[e.g. effect on growth, static water]	[nn.n]	[insert duration, temperature and other test conditions]	EC <sub>50</sub> = [n.n x]g/l NOEC = [n.n x]g/l	XX- nnn
[insert species, e.g. Earthworm]	[e.g. acute toxicity]	[nn.n]	[insert duration, temperature and other test conditions]	LC <sub>50</sub> = [n.n] mg/kg dry soil	XX- nnn
[insert species, e.g. <i>Apis mellifera</i> (honey bee)]	[e.g. acute oral toxicity]	[nn.n]	[insert duration, temperature and other test conditions]	LD <sub>50</sub> = [n.n] µg/bee	XX- nnn
[insert species, e.g. Bobwhite quail]	[e.g. acute toxicity]	[nn.n]	[insert duration, temperature and other test conditions]	TEL = [nn] mg/kg bw	XX- nnn
[insert species, e.g. Mallard duck]	[e.g. short-term toxicity]	[nn.n]	[insert duration, temperature and other test conditions]	TEC = [nn] mg/kg diet	XX- nnn

[Insert any necessary explanation, additional information, brief conclusions and/or interpretation, if applicable.]

<sup>11</sup> Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

[Insert a.i.] [was/has not been] evaluated by the WHO IPCS [insert years] [and/or] by the FAO/WHO JMPR [insert years]. [Insert brief summary of conclusions.]

The IPCS hazard classification of [insert a.i. or free acid/base] is: [insert hazard statement], class [insert class].

[Insert published hazard statements and classifications of any other authority, together with any other relevant conclusions of that authority.]

### Formulations and co-formulated active ingredients

The main formulation types available are [insert appropriate codes for formulations (as listed in appendix of each CIPAC Handbook) and differentiate between agricultural and public health formulations, if appropriate].

Either [insert a.i.] [is/may be] co-formulated with [insert other a.i.s]. Or [Insert a.i.] is not co-formulated with other pesticides.

These [define if necessary] formulations are registered and sold in [name the countries or, if more than a few, express as, e.g. "many countries in North, Central and South America", or as "many countries throughout the world", as appropriate.]

### Methods of analysis and testing

The analytical method for the active ingredient (including identity tests) is [insert reference(s)]. The [insert a.i.] is determined by [insert, for example, "normal phase LC, using UV detection at 235 nm and external standardisation", or "capillary GC with FID and internal standardisation with dibutyl phthalate"]. [Insert any modifications required for existing published methods and any details required for additional identity tests.]

The method(s) for determination of impurities are based on [insert brief description of method(s)].

[Insert and describe briefly the methods for the determination of proposed relevant impurities, if applicable.]

[Note. If the validation of the methods or method extensions has not been published or adopted by CIPAC, AOAC or similar, indicate the intended date(s) of submission. If publication or adoption is not essential under the requirements of the FAO/WHO Manual, as in the case of methods for relevant impurities, a brief justification and critical summary of the validation data should be provided as a minimum.]

Test methods for determination of physico-chemical properties of the technical active ingredient were [insert, for example, OECD, EPA, EC], while those for the formulations were [insert, for example, CIPAC], as indicated in the specifications.

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### Physical properties

The physical properties, the methods for testing them and the limits proposed for the [insert codes for formulations<sup>12</sup>] formulations, comply with the requirements of the FAO/WHO Manual (2006 edition). [Identify any exceptions and insert justification for them.]

[Notes. In general, limits that are reasonably achievable should be proposed in preference to default values. Generally, it is not necessary to justify more stringent limits than those required by the Manual but more lax limits must be justified. The following cases must also be justified:

- (i) use of non-standard methods;
- (ii) exclusion of standard clauses;
- (iii) inclusion of non-standard clauses;
- (iv) inclusion of clauses without specified limits;
- (v) inclusion of clauses and limits for water.]

### Containers and packaging

[Insert brief description of special requirements, or state "No special requirements for containers and packaging have been identified", as appropriate.]

### Expression of the active ingredient

The [insert a.i.] is expressed as [insert common name of free acid/base, salt, ester, etc., to define how the a.i. is to be quantified].

### References Section 2. Non-confidential data (sorted by study number)

Study number	Author(s)	year	Study title. Study identification number. Report identification number. GLP [if GLP]. Company conducting the study.
	FAO/WHO	2006	Manual on development and use of FAO and WHO specifications for pesticides. February 2006 Revision of First Edition. FAO Plant Production and Protection Paper. Revised. <a href="http://www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm">www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm</a> and <a href="http://whqlibdoc.who.int/publications/2006/9251048576_eng_update2.pdf">http://whqlibdoc.who.int/publications/2006/9251048576_eng_update2.pdf</a>
XX-nnn	Author AB and Writer CD	2007	Determination of melting point of pure and technical grade xoo6. Study XX-nnn. Report XX-nnn.03. GLP. XYZ Contract Laboratories, XXland. Unpublished.

[Notes. Insert additional rows as required.]

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<sup>12</sup> As listed in Appendix E the FAO/WHO Manual (FAO/WHO, 2006). Appendix E: CropLife International codes for technical & formulated pesticides.

Annex.

Revised<sup>13</sup> text for the Manual on Pesticide Specifications

**3.1 Minimum data requirements for support of the reference (first) specification for an active ingredient**

General notes

(vi) *Except for studies on the physical and chemical properties of active ingredient, original study reports will not normally be required, unless the evaluator or the JMPS are unable to resolve a particular issue without the information. However, the study report source of data should be summarized in the form of study number, author, year, title, report number and company conducting the study, to allow ease of reference between the proposer and FAO/WHO. Original study reports on the physical and chemical properties of active ingredient are required, and should be provided in the dossier for the evaluator.*

**3.1.A Data requirements for pure and technical grade active ingredients (TC/TK)**

**A.2 Physical and chemical properties of the active ingredient** (and the methods and conditions used to generate these data). Where the active ingredient is a mixture of diastereoisomers, physical and chemical data for each diastereoisomer should be submitted, if available. Where the biologically active moiety is formed from the active ingredient, physico-chemical data should also be submitted for the active moiety, if available. *Studies and data for pure active ingredient (equivalent in purity to analytical standard purity) are required for:*

- vapour pressure;
- melting point;
- temperature of decomposition;
- solubility in water;
- octanol : water partition coefficient;
- dissociation characteristics, if appropriate;
- hydrolysis, photolysis and other degradation characteristics.

*Studies and data for technical grade active ingredient are required for:*

- melting point (active ingredients that are solids above 0 °C).

*Studies and data for solubility in organic solvents at room temperature are required for pure or technical grade active ingredient.*

**A.5 Manufacturing maximum limits for impurities** present at or above 1 g/kg, supported by **batch analysis data** (minimum 5 typical batches)(all confidential data). *Recent 5-batch studies are required to be GLP studies.* If the manufacturing process is conducted at more than one site, 5 batch analytical data should be provided from at least two sites representing typical extremes

<sup>13</sup> Revised June 2009. Some paragraph numbers have been changed from the originals. Paragraphs from the 2006 Manual with no changes or additions are not included in this Annex.

Grey shading = new or revised text

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of impurity profile. The statistical basis for the manufacturing limits should be explained (for example: maximum level found in practice; average plus 3 standard deviations of levels found in practice; etc.). Proposed relevant impurities present at or above 1 g/kg must be identified in the submission. Typically the unidentified and/or unaccountable fraction of the TC/TK should not exceed 20 g/kg (confidential information, except for the published specification limits for relevant impurities).

**3.2 E. Data requirements for the determination of equivalence**

E.1 Tier-1 data requirements for technical grade active ingredients include the information required in Section 3.1, paragraphs A.1, A.2<sup>14</sup>, A.3 to A.8, A.10.3<sup>15</sup>, A.10.4(iii)<sup>16</sup>, and B1 to B5, and mutagenicity (bacteria, in vitro) test data.

Tier-2 data requirements for technical grade active ingredients include the information required in Section 3.1, paragraphs A.9.1<sup>17</sup>, A.10.4(i)<sup>18</sup> and 10.4(ii)<sup>19</sup>.

*Notes on 3.1 A.2 when data are submitted for determination of equivalence.*

*Studies and data on the physical and chemical properties of a pure active ingredient are required where its composition is presumed to be different from the composition of the pure reference material.*

*The composition of pure active ingredient is accepted as the same in both reference material and the proposed material when it is a single non-chiral compound, a single enantiomer or a chiral compound as a racemate of an enantiomeric pair. If the pure active ingredient is a mixture, apart from a racemate of an enantiomeric pair, the composition of the pure active ingredient is presumed to be different in the reference material and proposed material without evidence that the compositions are the same.*

*Physical and chemical property data available for the reference material on the pure individual isomers of an isomer-mixture are accepted as applying to the pure individual isomers of the proposed material.*

*In addition, studies and data are required where the measured value of a property is not in reasonable agreement with the recorded value in the evaluation supporting the reference specification.*

*Studies and data for solubility in organic solvents at room temperature are required for pure or technical grade active ingredient. However, if solvent solubility data for pure active*

<sup>14</sup> See Notes on 3.1 A2.

<sup>15</sup> A letter of authorization granting competent FAO/WHO and registration authorities access to registration data on behalf of FAO/WHO. This is to enable .....

<sup>16</sup> A.10.4 Statements to identify the links between purity/impurity data and the hazard information and risk assessments.

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

<sup>17</sup> A.9.1 Toxicological profile of the TC/TK based on acute oral, dermal and inhalation toxicity; skin and eye irritation, skin sensitization.

<sup>18</sup> 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.

<sup>19</sup> A.10.4 Statements to identify the links between purity/impurity data and the hazard information and risk assessments.

(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.

Grey shading = new or revised text

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*ingredient are already recorded in the evaluation supporting the reference specification, solvent solubility data are not required for the pure (or technical) active ingredient of the proposed material, provided it has the same composition as the reference pure material.*

**3.2 F. Determination of equivalence**

Equivalence is determined in a two-tiered approach.

**TIER-1 (F.1 – F.4)**

- F.1 Technical grade active ingredients from different manufacturers or manufacturing processes are deemed to be equivalent if:
- F.1.1 the materials meet the requirements of the existing FAO/WHO specifications; and
  - F.1.2 assessments of the manufacturing process used, the impurity profile and results of mutagenicity (bacteria, *in vitro*) testing have been carried out with the result that the profiles meet the requirements of section F.3 below.
- F.2 Where a producer changes the manufacturing process for a technical grade active ingredient which has previously been evaluated and incorporated into a specification, equivalence may be determined on the basis of paragraphs F.1.1 and F.1.2, above.
- F.3 Equivalence of the impurity profiles of technical grade active ingredients, determined by comparison of the manufacturing specification limits<sup>20</sup>.
- F.3.1 Where (i) the maximum level (manufacturing limit) of each non-relevant impurity is not increased by more than 50% (relative to the maximum level in the reference profile), or the maximum absolute level (manufacturing limit) is not increased by more than 3 g/kg (whichever represents the greater increase); (ii) there are no new relevant impurities; and (iii) the maximum level of the relevant impurities is not increased; the technical grade active ingredients will normally be considered equivalent.
  - F.3.2 Where these limits for differences in maximum non-relevant impurity concentration are exceeded, the proposer will be asked to provide a reasoned case, with supporting data as required, as to why the particular impurities remain “non-relevant”. The JMPS will evaluate the case to decide whether or not the technical active ingredient is considered to be equivalent. Where the material is not considered to be equivalent, additional information may be required.
  - F.3.3 Where new impurities are present at  $\geq 1$  g/kg, the proposer will be asked to provide a reasoned case, with supporting data if available, as to why these impurities are “non-relevant”. The JMPS will evaluate the case to decide whether or not the technical active ingredient is equivalent.
  - F.3.4 The mutagenicity (bacteria, *in vitro*) profile is considered equivalent to that of the reference material if there is no change in the assessments as either positive or negative.
  - F.3.5 Information about the assessment of the proposed material by a competent registration authority should be taken into account in Tier-1.

<sup>20</sup> Note. Although this procedure may be used by anyone with legitimate access to the data required, for the purposes of FAO and WHO specifications, equivalence must be determined by the JMPS.

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**F.3.6** Where relevant impurities are increased in maximum concentration and/or where new relevant impurities are present, appropriate toxicological, ecotoxicological or other appropriate information should be submitted, if available, for evaluation in Tier-2.

**F.4** Where the Tier-1 information is insufficient to decide on equivalence or is insufficient to decide on non-equivalence, further evaluation should proceed with the information and data available under Tier-2. Technical grade active ingredients from different manufacturers or manufacturing processes are deemed to be equivalent if Tier-1 non-equivalence is uncertain and the Tier-2 assessments of the toxicological/ecotoxicological profiles have been carried out with the result that the profiles meet the requirements of sections F.5 and F.6, below.

#### TIER-2 (F.5 – F.6)

**F.5** Equivalence of the toxicological profiles of a technical grade active ingredient

**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 either positive or negative results.

**F.5.2** Where necessary (see Manual, section E.2), additional toxicological data (see Manual, section E.2.1) will be assessed by the criterion applied in paragraph F.5.1, provided that, where appropriate, the organs affected are the same. The "no observable effect levels" (NOELs) or "no observable adverse effect levels" (NOAELs) should not differ by more than the differences in the dose levels used.

**F.6** Equivalence of the ecotoxicological profiles for the technical active ingredient (as appropriate to the intended use of the active ingredient). Where required (see Manual, section E.2), the ecotoxicological profile (see Manual, section E.2.2) will be considered equivalent to that of the reference profile if the data do not differ by more than a factor of 5 compared to the reference profile (or by a factor more than that of the appropriate dosage increments, if greater than 5), when determined using the same species.