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Specifications for pesticides
A training manual

Participant's guide

TRIAL EDITION 1

Food and Agriculture Organization of the United Nations

World Health Organization

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Contents

Pages to be inserted when distributed for the exercise.

List of abbreviations used in the training course

CIPAC	Collaborative International Pesticides Analytical Council
CS	capsule suspension
EC	emulsifiable concentrate
EU	European Union
GC-FID	gas chromatography, using a flame-ionization detector
GHS	Globally Harmonized System of Classification and Labelling of Chemicals of the United Nations Economic Commission for Europe (UNECE), accessible under the Transport of Dangerous Goods heading at http://www.unece.org/trans/
HPLC-UV	high performance liquid chromatography, using an ultraviolet light absorption detector
IPCS	International Programme on Chemical Safety, a joint programme of WHO, the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP)
ISO	International Organization for Standardization
JMPS	FAO/WHO Joint Meeting on Pesticide Specifications
LC-MS	high performance liquid chromatography, using a mass spectrometer as detector
LC-MS/MS	high performance liquid chromatography, using a tandem mass spectrometer as detector
LN	long-lasting insecticidal net
LOQ	limit of quantification
M1	Manufacturer 1 and/or the supporting data and test methods used by M1, which form the basis of a reference specification
M2	Manufacturer 2 and/or the supporting data and test methods used by M2, where a product of M2 is to be tested for equivalence with the corresponding product of M1
OECD	Organisation for Economic Co-operation and Development
OK	acceptable
OL	oil-miscible liquid
SE	suspo-emulsion
TC	technical material
TK	technical concentrate
UL	ultra-low volume (ULV) liquid
USEPA	Environmental Protection Agency of the United States of America
WG	water-dispersible granules
WHOPES	WHO Pesticide Evaluation Scheme
ZC	mixed capsule suspension (CS) and aqueous suspension concentrate (SC)
ZE	mixed capsule suspension (CS) and suspo-emulsion (SE)
ZW	mixed capsule suspension (CS) and oil-in-water emulsion (EW)

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Background and preparation

Why offer this course?

The International Code of Conduct on the Distribution and Use of Pesticides[1] promotes trade in, and use of, good-quality pesticides and discourages the distribution of poor-quality products. Specifications for pesticides are developed by the Food and Agriculture Organization (FAO) and by the World Health Organization (WHO) to enable good- and bad-quality products to be distinguished, using simple, robust and well-validated tests. The Code of Conduct further promotes the use of FAO/WHO procedures for the determination of equivalence.

The FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) provides independent expert scientific assessment of the data supporting FAO and WHO specifications. The JMPS has developed standard procedures for assessment of pesticide data, including the determination of equivalence which minimizes the requirements for additional animal testing of pesticide hazards. The principles and practice of JMPS procedures are of utility to anyone involved in setting and ensuring standards for pesticide product quality, especially pesticide registration authorities. However, although simple in principle, JMPS procedures require extensive technical knowledge and expertise in practice, because almost every case is different.

Who should take this course?

This course is intended for personnel with responsibility for defining and ensuring the acceptability of pesticide product quality.

What is the purpose of the course and what are its objectives?

The purpose of this course is to provide an introduction to the principles and practice of defining acceptable quality and equivalence of pesticides, to assist both governments and industry to strengthen the underlying procedures required for quality control of pesticides used in agriculture and public health. The course does not address the procedure and requirements for adapting national pesticide registration systems to implement the principles of determination of equivalence, as promoted by the Code of Conduct,[1] but FAO and WHO recognize that this may involve a step-wise approach given the limited resources in many developing countries.

The objectives of the course are that participants completing it should understand the principles underlying specifications for pesticide quality control and be able to:

- apply well-established quality criteria to specific characteristics;
- apply well-established procedures where quality criteria must be defined case by case;
- determine whether or not different sources of an active ingredient, supported by different data, are equivalent;

[1] *International code of conduct on the distribution and use of pesticides* (revised version). Rome, Food and Agriculture Organization of the United Nations, 2002.

- determine whether or not additional evidence or expert advice is required to support a decision on either equivalence or the acceptability of quality.

What approach is used to teach the course?

The course is comprised of two main parts. The first is a plenary session, which provides an overview of the principles underlying specifications development and pesticide quality assessment. The second part involves model exercises, with participants working in teams to address typical cases and problems. The teams' solutions to each exercise are discussed before moving on to the next, so that lessons learnt can be put to good use immediately. However, the exercises are not repetitive and new problems are posed in each one. This reflects the real-life situation, where every case is different and some may present decision-making problems for which there is no precedent or model.

The course offers a step-by-step approach to acquiring the knowledge and skills needed for basic decision-making on development of pesticide specifications. Throughout the course, you should ask questions and discuss opinions freely. During the exercises, you should seek external help or clarification (from facilitator in lieu of a real manufacturer of the pesticide), if required, to reach a conclusion. This simulates real-life circumstances, where the pesticide manufacturer is often required to provide some additional information or clarification, and where it may also be necessary to consult published scientific literature or an independent expert in a particular discipline. This approach reflects the fact that, when dealing with technical data which invariably contain gaps and/or shortcomings, decisions must be based on inputs and opinion from a range of scientific disciplines. The importance of every detail of, or gap in, the data cannot be assessed by a single person, and an experienced team will have learnt to recognize when it requires additional expertise or information.

In addition to the technical issues addressed in the course, an underlying theme is to raise awareness of the delicate balance between maintaining the confidentiality of commercially-sensitive information and ensuring transparency of decision-making. Adoption of the internationally-recognized JMPS procedures is a first step towards achieving an appropriate balance in this respect. The second step is to maintain clear records of the basis for conclusions. Both are important where the basis for conclusions is not published, because the web of interdependent decisions leading to the overall conclusion may be forgotten quickly in complex cases. The documentation provided for the team exercises is designed to simplify and encourage recording of the basis for decisions.

Technical content of exercises

The exercises are an essential part of the problem-based learning approach used in this course. The problems highlighted in the exercises were selected because of their frequency and/or importance in JMPS practice. The data in the exercises are not identifiable with any particular active ingredient or chemical structure, which minimizes preconceptions, bias and/or potential problems with confidentiality. You should use your imagination and follow this through with a logical, scientific consideration of your ideas. *Evaluation table*s are provided, to assist you in a logical approach to the evaluation of data and a methodical approach to record-keeping.

As in real-life cases, the information initially provided in the exercises is not comprehensive. Considering each criterion in turn, teams should decide whether or not there is enough information to make a rational conclusion with respect to that criterion. One objective of the training is to help you to differentiate between problems which are unimportant and those which, unless resolved, will prevent the team from reaching a rational and defensible overall conclusion.

Teams are expected to identify gaps or problems in the information provided and to request additional information where the gap/problem prevents a decision being made. Facilitators are provided with supplementary information which can help to fill in the gaps or resolve problems. The supplementary information will be provided when a team asks the facilitator for help with a particular issue, but it would defeat the objective of the exercise if such details are provided without specific request. Facilitators will record the supplementary information provided to each team, to help in the post-exercise discussions.

You should note that, as in real-life cases, although the exercises have logical conclusions, different opinions can lead to different conclusions.

Commercially-confidential information is not included in the standard exercises. If appropriate, and with strict controls on participation and the maintenance of confidentiality, exercises may be conducted using real-life examples, to address locally-important issues. In such an exercise, everyone involved must have legitimate access to the data and no conflict of interest. Such exercises may follow the format of those given in this *training manual* but they are not part of the FAO/WHO training course and local organizers must accept responsibility for them.

Teamwork

The multi-faceted nature of pesticide specifications issues require the combined expertise of a number of experts in various scientific disciplines, working together as an integrated team. Teamwork is therefore a key feature of the training course.

You should work in a team throughout the exercises. Each team should choose its own moderator, to coordinate discussions, and rapporteur, to record team decisions and the reasons for them.

All team members should contribute opinions and ideas freely, so that the team has a range of options to consider, before reaching conclusions. In these exercises, as in real-life cases, full participation by all team members will lead to better decisions and fewer mistakes. Superficially naive questions can sometimes challenge everyone to rethink their own assumptions and concepts.

Teams should record the reason(s) for decisions, or identify the information they would require before a decision can be made. The *Relevant impurities evaluation table* and *Equivalence evaluation table*s provided are designed to assist you towards logical overall conclusions.

What preparation is needed?

The course is based upon the FAO/WHO document, *Manual on development and use of FAO and WHO specifications for pesticides*,[1] which provides a comprehensive coverage of the subject. The FAO/WHO specifications manual is

[1] Available only on the Internet at http://www.fao.org/ag/agp/agpp/pesticid/ and htpp://www.who.int/whopes/quality; accessed October 2008.

supplemented by procedural updates, published annually in reports of the Joint Open Meetings of the Collaborative International Pesticides Analytical Council (CIPAC) and the JMPS, which are also available through the same web sites. Before the course, you should read the two chapters of the FAO/WHO specifications manual on: *Data requirements and procedures*; and *Aims, applicability and requirements of clauses*.

Other requirements for the course

At the start of the course, you should have, or be provided with, a copy of the *Participant's guide*, preferably in a ring-binder. A ball-point pen (or pencil) and notebook (or paper) may also be required.

Tables of data and the appropriate blank *Evaluation table*s for exercises (Learning Unit G) will be distributed immediately before each exercise begins. At the end of each exercise, completed *Evaluation table*s will be distributed. The tables are page-numbered for insertion into your copy of the *Participant's guide*, to complete it as a reference volume.

Each team of participants should have access to a suitable electronic calculator or spreadsheet program for the exercises (capable of calculating standard deviation values in Exercises 2–4).

Shortly before the end of the course, you will be given a course evaluation form. Please take a few minutes to complete it and return it to the local organizer before departing from the course.

A course completion certificate, if required by local custom, will be provided at the end of the course.

LEARNING UNIT A

Introduction to the course

Slide A-01

Goal of the training course
To enable you to make sound decisions about the control of quality of pesticides used in agriculture and/or public health.

Slide A-02

Objectives of the training course
By the end of this course, you should be able to: apply well-established quality criteria for specific characteristics; apply well-established procedures where quality criteria must be defined case by case; determine whether or not different sources of an active ingredient, supported by different databases, are equivalent; determine the additional evidence or expert advice required to support decisions on equivalence or the acceptability of quality.

Slide A-02. **Note that ...**

(i) The purpose of this course is to provide an introduction to the principles and practice of defining acceptable quality and equivalence of pesticides, to assist both governments and industry to strengthen the underlying procedures required for quality control of pesticides used in agriculture and public health. The course does not address the procedure and requirements for adapting national pesticide registration systems to implement the principles of determination of equivalence, as promoted by the Code of Conduct,[1] but FAO and WHO recognize that this may involve a step-wise approach due to the limited resources in many developing countries.

(ii) The principles and procedures described in this course have been developed by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). Although FAO and WHO are not international regulatory authorities, the JMPS principles and procedures are expected to be broadly applicable within most regulatory systems. Part of the overall purpose is therefore to encourage harmonization of registration requirements and procedures.

(iii) The technical issues involved in dealing with each active ingredient and formulation tend to differ, and therefore the JMPS procedures must be applied intelligently and according to the requirements of each particular case. However, the following general principles are applicable in all cases:

[1] *International Code of Conduct on the distribution and use of pesticides* (revised version). Rome, Food and Agriculture Organization of the United Nations, 2002.

(a) maintenance of commercial confidentiality;
(b) transparency of decision-making procedures;
(c) basing decisions on inputs from a team of scientists with expertise and experience in a range of appropriate disciplines;
(d) basing decisions on sound science and the best evidence available;
(e) keeping clear records of decisions and the rationales for decisions, especially where the decisions are made case by case.

Slide A-03

Boundaries of the training course
Does not consider the safety and efficacy of active ingredient.
Does not consider hazard or risk assessment of active ingredient.
But it does consider the potentially adverse effect of impurities on safety or product stability.

Slide A-03. **Note that ...**

(i) For the purposes of this course, hazard is an inherent property of a chemical, whereas risk is an expression of potential exposure to a hazard.

LEARNING UNIT B

Introduction to specifications for pesticides

Slide B-01

Learning objectives
After this *Introduction*, you should understand: the need for good-quality pesticide products; the role of pesticide specifications in improving pesticide product quality.

Slide B-02

Importance of pesticides in food security and quality
Pests and diseases are major causes of loss and quality degradation in agricultural production and food storage throughout the world. Migratory pests, such as locusts, can cause particularly dramatic losses within a region. The consequences, in terms of hunger, malnutrition and pressure to cultivate yet more land, are incalculable. Use of pesticides is very important element in an integrated approach to control agricultural and food pests.

Slide B-03

Importance of pesticides in controlling vector-borne diseases
Vector-borne diseases are major causes of illness and death in many tropical and subtropical countries. Vector control has a key role in prevention and control of vector-borne diseases such as malaria, dengue and Chagas disease. Use of pesticides is the most important element in an integrated approach to vector control, especially in epidemics.

Slides B-02 and B-03. **Note that ...**

(i) These points highlight the importance of pesticides in an integrated approach to pest control. Used judiciously, pesticides are essential tools in improving agricultural production and economies, as well as in vector and public health pest control.

Slide B-04

Poor-quality pesticides …
are unlikely to serve the intended purpose;
are likely to provide poor value to users;
are likely to be more harmful, directly or indirectly, to humans and the environment;
may be phytotoxic to treated crops or taint the food.

Slide B-05

Adverse effects of poor-quality pesticides
Blank slide: facilitator to insert examples

Slide B-05. **Examples of adverse effects of poor-quality pesticides ...**

(i) Excessive level of a hazardous impurity increases risks of adverse effects on users, crops, food consumers and/or the environment.

(ii) Insoluble particulates present in products intended for spray application may block nozzles and/or filters, delaying operations and increasing the risk of user exposure to active ingredient.

(iii) Granular formulations which are too fragile may produce respirable dust when handled and applied, again increasing the risk of user exposure to active ingredient.

(iv) Poor suspensibility of dispersions may produce uneven distribution of active ingredient in the spray tank and uneven application.

(v) Poor retention/migration of insecticide through successive washes in a long-lasting insecticidal mosquito net (LN) leads to reduced personal protection of the user.

(vi) If poor quality leads to poor efficacy, users may increase dose rates or the number of applications and unknowingly increase other risks.

(vii) Users may dump poor-quality products into the environment, with potentially adverse effects on wildlife and drinking-water.

(viii) Selectivity may be adversely affected.

(ix) Any the above consequences will usually have a negative impact on the marketability of a pesticide product and its registration could be withdrawn or restricted.

As an aside to the Learning unit, but nonetheless very important, note that ...

(i) Even high-quality pesticides must be used carefully and judiciously, for good control of pests and vectors while avoiding adverse side-effects to people and the environment.

Slide B-06

What is a pesticide specification?
A list of basic quality criteria for distinguishing between good and bad products (of the same type).
It does **not** define the best product, **nor** that the product is suitable or safe for a particular purpose.

Slide B-06. **Note that ...**

(i) Safety and suitability for purpose are the responsibility of registration authorities, although assessments are made by WHO in support of WHO specifications for public health pesticides intended for specific purposes.

(ii) Deciding which product is the best available for the purpose is the responsibility of the buyer or the buyer's advisers.

Slide B-07

A pesticide specification includes criteria for properties in some or all of the following categories ...
description of the product
active ingredient identity and content
relevant impurities
physical properties
storage stability.

Slide B-07. **Note that ...**

(i) These categories and criteria will be addressed in more detail later in the training course.

(ii) Specifications do not include clauses to control inherent properties of the active ingredient, which are not influenced by product quality. Information on such properties is provided in the evaluations which are published in support of FAO and WHO specifications.

Slide B-08

Test methods supporting specifications
Widely-accepted, well-validated test methods are essential.
Test methods should be straightforward and robust.
Well-trained technicians and a suitably-equipped laboratory are required for reliable results.

Slide B-08. **Note that ...**

(i) Clearly defined, widely-accepted and/or well-validated methods are essential for making reliable, reproducible and comparable physical and chemical measurements. This is true both for developing specifications in the first place and for subsequent compliance testing. In the case of physical tests, methods must be applied without deviation, because the physical properties involved are defined by the method of measurement.

(ii) Various international organizations provide the means by which test methods can be validated to an acceptable standard. CIPAC has provided the majority of well-known methods for compliance testing of physical and chemical properties of pesticide products, but other organizations such as AOAC International and ASTM International also provide methods. Test methods for the physical properties of active ingredients tend to be those adopted by OECD, USEPA and the EU but, while these methods provide important supporting information for evaluating specifications, they are not appropriate for compliance testing because pesticide specifications do not define the properties of the active ingredient.

Slide B-09

FAO and WHO specifications
FAO and WHO specifications are international points of reference for quality of agricultural pesticides (FAO) and public health pesticides (WHO).
FAO/WHO development of specifications has changed to a "new procedure" in recent years.

Slide B-09. **Note that ...**

(i) FAO/WHO specifications form international points of reference in those cases where the standards have been developed. For pesticide products for which FAO/WHO specifications do not exist, the general provisions of the FAO/WHO specifications manual apply. Although more limited and less detailed in scope, the provisions of the FAO/WHO specifications manual provide certain basic points of reference which are expected to apply to most, if not all, pesticide products.

(ii) The "new" procedure for development of pesticide specifications, which was introduced by FAO in 1999 and by WHO in 2002, links specifications to the products of manufacturer(s) whose data package(s) on the manufacturing process and chemical and hazard profiles have been evaluated by the JMPS. In contrast, FAO and WHO specifications developed under the "old" procedure apply to the products of all manufacturers, irrespective of whether or not their products had been evaluated. Evaluations conducted under the "old" procedure were also less detailed than those of the "new" procedure. Existing FAO and WHO specifications developed under the "old" procedure remain valid until reviewed under the "new" procedure.

LEARNING UNIT C

Specifications for technical grade active ingredients (TC and TK)

Slide C-01

Learning objectives

After completing this *Learning unit*, you should understand:

- the structure and aims of specifications for TC and TK and their role in the development of specifications for formulated products;
- data requirements for developing TC and TK specifications and why it may be necessary to work with incomplete information;
- the need for confidence in the validity of data evaluated;
- the concept of "reference profiles";
- the importance of openness and transparency in decision-making, while maintaining confidentiality of secret information.

Slide C-02

Specifications for technical grade active ingredients

Technical grade pesticides are relatively pure active ingredients, used to prepare formulations.

TC = technical material; TK = technical concentrate

TC and TK are not clearly distinguished; TC is usually ≥900 g/kg with solvent(s) completely removed during synthesis and no solvent added subsequently.

Slide C-02 **Note that ...**

(i) TC and TK are international codes for technical grade active ingredients.

(ii) TC is usually the final product from preparation of the active ingredient, which may contain a stabilizer and/or anti-caking or anti-static agents (if required) but no other additives. It is the purest form of active ingredient that is economic for use in formulations.

(iii) TK may also be the final product from preparation of the active ingredient but it may contain additives (not formulants) in addition to a stabilizer, for example as safety agents. TK may also contain solvent(s) (including water), either deliberately added to a TC or not removed during preparation. TK may be preferred where TC preparation is uneconomic, unnecessary, particularly hazardous, or destabilizes the active ingredient.

Slide C-03

Why distinguish between TC and TK?
TC specification has no upper limit for active ingredient content.
Increasing the purity of a TC cannot increase its overall hazard significantly and may decrease it.
TK specification has upper and lower limits because accidentally higher content may increase hazard.

Slide C-03 **Note that ...**

(i) Both TC and TK specifications have lower limits for active ingredient content.

(ii) FAO and WHO wish to encourage production of the highest purity active ingredients, because an increase in active ingredient content (say) from 900 g/kg to 990 g/kg in a TC will not significantly increase hazards due to active ingredient (because the content is raised by only 10%), whereas hazards associated with impurities may be greatly reduced (on average by a factor of 10 in this case).

(iii) The upper limit in a TK specification is to ensure that the TK hazard cannot be increased significantly (potentially by more than 10%), should the content of active ingredient be unexpectedly high.

Slide C-04

What is a good TC or TK?
Correct physical appearance.
Not less than the minimum content of active ingredient.
Not more than the maximum content of "relevant impurities".
Acceptable physical properties, if applicable.

Slide C-04 **Note that ...**

(i) Relevant impurities will be considered later in the course.

Slide C-05

Is a TC or TK specification required before specifications can be developed for formulations?
Most formulations are produced from a TC or TK.
The approach to cases where a TC or TK is not isolated may appear to be different but the principle is the same.
Specifications are related to the hazard data for the source of active ingredient under consideration, which is usually TC or TK.
If the hazard data relate only to a formulation (produced without isolation of a TC or TK), that formulation is unlikely to be used by other formulators.

Slide C-06

Information to support a TC or TK specification
Active ingredient identity.
Manufacturing route, materials, conditions (*confidential information*).
Content of active ingredient, impurities, stabilizers, etc. – manufacturing limits and data on five process batches and their source(s) *(confidential information*).
Name of the company responsible for the quality of the TC or TK.

Slide C-06 **Note that ...**

(i) Information on the manufacturing process and data on most impurities are regarded as confidential and are never published or revealed to a third party. Limits for the content of active ingredient, critical additives and relevant impurities are published by FAO and WHO as part of the specification. Information on hazards and physico-chemical properties is also published as part of the evaluation.

(ii) Information on non-critical additives is also confidential, as is any information on the composition and method of preparation of formulations.

(iii) Additional information and data may be required in some cases, for example to support unusual specification clauses or limits. Such data are also confidential, although conclusions drawn from them may be published by FAO/WHO to explain JMPS decisions.

Slide C-07

Information to support a TC or TK specification
Physico-chemical characteristics, vapour pressure, decomposition temperature, water solubility, log P K_{OW}, degradation characteristics, etc.
Methods of analysis and testing used to generate reference data and for testing compliance with specifications (if different), including extent of validation

Slide C-07 **Note that ...**

(i) Data on physico-chemical characteristics of the active ingredient help to understand the basis for test methods and specification requirements for TC, TK and formulations. For example, a low temperature of decomposition of the active ingredient may justify the use of a lower-than-usual temperature in storage stability tests.

Slide C-08

Information to support a TC or TK specification
Toxicology: acute, chronic, carcinogenicity, teratogenicity, mutagenicity, with purity data for the product tested.
Ecotoxicology: fish, birds, bees, aquatic plants and animals, etc., with purity data for the product tested.
At least one national registration, and/or a WHO recommendation, for use of the active ingredient.

Slide C-08 **Note that ...**

(i) FAO and WHO specifications are not developed unless the hazards, and risks in one or more applications, have been assessed as acceptable by at least one more national authority or by WHO (for certain public health pesticide products). It is very important to recognize that this does not mean that risks will be acceptable in all possible use scenarios. All registration authorities should satisfy themselves that the risks involved in the intended uses of a particular product within their country or region are acceptable before permitting such uses.

(ii) The terms "hazard" and "risk" tend to be defined similarly, or used interchangeably, in many dictionaries and some technical literature. For those involved in hazard and risk assessment, as well as for the purposes of developing pesticides specifications, the terms are applied with different meanings. Various definitions[1] of both "hazard" and "risk" have been proposed to clarify the distinction, but the following definitions have been published by IPCS.[2]

"Hazard: an inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub)population is exposed to that agent."

"Risk: the probability of an adverse effect in an organism, system, or (sub)population in reaction to exposure to an agent."

Slide C-09

Data are evaluated to ...
identify "reference profiles" of purity/impurities and hazards;
identify relevant impurities;
ensure correct identification of the active ingredient, especially when it is present as, or in, a mixture that is defined by the specification;
ensure that specification clauses and limits are valid quality criteria;
ensure that specification clauses and limits are supported by evidence.

Slide C-09 **Note that...**

[1] Hazard and risk terminology, cross-referenced to the sources of the definitions are available, in English and German, at the web site of the German Institute for Risk Assessment, (http://www.bfr.bund.de/cm/228/risiko_glossar.pdf; accessed October 2008).

[2] International Programme on Chemical Safety. *IPCS risk assessment terminology. Part 1: IPCS/OECD key generic terms used in chemical hazard/risk assessment. Part 2: IPCS glossary of key exposure assessment terminology*. Geneva, World Health Organization, 2004 (available at: http://www.inchem.org/documents/harmproj/harmproj/harmproj1.pdf; accessed October 2008).

(i) "Reference profiles" are the purity/impurity, physico-chemical and hazard data associated with active ingredient from the source that is supported by the most comprehensive hazard data available. The "reference specifications" also relate to the product from this source. Reference profiles are used for the determination of equivalence, which is addressed in Learning Unit F.

(ii) Relevant impurities are by-products of the manufacture or storage of an active ingredient which, **compared with the active ingredient**, are toxicologically significant to health or the environment, phytotoxic to treated crops, cause taint in food, affect the stability of the pesticide, or cause any other adverse effect. Water may be a relevant impurity if it can adversely affect pesticide stability or formulation quality. Insoluble material may also be a relevant impurity in a TC or TK if the subsequent formulations would fail a wet sieve test and be likely to block sprayer filters and nozzles in use, for example.

Relevant impurities will be dealt with more fully in Learning Unit E.

Slide C-10

Who evaluates the data?
Teams of scientists with sound knowledge and experience in many areas of chemistry and physical properties, toxicology and ecotoxicology. No single person can do the job, no matter how good they are.

Slide C-10 **Note that ...**

(i) A thorough knowledge of several different scientific disciplines is essential. Because there is seldom a single "correct" conclusion, exchange of opinions and sharing of knowledge are very important in reaching optimum conclusions. Physico-chemical data should be assessed by people with sound knowledge and experience in synthesis, analysis and physical testing. Toxicology and ecotoxicology data should be assessed by those suitably knowledgeable and experienced in these fields. Those involved in the evaluation should work cooperatively, as a team, not competitively.

Slide C-11

What about missing or questionable data?
Despite the best effort of regulators and manufacturers, gaps, inadequacies or inconsistencies in the data are frequent. It is important to decide whether or not limitations in the data are serious and require follow-up action.

Slide C-11 **Note that ...**

(i) Unlike national registration authorities, FAO and WHO cannot prevent, directly, the trade in pesticide products supported by poor or inadequate data, although specifications may not be developed for, or extended to, such products and therefore trade in them is discouraged.

Slide C-12

Checking questionable data
It is essential to have confidence that the data considered are valid and produced by well-validated test methods. Data obtained from published literature may be of little use in assessing the TC or TK of another manufacturer. Data identical to those in published sources should be verified by checking the manufacturer's study report(s).

Slide C-12 **Note that ...**

(i) Data generated by test methods of questionable validity, or data which are themselves of questionable validity, must be considered cautiously in decision-making. Checking the validity of test methods and data is not a trivial part of the overall job of data evaluation but it is important to be aware of the soundness, or otherwise, of the data used as the basis for decisions.

(ii) If data submitted are identical to those in published sources, the origin of the information should be verified. Replicate measurements usually differ when made on a single sample in the same laboratory, so measurements on the TCs or TKs of two different manufacturers are likely to differ. If there is any doubt about the source or validity of data, the manufacturer should be asked to provide the full study report(s).

(iii) If batch-analysis or manufacturing specifications data add up to exactly 1000 g/kg, or if there is essentially no batch-to-batch variation, the data should be checked in the full study reports. Although such occurrences are not impossible, they are unusual and should be investigated.

Slide C-13

Other checks
Chemical names, structures or analytical methods for impurities may be questionable, leading to errors of interpretation and mistakes in determination of equivalence. Hazard assessments, especially of irritation and sensitization test data, may be non-standard (OECD and other internationally-adopted protocols are considered to be "standard").

Slide C-14

Manufacturing limits and 5-batch analytical data
Purity/impurity profile is based on manufacturing limits, not values for individual batches (often provided as a series of 5).
Basis of manufacturing limits should be known.
Apparent conflicts between 5-batch data and manufacturing limits may not be a problem if there is a rational explanation.
Some impurities may be less well-controlled than is apparent from the 5-batch data.
Therefore, limits for some impurities may be lower or higher than expected from the 5-batch data.

Slide C-14 **Note that ...**

(i) Manufacturing limits may be set statistically (for example, the average ±3 standard deviations from 5-batch data) or on the highest/lowest values found with experience, for impurities or active ingredient, respectively.

(ii) The purity/impurity profile (manufacturing limits) cannot correspond to the component profile in any one batch. All components cannot be present at their limits in a single batch.

(iii) The manufacturing limits may not appear to correspond to the 5-batch analysis data. This is not unusual, but the manufacturer should explain extreme cases. The 5-batch data are unlikely to be fully representative of all batches and, in certain cases, may represent batches produced over a relatively short time period (which is not a problem if between-batch variation is random). Bearing these limitations in mind, a useful method for deciding when to question manufacturing limits is to check whether the limit for an impurity exceeds the 5-batch average plus 3 standard deviations. If it does so, it may indicate that the impurity is poorly controlled, which may not be a problem if the impurity poses no special hazard. Alternatively, if the manufacturing limit for an impurity is lower than that implied by the 5-batch data, perhaps the manufacturing process has been refined to control that impurity. Similarly, refinements in the manufacturing process can lead to active ingredient of greater purity than that implied by the 5-batch data.

(iv) Sums of individual batch data usually do not add up exactly to 100%, because analytical methods produce estimated values which incorporate unavoidable variations and bias in measurement, rather than true values for content. Generally, the greater the number of analytical methods involved in the analysis of a TC or TK, and the more technically challenging the procedure, the greater will be the contribution of analytical variation (and perhaps bias) to the measurement of batch-to-batch variations in active ingredient and impurity content.

(v) In general, individual batch data sums in the range 980 to slightly >1000 g/kg indicate acceptable material accountability. That is, no significant component has been missed or seriously underestimated. Sums outside this range should be considered case by case. Sums <980 g/kg may indicate that significant components have been missed or under-estimated, although if only 1 or 2 of the

5 sums is <980 g/kg, this could be due to analytical variation. Sums significantly >1000 g/kg may indicate poor analytical control or poor accuracy, with one or more components being overestimated.

(vi) Manufacturing limits must not be summed, because the sum has no meaning.

Slide C-15

Links between purity/impurity and hazard profiles
Conceptual rather than direct.
Manufacturing limits represent the worst-case for every component, a statistical "envelope" for purity/impurity which does not describe any single batch or blend of batches.
Hazard data represent one or more impurity profiles within the statistical envelope.
The purity of TC or TK used for hazard data may be the only information available on the link between profiles.

Slide C-15 **Note that ...**

(i) The lowest content of active ingredient is coupled with the highest level total impurities but, in most cases, it is not possible for every component of a technical grade active ingredient to be present at its manufacturing limit.[1]

Slide C-16

Links between purity/impurity and hazard profiles
Most hazards, qualitatively and quantitatively, are derived from the active ingredient because it is by far the most abundant component of a TC or TK.
Relatively small variations in the high level of active ingredient content cannot produce big differences in hazard.
Correspondingly large variations in impurity content could produce big differences in hazard if the impurity is much more hazardous than the active ingredient
Chemical structures associated with exceptional hazards are mostly well-known.

Slide C-16 **Note that ...**

(i) The purity of TC or TK used to generate the hazard data is very important information because hazard data generated from exceptionally pure material may exclude a contribution, otherwise made by impurities, to the hazard. However, hazard data generated from active ingredient of lower purity than the manufacturing specification may be helpful, being more likely to represent a worst-case scenario.

(ii) Relevant impurities are identified in FAO/WHO specifications. Some national authorities also publish lists of relevant impurities in TC and TK, e.g. Germany.[2]

[1] Generally, a sum of manufacturing limits would exceed 1000 g/kg.

[2] http://www.bvl.bund.de/cln_007/nn_492022/DE/04__Pflanzenschutzmittel/09__Produktchemie/ListeRelevanterVerunreinigungen.html; accessed October 2008.

Slide C-17

Questionable links between purity/impurity and hazard profiles?
If the manufacturing process has evolved and/or the manufacturer sets up a new plant, manufacturing limits may be revised.
If the hazard data are purchased with process and rights to produce active ingredient, but the process is changed, manufacturing limits may be different.
The changes in manufacturing limits weaken the links with the original hazard data.

Slide C-18

Records of evaluations
FAO/WHO evaluations are published on the Internet, recording non-confidential data, data problems and the basis for all decisions
National/regional evaluations may not be published, but the basis for decisions should be recorded and preferably published.

Slide C-18 **Note that ...**

(i) All JMPS decisions on relevant impurities, equivalence, non-standard clauses and limits are explained in published evaluations.

(ii) FAO/WHO specifications for TC and TK should not be applied indiscriminately to manufacturers whose products have not been evaluated.

(iii) Given the limited resources available to most registration authorities, and for the purposes of transparency in decision-making, sharing of information and the publication of evaluations are encouraged.

The following clauses are included in FAO/WHO specifications for technical grade active ingredients.

Slide C-19

TC and TK specification clauses
<u>Description</u>
Physical appearance and chemical form (e.g. salt, ester) – simplest and most rapid test.
Stabilizer, if critical, is identified and a validated test method is provided.
If the identity and/or quantity of stabilizer is not critical, the clause indicates only that a stabilizer is present.
If a solvent is added (TK only), a clause and analytical method are not usually required for the solvent.

Slide C-19 **Note that ...**

(i) If the material visibly does not match the specified description, it has failed the specification and there is no point in further, more expensive, tests. For

example, if the material presented is a viscous brown liquid and the specification indicates that it should be a white crystalline solid, it is non-compliant.

(ii) If a solvent is present, the manufacturer must ensure that the active ingredient cannot react with it. For example, methanol may not be a suitable solvent for esters because of potential for a transesterification reaction.

Slide C-20

TC and TK specification clauses
Identity
Unambiguous name … can be problematic for mixtures, especially if derived from plants or microorganism cultures – and also for some pyrethroids.
Primary identity test usually based on measurement of active ingredient content; back-up test required for cases of doubt.
If the active ingredient is a salt, ester or other derivative, it may be necessary to identify the derivative component.
No external validation of identification methods required, except where the active ingredient is a mixture of defined ratio.

Slide C-20 **Note that ...**

(i) For example, an unambiguous name is difficult in the case of neem-based pesticides. The FAO specifications are identified as azadirachtin A, but this is a "marker compound" and azadirachtin, in the broad sense, is the name given to an incompletely defined group of compounds extracted from seeds or leaves of *Azadirachta indica*, for use as an insecticide. Among synthetic pesticides, some pyrethroids also pose problems, as a name may apply to one or several of the possible stereo-isomers or, in some cases, only to a specific ratio of those isomers.

(ii) It is only necessary to identify the specific salt or other derivative present if that particular form of active ingredient is critical for product stability or performance.

(iii) Identity tests for specific ratios of isomers must be quantitative and validated by inter-laboratory study.

Slide C-21

TC and TK specification clauses
Active ingredient content
Analytical methods validated by collaborative study.
Limit based on manufacturing specification, not 5-batch data.
Limit applies to the average of measured values.
Content expressed as g/kg, or g/l at 20ºC, of appropriate chemical form (e.g. free acid, sodium salt, marker compound, etc.).

Slide C-21 **Note that ...**

(i) Various international organizations (e.g. CIPAC, AOAC International) elaborate and publish validated test methods for pesticides.

(ii) Where FAO/WHO specifications exist for a product, national authorities are encouraged to adopt the test methods referenced in those specifications.

Slide C-22

TC and TK specification clauses

Relevant impurity content

Analytical methods peer-validated in two or more laboratories.

Limit based on manufacturing specification, not 5-batch data.

Limit applies to the average of measured values.

Content expressed as g/kg, or g/l at 20 ºC.

Slide C-22 **Note that ...**

(i) Relevant impurities will be considered in detail later in the course.

(ii) Peer-validated methods for certain relevant impurities are provided free of charge by CIPAC.

Slide C-23

TC and TK specification clauses

Other clauses

Acidity, alkalinity or pH range, if required.

Other characteristics, if critical for TC, TK or formulation quality.

Storage stability is not specified, because manufacturers can usually re-purify an aged TC or TK.

If a TC or TK is sold to end-users as a "formulation" (e.g. certain UL), the formulation specification applies and storage stability is specified.

Slide C-23 **Note that ...**

(i) Acidity, alkalinity or pH range resemble relevant impurities and are also dealt with later in the course.

An example of a specification for TC follows.

Slide C-24

HAPPYFOS TECHNICAL MATERIAL

WHO Specification 999/TC (December 2007*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*999/2007*). It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for TC produced by other manufacturers. The evaluation report (*999/2007*), as PART TWO, forms an integral part of this publication.*

1 **Description**

The material shall consist of happyfos together with related manufacturing impurities and shall be a viscous yellow-to-brown liquid, containing not more than a trace of insoluble material, and shall be free from extraneous matter and added modifying agents.

Slide C-24 **Note that ...**

(i) The name "happyfos" is fictional. FAO/WHO specifications use a standard coding system, explained in the FAO/WHO specifications manual. The number "999" represents the CIPAC number of the active ingredient – a fictional number is used in this example.

(ii) The "header note" (given in *italics*) is standard information, drawing attention to the published evaluation and indicating that the specification applies only to products evaluated by FAO/WHO.

Slide C-25

2 **Active ingredient**

2.1 **Identity tests** (999/TC/M/2, CIPAC X, p.193, 2003)The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Happyfos content** (999/TC/M/3, CIPAC X, p.193, 2003) The happyfos content shall be declared (not less than 930 g/kg) and when determined, the average measured content shall not be lower than the declared minimum content.

3 **Physical properties**

3.1 **Alkalinity** (MT 31, CIPAC F, p. 96, 1995) Maximum: 0.5 g/kg calculated as NaOH.

Note 1....

* *Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.who.int/whopes/quality/.*

Slide C-25 **Note that ...**

(i) Test methods are clearly referenced, including any appropriate coding. Code numbers for active ingredients are published by CIPAC, but the code number 999 for happyfos is fictional. Two-letter codes for technical and formulated products are produced by industry.

(ii) The simple existence of a CIPAC code number for an active ingredient does not necessarily mean that either FAO/WHO specifications or CIPAC test methods have been published for it. The reference to CIPAC Handbook X is fictional and intended only to reflect the fact that CIPAC handbooks, containing test methods, are identified alphabetically in the sequence published.

(iii) "Notes" may be required, for example to explain the function or meaning of a clause, or how the clause or test method should be applied.

(iv) The asterisk (*) note provides a standard warning that the specification, or its status, may be subject to change over time.

LEARNING UNIT D

Specifications for formulated pesticides

Slide D-01

Learning objectives
After completing this *Learning unit*, you should understand: the structure and aims of specifications for formulated products; data requirements for developing specifications for formulated products.

Slide D-02

Formulations
What is a formulated pesticide? Active ingredient in the form sold for use. Active ingredient plus formulants (excipients, "inerts") assembled to optimize delivery to target pest, optimize activity, stabilize active ingredient, minimize user exposure, simplify use, etc.

Slide D-02 **Note that ...**

(i) There are rare exceptions to the definition given in the slide. For example, in a few cases, a UL product intended for dilution with solvent by the user before application may contain essentially no formulants. Nonetheless, such products are required to conform to the appropriate formulation specification.

Slide D-03

Prerequisites for formulation specifications
A TC or TK specification is normally required, except in unusual cases where a TC or TK is not isolated. Because this ensures the strongest possible links to hazard and risk assessments.

Slide D-03 **Note that...**

(i) The issues of links to hazard and risks assessments was considered in the previous Learning Unit, especially slides C-15 to C-17.

Slide D-04

Additional supporting data required?
Few additional data are normally required, over and above those supporting the TC or TK specification, except: to support proposed specification limits which would normally be considered borderline for good quality; non-standard clauses or limits require supporting information; novel or unique formulations may require additional supporting information.

Slide D-04 **Note that ...**

(i) Slow-release CS and LN products may require unique specification limits, supported by adequate information to show that the limits truly distinguish between good and bad products.

Slide D-05

Efficacy data
National authorities are responsible for efficacy assessment, before developing specifications. Existing efficacy assessments (e.g. WHO evaluations of public health pesticides), of comparable scenarios, may be used to minimize requirements for national or local testing.

Slide D-05 **Note that ...**

(i) Efficacy data are not required to support FAO specifications (agricultural pesticides), because the corresponding application scenarios vary widely throughout the world. However, they are required to support WHO specifications (public health pesticides), because these relate to one, or a few, well-defined application scenario(s).

Slide D-06

Scope of formulation specifications
Similar to TC and TK specifications but also specify physical properties and synergist (if applicable). Essential additives for safety or stability. Unlike FAO and WHO, national authorities should control formulants.

Slide D-06 **Note that ...**

(i) Emetics, stabilizers or other additives essential for product safety or stability may be referenced in a "Note" appended to the specification. Where the identity and content of the additive are critical, a peer-validated test method must be provided.

(ii) Adjuvants, added by the user, are not within the scope of FAO/WHO specifications.

(iii) FAO/WHO specifications do not provide clauses for direct control of formulants ("inerts") or formulant impurities, because many formulants are complex materials which, although having appropriate physical characteristics, may vary

in composition, over time and around the world. Instead, formulants and their impurities are specified indirectly, through the physical properties and storage stability of the product. National registration authorities may provide controls for the identity and content of formulants, although identification and quantification of certain formulants are technically challenging.

Slide D-07

Specifications for mixed active ingredients and formulations
In most cases, separate specifications apply to each active ingredient.
SE, ZC, ZE, ZW are treated differently because of the complexity of these products.
Where the ratio of active ingredients is critically important, a specification may be developed for an individual formulated product.
Where two or more solid formulations are mixed, expanded tolerances for active ingredient content take account of the tolerance on formulation ratio and increased heterogeneity (Appendix K, FAO/WHO specifications manual).

Slide D-07 **Note that ...**

(i) **SE** = suspo-emulsion; **ZC** = mixed capsule suspension and aqueous suspension concentrate (CS + SC); **ZE** = mixed capsule suspension and suspo-emulsion (CS + SE); **ZW** = mixed capsule suspension and oil-in-water emulsion (CS + EW).

(ii) FAO/WHO specifications normally refer only to a single active ingredient. Where two or more active ingredients are co-formulated, the specification for each active ingredient is expected to apply. Manufacturers should therefore ensure that the limits provided in two or more proposed specifications are mutually compatible. In exceptional cases (for example, if the ratio of co-formulated active ingredients is critical for efficacy), an FAO or WHO specification may be developed for a co-formulated product.

The following clauses are included in FAO/WHO specifications for formulated products.

Slide D-08

Description clause
Physical appearance of product and chemical form of the active ingredient.
Provides a simple and rapid means to determine compliance.
Corresponding TC or TK specification is referenced.

Slide D-09

Active ingredient identity and content

Test methods similar to those for TC and TK, but extraction (and purification for identification) of active ingredient may be required.

May be necessary to identify the counter-ion, etc., if it is critical for product stability or performance.

Analytical test methods for determination of content validated by international collaborative study, to provide evidence of the reliability of the methods and the data provided.

Slide D-09 **Note that ...**

(i) Various international organizations (e.g. CIPAC, AOAC International) elaborate and publish validated test methods for pesticides.

(ii) An existing CIPAC method for an active ingredient in one formulation may be "extended" to another formulation, using a simpler form of validation. Requirements and procedures for extension of CIPAC methods can be found on the CIPAC web site at http://www.cipac.org.

(iii) One of the requirements for "extension" of an FAO/WHO specification to another manufacturer's *equivalent* product is confirmation that analytical and test methods referenced in the existing specification are suitable for use with the "new" product.

(iv) Where FAO/WHO specifications exist, national authorities are encouraged to adopt the test methods for active ingredient referenced in those specifications.

Slide D-10

Tolerances for active ingredient content

Declared content, g/kg or g/l	Tolerance
up to 25	± 15% for "homogeneous" products (e.g. EC, SC, SL)
	± 25% for "heterogeneous" products (e.g. GR, WG)
above 25 up to 100	± 10% g/kg or g/l
above 100 up to 250	± 6% g/kg or g/l
above 250 up to 500	± 5% g/kg or g/l
above 500	± 25 g/kg or g/l

Slide D-10 **Note that ...**

(i) Tolerances apply to the average measured value and are intended to take into account variations arising from manufacturing, sampling and analysis. However, sample sizes must be practical for analysis and meaningful in terms of product use. For example, variation in results due to sampling (statistical "sampling error") is minimized by maximizing sample size but excessively large samples increase analytical costs and could obscure variation significant to the user.

Slide D-11

Relevant impurities
Criteria as for TC and TK but insolubles (particulates) and acidity/alkalinity are treated as physical properties.
Limits usually based on active ingredient content but may be higher if concentrations can increase in storage or through reactions with formulants.
An impurity relevant in TC or TK may become non-relevant in formulations containing only low levels of active ingredient, e.g. if the impurity concentration is diluted to a level too low to measure.

Slide D-11 **Note that ...**

(i) Limits for relevant impurities are usually expressed on the basis of active ingredient content, because they are usually correlated with TC or TK content (which cannot be measured but is similar to the active ingredient content, in the case of TC).

(ii) Analytical methods for relevant impurities must be peer-validated for the formulation, to provide evidence that the methods and data are reliable.

(iii) Various international organizations (e.g. CIPAC, AOAC International) elaborate and publish peer-validated analytical methods for relevant impurities. However, a few peer-validated methods for relevant impurities are published on the FAO and WHO web sites.

(iv) Where FAO/WHO specifications exist for a product, national authorities are encouraged to adopt the analytical methods for relevant impurities referenced in those specifications.

(v) Relevant impurities will be considered in more detail in Learning Unit E.

Slide D-12

Physical properties
Specified properties are the minimum to distinguish good and bad products.
Clauses and limits may differ from FAO/WHO guidelines, if justified for a particular product.
Test methods for physical properties are simple models; they do not demonstrate field performance.
Results are method-dependent, so test methods must be performed exactly as described.
If the test method for a physical property has not been suitably validated and/or published, the specification cannot be developed.

Slide D-12 **Note that ...**

(i) The physical properties controlled by FAO/WHO specifications represent a basic minimum required to define product quality. If required, appropriate additional physical properties may be incorporated into national or manufacturer's programmes for the purposes of monitoring product quality.

(ii) Test methods for physical properties do not measure performance in the field, because this is dependent on local conditions and practices.

(iii) Alternative test methods are likely to require different limits for distinguishing between good and bad products, and their use should be avoided.

(iv) Most physical test methods for pesticide formulations are validated under the auspices of, and/or published by, CIPAC. A few are ASTM International, ISO or European Pharmacopoeia standards. A few are "convention" methods, which are published but validated primarily through long or widespread use. The use of "convention" methods may be necessary to measure unstable physical characteristics that are not amenable to normal validation procedures.

(v) Where an FAO/WHO specification exists for a formulation of an active ingredient, national authorities are encouraged to adopt the test methods for physical properties referenced in that specification.

Slide D-13

Low temperature storage stability
Storage test at 0 ºC required for liquid formulations, which may grow crystals, aggregate particles or develop separate phases. CS formulations may require freeze-thaw test to show that capsules are not weakened by freezing.

Slide D-14

High temperature storage stability
Test required for all formulations. Simulates two years' storage under "cool" conditions. Standard requirement is 54 ºC for 14 days. If 54 ºC is not appropriate for the product, alternative conditions are: 45 ºC for 6 weeks 40 ºC for 8 weeks 35 ºC for 12 weeks 30 ºC for 18 weeks.

Slide D-14 **Note that ...**

(i) Formulations are intended to be stored away from direct sunlight in cool, well-ventilated conditions.

(ii) The alternative temperature-time regimes correspond approximately to the same extent of ageing, based on the Arrhenius equation for chemical reaction rates.

Slide D-15

Post-storage tests required
Active ingredient content – usual minimum is ≥95% of pre-storage level.
Relevant impurities, if they could increase in storage.
Physical properties, if they could worsen with storage.

Slide D-15 **Note that ...**

(i) The usual requirement of ≥95% for storage stability of the active ingredient in formulations takes into account the normal range of analytical and sampling variation and thus essentially corresponds to an assessment of "no significant decline". In cases where a significant decline is unavoidable and a lower limit is justifiable, it should be supported with experimental data and the stored product must remain acceptable for use.

(ii) Most physical properties do not improve with ageing but, for example, persistent foam is not tested post-storage because surfactants are not expected to improve with storage and therefore persistent foaming is unlikely to increase.

An example of an FAO specification for a formulation follows.

Slide D-16

HAPPYFOS WATER DISPERSIBLE GRANULES

FAO Specification 999/WG (December 2007*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*999/2007*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation report (*999/2007*), as PART TWO, forms an integral part of this publication.*

1 **Description**

The material shall consist of a homogeneous mixture of technical happyfos, complying with the requirements of FAO specification 999/TC (December 2007), together with carriers and any other necessary formulants. It shall be in the form of granules for application after disintegration and dispersion in water. The product shall be dry, free-flowing and free from visible extraneous matter and hard lumps.

Slide D-16 **Note that ...**

(i) The "header note" (given in *italics*) is standard information, drawing attention to the evaluation and indicating that the specification applies only to products evaluated by FAO/WHO. The "header note" differs from that applied to TC or TK specifications, and two alternative forms of wording are used for formulation specifications. The general "header note", shown above, is used for most formulation specifications. The alternative "header note" is used for specifications such as those for slow-release CS and LN, explaining that it may not be appropriate for the products of any other formulator (even those using TC

or TK from evaluated sources), because active ingredient release and bioavailability are likely to be product-dependent.

(ii) FAO/WHO specifications for TC and TK should not be applied indiscriminately to manufacturers whose products have not been evaluated. With the exception of certain slow-release CS and LN, FAO/WHO specifications for formulations apply to the products of any formulator who uses active ingredient from a source to which the corresponding TC or TK specifications apply.

(iii) FAO specifications should not be applied to public health products, and WHO specifications should not be applied to agricultural products. Users should always adhere to recommendations given on the product label, even in cases where the FAO and WHO specifications are similar, because the product may be inappropriate for other uses.

Slide D-17

2 **Active ingredient**

2.1 **Identity tests** (999/WG/M/2, CIPAC X, p.196, 2003)The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Happyfos content** (999/WG/M/3, CIPAC X, p.196, 2003)
The happyfos content shall be declared (g/kg) and, when determined, the average measured content shall not differ from that declared by more than the following amounts.

Declared content, g/kg	tolerance
above 100 up to 250	± 6% g/kg
above 250 up to 500	± 5% g/kg

3 **Physical properties**

3.1 **pH range** (MT 75.3, CIPAC J, p. 131, 2000)
pH range: 5.0 to 7.0.

3.2 **Wettability** (MT 53.3, CIPAC F, p. 160, 1995)
The formulation shall be completed wetted in 5 seconds without swirling.

Slide D-17 **Note that ...**

(i) In FAO specifications, the active ingredient concentration ranges reflect agricultural products in the market. In WHO specifications, the active ingredient content is restricted to the concentrations evaluated by WHOPES.

Slide D-18

3.3 **Wet sieve test** (MT167, CIPAC F, p. 416, 1995)A maximum of 0.5 % w/w shall be retained on a 75 µm test sieve.

3.4 **Degree of dispersion** (MT 174, CIPAC F, p. 435, 1995)

The minimum dispersibility shall be 70% after 1 minute of stirring.

3.5 **Suspensibility** (MT 168, CIPAC F, p. 417, 1995)A minimum of 50% of the happyfos content found under 2.2 shall be in suspension after 30 minutes in CIPAC standard water D at 30 ± 2 °C.

3.6 **Persistent foam** (MT 47.2, CIPAC F, p. 152, 1995)

There shall be a maximum of 10 ml after 1 minute.

3.7 **Dustiness** (MT 171, CIPAC F, p. 425, 1995))

The formulation shall be essentially non-dusty.

3.8 **Flowability** (MT 172, CIPAC F, p. 430, 1995)

At least 98% of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve.

Slide D-19

4 **Storage stability**

4.1 **Stability at elevated temperature** (MT 46.3, CIPAC J, p.128, 2000)

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content shall not be lower than 95%, relative to the determined average content found under 2.2 before storage, and the material shall continue to comply with clauses for:

pH range (3.1),
wet sieve test (3.3),
degree of dispersion (3.4),
suspensibility (3.5),
dustiness (3.7),
flowability (3.8).

Note 1....

* *Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/ag/agp/agpp/pesticid/.*

LEARNING UNIT E

Relevant impurities

Slide E-01

Learning objectives
After completing this *Learning unit*, you should understand: The concept of relevant impurities How to distinguish between relevant and non-relevant impurities The principles of setting limits for relevant impurities Why it is necessary to check the validity of data used to determine the relevance of impurities

Slide E-02

Impurities
Impurities derived from the manufacturing process and/or product storage are present in all pesticide active ingredients. Impurities in formulants are not dealt with here, although the same general principles apply. Designation of TC or TK components as relevant impurities is generally simple and only potentially problematic in a few special cases where they may be considered to be physical properties.

Slide E-02 **Note that ...**

(i) Impurities in formulants are not considered in this course because the formulants incorporated into a product may vary in composition, over time and in different countries.

(ii) The collective term "impurities" is simple and convenient for most purposes but, in a few cases, it can be difficult to decide whether a component or characteristic should be designated as an impurity or something else. For example, are acidity, alkalinity or pH physical properties or do they represent impurities?

Slide E-03

Impurities
Cannot be eliminated but should be kept to a minimum. Manufacturing processes cannot be optimized for control of all impurities, so some will vary more than others, batch to batch. Tend to have physical and/or chemical characteristics similar to the active ingredient, but the hazards usually differ. May originate from starting materials or side-reactions occurring during active ingredient synthesis, or may be produced during manufacture or storage of formulations.

Slide E-04

Which impurities should be controlled?

Depends on the consequences of their presence.

Consequences depend on impurity hazards **relative to the active ingredient** and impurity concentration.

Impurity hazards may be toxic or non-toxic in effect (e.g. adverse effects on product stability, block sprayer nozzles, etc.).

For toxic hazards, impurity concentration is considered in terms of its contribution to the overall hazard of the active ingredient, not potential for exposure to the impurity, which is dependent on the application and conditions.

Slide E-05

A "grey area" between impurities and physical properties

Some physical characteristics also represent hazards.

The dividing line between hazards associated with physical properties and chemical impurities is not completely clear, so a few characteristics are designated by convention.

For example, if required for product quality:

- water is designated as a relevant impurity;
- acidity, alkalinity, pH are designated as physical properties;
- "insolubles" may be a relevant impurity in TC or TK but particulates become a physical property in formulations.

Slide E-05 **Note that ...**

(i) In some cases, the terms "insolubles" and "particulates" may refer to the same solid materials, originally present in TC or TK and carried through to the formulation. Such solids are important in formulations intended for spray application, because of their potential to block sprayer filters and nozzles.

(ii) In other cases, undesirable particulates in formulations, developing before or after dispersal in water and detected using a "wet sieve test", may derive from either the formulants or the active ingredient, rather than from particulate impurities in the TC or TK. For example, crystals of active ingredient can grow during product storage or on standing of the diluted product. It is generally easier and/or more meaningful to control such particulates in the formulated product, rather than in the corresponding TC or TK.

(iii) It may be difficult to measure the particulate content of certain oil-based formulations, such as EC (emulsifiable concentrate), UL (ultra-low-volume liquid) and OL (oil-miscible liquid). Therefore, solvents for incorporation into formulations intended for spray application should be filtered before use, to avoid introducing particulates into the product. Although particulates can be difficult to remove from a solid or viscous liquid TC or TK, it is usually easier to control them (as insolubles) at that stage than in oil-based formulations (as particulates).

Slide E-06

How is the relevance or non-relevance of an impurity determined?

A relevant impurity is one which, at its maximum concentration, increases or extends the hazards of the active ingredient; otherwise it is considered non-relevant.

Hazard contribution of the impurity **relative to the active ingredient** hazards is the key factor.

In this context:

- increased hazard = a quantitative increase in an effect of the active ingredient;
- extension of hazards = a qualitatively different effect to those of the active ingredient;
- the concentrations used to assess hazard contribution are the manufacturing limits for the impurity (i.e. the maximum permitted) and the active ingredient (i.e. the minimum permitted).

Slide E-06 **Note that ...**

(i) "Increasing" the hazards of the active ingredient means that one or more hazards of the active ingredient is quantitatively increased by the presence of the impurity. "Extending" the hazards of the active ingredient means that the impurity presents one or more hazards that are qualitatively different from those of the active ingredient.

(ii) For quality control purposes, "grey area" characteristics such as pH, acidity, alkalinity, insolubles and particulates should be assessed for relevance, irrespective of whether they are classified in specifications as relevant impurities or physical properties. As with other relevant impurities, these characteristics are capable of producing adverse effects in some cases and not in others, and therefore their relevance should be assessed in the context of the particular technical grade active ingredient and formulations.

(iii) However, other aspects of "grey area" characteristics such as pH, acidity and alkalinity should also be taken into consideration. For example, these characteristics have no utility for quality control purposes if the measured value is due to the active ingredient itself. On the other hand if, for example, the active ingredient is stable in the form of a salt but unstable as the free acid (or base), pH control may be necessary. Although in such cases the characteristic would provide control of what is effectively a stabilizer, rather than an impurity, the same general approach may be used to determine the need for a clause and the limit(s) to be adopted.

Slide E-07

Relevance depends on more than just impurity hazards
An impurity which occurs in two active ingredients may be relevant in one and non-relevant in the other, depending on the magnitude or type of hazards presented by the active ingredients. An impurity in a single active ingredient may be relevant in a formulation with high active ingredient content but not in another with low active ingredient concentration if, in the first case, the impurity concentration is too low for its hazards to be manifested. An impurity which could be present in principle, and which poses hazards that would otherwise qualify it as relevant, is not specified as relevant in any product (including TC or TK) in which it is known to be undetectable.

Slide E-07 **Note that ...**

(i) Relevance depends on the relative hazards presented by the active ingredient and impurity, taking into account their relative concentrations. If it occurs in both, an impurity which is relevant in a low-hazard active ingredient may be non-relevant in a high-hazard active ingredient.

(ii) If the concentration of an otherwise relevant impurity is too low for its hazards to be manifested, or too low for it to be measured by current analytical technology, it is considered non-relevant. However, in both cases, the specification incorporates a footnote alerting the user to the possibility that, in certain products, the impurity could occur at levels which would make it relevant. The following two examples illustrate these scenarios.

(a) FAO specifications for ethofumesate (2005) indicate in a footnote that "...there are no relevant impurities to be controlled in products of the manufacturer identified in evaluation report [but] ethyl methane sulfonate and/or *iso*-butyl methane sulfonate can occur as a result of certain manufacturing processes. If these impurities could occur at ≥0.1 mg/kg (relative to ethofumesate) in the products of other manufacturers, they would be designated as relevant impurities and clauses would be required to limit their concentration ...".

(b) The WHO specification for *d*-allethrin TC (2002) includes a clause to limit the relevant impurity chrysanthemic anhydride to 10 g/kg. However, the corresponding evaluation notes that, "... given the low level of active ingredient in...vaporizing mats and ... mosquito coil formulations and very low probability of substantial dermal contamination of users ... chrysanthemic anhydride should not be considered a relevant impurity in these formulations ..."

Slide E-08

Effects of concentration on hazards of active ingredient and impurities

If active ingredient content of TC is increased from 900 g/kg to 990 g/kg (a 0.1-fold increase), it represents no significant change in hazards due to active ingredient... and hazards could actually decrease if impurities contribute to them.

The increase in active ingredient content in a TC may not be carried through into formulations, as the formulation concentration is usually based on active ingredient content, not TC content.

But if active ingredient content of the TC is decreased from 990 g/kg to 900 g/kg, total impurities increase from 10 g/kg to 90 g/kg (increasing impurity hazard contributions an average of 9-fold).

The increase in impurity levels is carried through into formulations.

Slide E-09

Relative hazards of impurities and the active ingredient

In most cases, impurity concentrations are low, relative to active ingredient.

Therefore, in most cases an impurity must present one or more significantly greater hazards than the active ingredient, to influence the overall hazard profile of a TC or TK.

The lower the impurity concentration, the less likely that its potential impact will be manifested in practice.

Slide E-10

Default limits for relevant impurities

FAO/WHO JMPS principles for control of relevant impurities are similar to guidelines of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS); accessible at http://www.unece.org/trans/.

GHS guideline limit is 10 g/kg (of active ingredient) for all toxic hazards except carcinogens, reproductive toxins and class I mutagens, for which the limit is 1 g/kg (of active ingredient).

The JMPS uses these as default maximum limits, where a more refined approach is not possible.

Slide E-10 **Note that ...**

(i) There are some unavoidable technical differences between GHS and JMPS guidelines.

(ii) In GHS terminology, a "substance" (corresponding to TC, or a TK without diluent) is the starting point for hazard classification purposes and therefore limits are recommended for "substances". In contrast, an important function of FAO/WHO specifications is to restrict the hazards of a "substance" (TC or TK) to those of the active ingredient, by limiting the content of relevant impurities.

(iii) The specification limits of the GHS guidelines apply to both substances (alone) and "mixtures" of substances (corresponding to formulations or TKs with diluent). In contrast, FAO/WHO specifications for relevant impurities are normally based on the active ingredient content, to ensure that formulations are prepared from a good-quality TC or TK.

Slide E-11

Impurity data – concentration issues
Manufacturing limits required only for impurities which can be present at or above 1 g/kg, unless exceptionally hazardous. 1 g/kg cut-off point corresponds to GHS guideline for the most hazardous chemicals. The cut-off point avoids costs and technical difficulties of identifying and measuring insignificantly low levels of impurities, except where justified by the exceptional hazard presented by the impurity.

Slide E-11 **Note that ...**

(i) The 1 g/kg cut-off point is pragmatic, based on the following arguments.

(a) Detection, identification and measurement of impurities <1 g/kg can be difficult and very costly.

(b) Impurities occurring below 1 g/kg must be exceptionally hazardous if they contribute significantly to the overall hazard of the active ingredient. Although 1 g/kg is the maximum acceptable limit for well-known highly hazardous chemicals (such as dioxins, dibenzofurans, phenazines, terpyridines, some *N*-nitroso compounds and so on) and persistent organic pollutants (POPs), in practice lower limits are adopted for FAO/WHO specifications wherever practicable, as an additional precaution.

(c) In principle, there may be no lower limit to the levels at which impurities could be detected if unlimited resources could be devoted to the effort. However, there is no point in generating data on exceptionally low concentrations just because it becomes technically possible. Analytical costs and problems of sample handling and data interpretation all increase dramatically at very low concentrations so, unless such data are meaningful in terms of hazard or quality criteria, they have little or no value for quality control. Therefore, although FAO and WHO wish to encourage production of active ingredients with the highest purity practicable, the specified limit for a relevant impurity is usually based on manufacturing practicability – as long as this basis does not involve exceeding the maximum acceptable level for the hazard involved.

Slide E-12

Is the impurity relevant or non-relevant?
4-step procedure used to assess relevance. Steps applied to each hazard of each impurity in turn, though many cases will be simple and clear-cut, requiring no formal assessment. Before starting the 4-step procedure, check the validity of data on impurities.

Slide E-13

Data checks

Are any of the data required missing or questionable?

For each component of the TC or TK, has the analytical method been acceptably validated?

Where hazard characteristics of impurities are reported, are the data considered sufficiently robust and is it known if the hazard is additive to that of the active ingredient?

For any characteristic (identity, concentration, hazard), is there any reason to question the validity of the reported result?

Slide E-13 **Note that ...**

(i) As with all other data evaluated in support of pesticide specifications, impurity data generated by test methods of questionable validity, or impurity data which are themselves of questionable validity, must be considered cautiously in decision-making. Checking the validity of test methods and data is not a trivial part of evaluating the relevance of impurities but it is important to be aware of the soundness, or otherwise, of the data used as the basis for decisions. Checks on the validity of data are also considered in Learning Unit F.

(ii) The hazards posed by many impurities are essentially uncharacterized (though their contribution is included during tests for hazards of the technical grade active ingredient). However, the chemical structures associated with a wide range of hazards are now well-known and, where structural analogies are apparent, it may be possible to infer something about the hazards of a particular impurity. Where nothing can be inferred, it must be assumed that the impurity does not increase or extend the hazards of the active ingredient.

(iii) The potential need for control of a particular impurity should be taken into account in deciding whether or not additional information is required on its identity, quantity or hazards, or on the validity of the test methods used.

Slide E-14

Step 1: assess impurity hazards relative to active ingredient

(a) impurity presents the same type of hazard as the active ingredient but is more hazardous: → step 2

(b) impurity presents a different type of hazard to those the active ingredient: → step 2

(c) impurity chemical structure, or some other information, suggests a hazard in categories 1(a) or 1(b): → step 2

(d) impurity presents the same type of hazard as the active ingredient but is not more hazardous: → **non-relevant**

(e) impurity hazards not known and not considered to be in category (c): → **non-relevant**

Slide E-15

Step 2: assess impurity occurrence

(f) impurity occurs, frequently or infrequently, at quantifiable levels in the TC or TK: → step 3

(g) impurity occurs, frequently or infrequently, at quantifiable levels in the TC or TK, but only after storage: → step 3

(h) impurity occurs, frequently or infrequently, at quantifiable levels in formulations only, before or after storage: → step 3

(i) impurity does not occur at quantifiable levels in the TC, TK or formulations: → step 4

Slide E-16

Step 3: assess contribution to overall hazard

(j) calculated* worst-case-possible contribution to hazard exceeds the threshold for negligible contribution: → **relevant**

(k) worst-case-possible contribution to hazard cannot be calculated:* → **relevant**

(l) calculated* worst-case-possible contribution to hazard does not exceed threshold for negligible contribution: → **non-relevant**

* Calculated according to Appendix 1 of the *training manual*. Calculation is not possible if data required do not exist, if the hazard is not amenable to calculation of the contribution or if a negligible contribution threshold cannot be estimated.

Slide E-17

Step 4: assess hazard contribution of non-quantifiable impurities

(m) impurity occurs infrequently and is rendered non-quantifiable by blending TC or TK batches: → step 3
applying pre-blending limit in calculation

(n) impurity could occur in principle but in practice:
it has never occurred, or
it is unlikely to be formed in the process used, or
it has not occurred since changing the process, or
it could be derived from impurities in starting materials but not from those used by the manufacturer whose data are evaluated: **non-relevant**
(may be relevant in other manufacturers' products)

Slide E-18

Maximum acceptable limits for relevant impurities
GHS guidelines, 10 g/kg or 1 g/kg for exceptionally hazardous compounds.
More refined estimates are preferred, if Appendix 1 calculations are applicable.
Limits lower than the maximum acceptable should always be adopted where practicable, as a precaution.

Slide E-18 **Note that ...**

(i) Where active ingredient and impurity hazards are similar in nature and considered to be quantitatively additive, a more refined maximum acceptable limit for the impurity is based on a maximum of 10% increase in hazard relative to the active ingredient. Examples of the calculation are given in the Appendix to this *training manual*.

LEARNING UNIT F

Determination of equivalence

Slide F-01

Learning objectives

After completing this *Learning unit*, you should understand:

the principles and practice of equivalence determination.

Slide F-02

Determination of equivalence

The objective is to determine whether or not the product of another manufacturer (identified in this Learning Unit and the exercises as "M2") is **not worse** than the product (produced by the manufacturer identified as "M1") on which the "reference" specification is based.

Note that the M2 product could be better than the M1 product but this is difficult to prove, so it is only practicable to show that it is not worse.

Equivalence is a simple concept but determination is complex and requires a team of experts in various scientific disciplines.

Slide F-02 **Note that ...**

(i) A general overview will be given first, allowing some of the complexity to be seen in context, before giving examples.

Slide F-03

Data requirements for equivalence determination

Access to manufacturing process information and purity/impurity and hazard data from M1 and M2.

The more data available for comparison, the greater confidence in equivalence decisions.

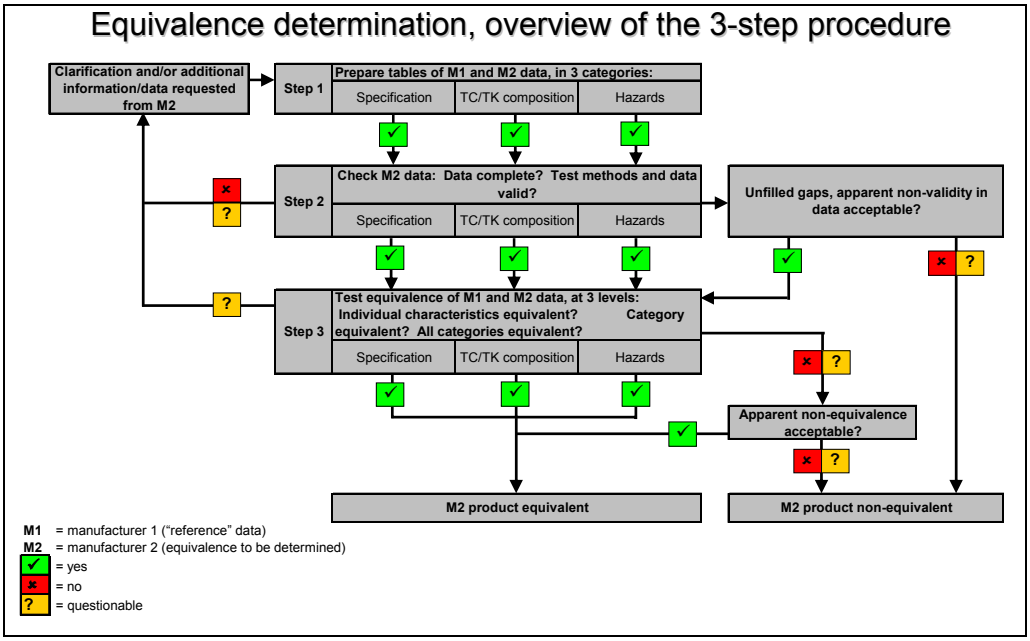
Data are compared in a simple 3-step procedure – the complexity arises from gaps and inconsistencies which inevitably occur in the two sets of data.

Slide F-03 **Note that ...**

(i) Although information on the manufacturing process is not used directly in the determination of equivalence, it provides the basis for understanding and assessing impurity profiles. Somewhat similarly, data on physico-chemical characteristics of the pure active ingredient are not used directly to determine equivalence but they form supporting information.

(ii) Documentation of the basis for decisions is essential, because the determination of equivalence nearly always involves making one or more decisions based on data that are incomplete or problematic in some way.

Slide F-04



Slide F-04 **Note that ...**

(i) The reference data ("reference profiles") for a particular active ingredient generally relate to the technical grade product supported by the most complete sets of toxicological and ecotoxicological data available (see Appendix C, *Manual on development and use of FAO and WHO specifications for pesticides*, 2006).

(ii) Other manufacturers' data are compared with the reference profiles. If the equivalence of several different sources of active ingredient is to be determined, each is compared separately against the reference profiles.

(iii) By assembling the data into a table (step 1), missing or questionable data can be identified quickly and efforts can be focused on important problem areas which may arise in step 2.

(iv) Data will not be shown in the wide variety of forms in which they may be available prior to step 1. Although data submission templates are provided by FAO/WHO for manufacturers, the data may have to be extracted from relatively diffuse documentary sources.

(v) Validity of test methods and data supporting the reference specification (M1) should have been established before designating a set of data as the reference profiles. Therefore, in the determination of equivalence it is normally only necessary to check the validity of the M2 methods and data.

(vi) It is possible that some problems in understanding M2 data may be resolved by seeking further expert advice, in addition, or as an alternative, to requesting more information from the manufacturer.

(vii) ✘ and ? assessments appear on the right-hand side of the diagram at steps 2 and 3 because, if appropriate information and data cannot be obtained from the manufacturer, a decision on equivalence must still be made. If the team of experts evaluating the data considers that the data gaps and/or apparent non-equivalences leading to ✘ or ? assessments do not reflect, or obscure, some

evidence that the M2 product is worse than the M1 product, the products may be considered equivalent.

(viii) The TC or TK composition data used for equivalence determination are the manufacturing limits, not the 5-batch data. Note that, apart from exceptionally hazardous (relevant) impurities, data on impurities with manufacturing limits <1 g/kg are not considered in the determination of equivalence.

Slide F-05

Step 1, tabulate data

Characteristic of the TC or TK	Manufacturer 1 (reference)	Manufacturer 2
Active ingredient content		
active ingredient, min. g/kg	930	950
Impurity content		
impurity 1, max. g/kg (relevant)	1	2
impurity 2	10	5
impurity 3	1	5
etc...	...	...
Other specified characteristics		
pH range	4–7	5-6
etc...	...	...
Hazard data		
acute oral LD_{50}, mg/kg bw	500	650
acute dermal LD_{50}, mg/kg bw	>2000	>3000
etc...	...	...

Slide F-05 **Note that ...**

(i) Tabulating data in this way provides a simple overall picture in which data gaps and questionable data are easily seen and which helps to focus attention on problematic equivalence issues.

(ii) The TC or TK composition category should include all impurities reported by both manufacturers. The hazard category should include acute toxicity data (oral, dermal, inhalation, skin and eye irritation, skin sensitization), as a minimum. Any other hazard data provided by both manufacturers, if produced by comparable testing procedures, should also be included for assessment of equivalence.

(iii) Units of measurement should be entered, because they may differ between manufacturers. For example, concentrations may be expressed as g/kg and mg/kg, or as mg/l and mg/m^3, which could lead to confusion if the units are not included. Values must be converted to common units for comparison of the data, but inclusion of both reported and converted data in the table makes it easier to spot conversion errors.

Slide F-06

Step 2, data checks
Are any data missing from each category?
For each component of the TC or TK, had the analytical method been acceptably validated?
For each hazard characteristic, were the tests conducted to a widely accepted guideline?
For any characteristic (composition, hazard, physical property), is there any other reason to question the validity of the reported result?

Slide F-06 **Note that ...**

(i) Step 2 will be addressed in more detail later in this Learning unit.

Slide F-07

Step 3, equivalence tests of each characteristic
Specification: does M2 product comply with clauses and limits of the existing specification (based on M1)?
TC or TK composition: is the manufacturing limit for any **non-relevant** impurity in M2 >3 g/kg or >50% higher (whichever is the greater) than the corresponding M1 limit?
Toxicity: is M2 apparently >2x (or the factor from dosage intervals if >2) as hazardous as M1? Or, in the case of qualitative assessments, is M2 "worse" than M1?
Ecotoxicity: is M2 apparently >5x (or the factor from dosage intervals if >2) as hazardous as M1? Or, in the case of qualitative assessments, is M2 "worse" than M1?

Slide F-07 **Note that ...**

(i) Non-toxic hazards are usually addressed within the "Other specified characteristics" category.

(ii) The 2x and 5x factors reflect the inherent variability of results observed in biological experiments.

(iii) The 1 g/kg cut-off limit for impurities can produce anomalies in the determination of equivalence. For example, if an impurity has a manufacturing limit of 0.1 g/kg in the M1 profile and 3 g/kg in the M2 profile, the products are considered equivalent by that criterion. However, if the same impurity is not reported in the M1 profile because it always occurs at some value below 1 g/kg, it would be regarded as a new impurity in the M2 profile if its limit is ≥1 g/kg.

(iv) Step 3 will be addressed in more detail later in this Learning unit.

(v) In special cases, it may be possible (or necessary) to incorporate a test for equivalence of efficacy, such as that performed by WHO for some public health pesticide products.

The **following five slides** show the three-step procedure applied to a fictional example.

Slide F-08

Step 1, tabulate data

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950		
impurity 1 (relevant)	0.001	–		
impurity 2 (relevant)	1	–		
impurity 3	32	ND		
impurity 4	10	16		
impurity 5	12	24		
impurity 6	9	ND		
impurity 7	11	9		
impurity 8	2	ND		
impurity 9	1	ND		
impurity 10	3	ND		
impurity 11	4	ND		
impurity 12	2	1		
impurity 13	–	6		

M1 = manufacturer 1
M2 = manufacturer 2
ND = not detected
– = no data

Slide F-08 **Note that ...**

(i) For simplicity of presentation, equivalence determination is shown here only for TC composition (purity/impurity profiles). In real-life cases and the exercises, tests of equivalence of hazard data and various other specified characteristics are also essential steps in the overall procedure, as shown in the earlier slides.

(ii) In this hypothetical example, imagine that the synthesis pathways used by the two manufacturers (M1 and M2) are broadly similar but that the processes differ in many details.

(iii) M1 data should have been checked for completeness and validity already. It is only necessary to recheck M1 data if the M2 data raise questions which were not considered during the original evaluation of M1 data. This would be an unusual occurrence and highlights the need for good documentation of decisions.

(iv) Maintenance of confidentiality is critical in all cases of equivalence determination and thus great care is required in all communications with either M2 or M1, when trying to resolve problems arising during step 2 (the data check).

Slide F-09

Step 2, check data

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	
impurity 1 (relevant)	0.001	–	?	
impurity 2 (relevant)	1	–	?	
impurity 3	32	ND	?	
impurity 4	10	15	✓	
impurity 5	12	24	✓	
impurity 6	9	ND	?	
impurity 7	11	9	✓	
impurity 8	2	ND	?	
impurity 9	1	ND	?	
impurity 10	3	ND	?	
impurity 11	4	ND	?	
impurity 12	2	3	✓	
impurity 13	–	6	✓	

✓ = checked validated method, data OK, impurity 13 consistent with process used
? = unsure how to interpret the data

Slide F-09 **Note that ...**

(i) Before asking M2 about relevant impurities 1 and 2, it is essential to check that they are likely to occur in the process used by M2. If not, their occurrence should not be revealed to M2 because the information is confidential to M1 – unless the specification based on M1 has already been published. However, assuming that they could occur in the M2 process, it is legitimate and essential to ask M2 for manufacturing limits for the two relevant impurities.

(ii) It is impossible to know what is meant by "not detected" (i.e. it could mean <10 g/kg, <0.01 g/kg or almost anything else). For this reason, M2 should be asked to provide limits of quantification (LOQ) for the impurities which were "not detected". We will assume that the method has been validated acceptably for these impurities.

(iii) As with all other data evaluated in support of pesticide specifications, data generated by test methods of questionable validity, or data which are themselves of questionable validity, must be considered cautiously in decision-making. Checking the validity of test methods and data is not a trivial part of equivalence determination, but it is important to be aware of the soundness, or otherwise, of the data used as the basis for decisions.

The **following slide** incorporates the responses from M2, who also provided evidence of acceptable validation of the methods used for the relevant impurities.

Slide F-10

Step 2, check data - with additional information from M2

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	
impurity 1 (relevant)	0.001	0.002	✓	
impurity 2 (relevant)	1	<1	✓	
impurity 3	32	<1	✓	
impurity 4	10	15	✓	
impurity 5	12	24	✓	
impurity 6	9	<1	✓	
impurity 7	11	9	✓	
impurity 8	2	<1	✓	
impurity 9	1	<1	✓	
impurity 10	3	<1	✓	
impurity 11	4	<1	✓	
impurity 12	2	3	✓	
impurity 13	–	6	✓	

data in red = new data from M2
✓ = yes (i.e. checked validated method, data OK)

The **following slide** begins the determination of equivalence.

Slide F-11

Step 3, equivalence tests

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	✓
impurity 1 (relevant)	0.001	0.002	✓	✗
impurity 2 (relevant)	1	<1	✓	✓
impurity 3	32	<1	✓	✓
impurity 4	10	15	✓	✓
impurity 5	12	24	✓	✗
impurity 6	9	<1	✓	✓
impurity 7	11	9	✓	✓
impurity 8	2	<1	✓	✓
impurity 9	1	<0.1	✓	✓
impurity 10	3	<1	✓	✓
impurity 11	4	<1	✓	✓
impurity 12	2	3	✓	✓
impurity 13	–	6	✓	✗

data in red = new data from M2
✓ = yes (i.e. checked validated method, data OK, or equivalent by this criterion)
✗ = no (i.e. non-equivalent by this criterion)

Slide F-11 **Note that ...**

(i) Where M2 limits for impurities are <3 g/kg or <50% higher (whichever is the greater) than those of M1, the values are considered equivalent.

(ii) The focus now shifts to impurities 1, 5 and 13, which indicate non-equivalence.

(iii) The evaluation team should check with M2 (and the scientific literature if necessary) for any evidence that impurities 5 and 13 could increase or extend the hazards of the active ingredient (i.e. that they may be relevant impurities, see Learning Unit E). In the **following slide**, it is assumed that they could not.

Slide F-12

Step 3, equivalence tests

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	✓
impurity 1 (relevant)	0.001	0.002	✓	✗
impurity 2 (relevant)	1	<1	✓	✓
impurity 3	32	<1	✓	✓
impurity 4	10	15	✓	✓
impurity 5	12	24	✓	✗.→.✓
impurity 6	9	<1	✓	✓
impurity 7	11	9	✓	✓
impurity 8	2	<1	✓	✓
impurity 9	1	<0.1	✓	✓
impurity 10	3	<1	✓	✓
impurity 11	4	<1	✓	✓
impurity 12	2	3	✓	✓
impurity 13	–	6	✓	✗.→.✓

✓ = yes (i.e. checked validated method, data OK, or equivalent by this criterion)
✗.→.✓ = not strictly equivalent but considered acceptable because no tangible change in hazards is implied

Slide F-12 **Note that ...**

(i) This leaves only relevant impurity 1 to consider, for which there are several possible consequential scenarios, such as the following.

Scenario A M2 could actually comply with a limit of 0.001 g/kg for impurity 1. This would change the assessment for this impurity, and overall conclusion, to ✓.

Scenario B M2 cannot comply with a limit of 0.001 g/kg for impurity 1 but, because 0.002 g/kg is well below the maximum acceptable (see Learning Unit E), the specification limit may be raised to 0.002 g/kg. The assessment therefore changes: ✗.→.✓, i.e. not strictly equivalent but considered acceptable because the increased limit implies no tangible change in hazards.

Scenario C M2 cannot comply with a limit of 0.001 g/kg for impurity 1 and 0.001 g/kg is the maximum acceptable for this impurity (see Learning Unit E). The assessment for the impurity and overall becomes ✗, because the M2 product is neither equivalent to that of M1 nor is it acceptable to develop a separate specification for it.

(ii) The reference profiles are not changed by a determination of equivalence and so, for any particular active ingredient, successive determinations of equivalence involve comparisons with the same reference data.

The previous slides and discussions related to TC and TK only. Before concluding this part of the overview, it is therefore appropriate to consider the equivalence of formulations.

Slide F-13

Equivalence of formulations
If the source of TC or TK incorporated into the formulation has been assessed as equivalent, and ...
If the formulated product complies with the existing specification for that formulation ...
The formulation is considered to be equivalent.
But, this test of equivalence may not be sufficient for certain products, e.g. certain slow-release LN and CS, in which the release profile is critical for efficacy.
In all cases, "equivalent" means only that basic quality characteristics are shared. It does not mean that products are equally suitable for an application or provide equal efficacy.

Slide F-13 **Note that ...**

(i) For extension of WHO specifications, demonstration of acceptable efficacy is currently an essential prerequisite for the determination of equivalence of slow- or controlled-release products, such as LN and CS. This is because, at present, the relationship between efficacy and physico-chemical measurement of release characteristics remains unclear.

The remaining six slides address the completeness and validity of data tabulated for the determination of equivalence.

Slide F-14

Incomplete or questionable data?
Gaps and limitations can occur, even in the best reference profiles.
For the particular case under review, ask the question: do the gaps and limitations prevent determination of equivalence?
Remember that new data may be costly in terms of money, time and/or animal welfare, so requests for new data must be justifiable.
"Missing" data sometimes already exist, so ask the manufacturer.
Check the study reports if data are questionable.

Slide F-14 **Note that ...**

(i) Shortcomings in the data are a challenge to rational decision-making but should not preclude decisions, if they can be justified by the evidence available. Where the consensus of opinion of the evaluation team is that the data are appropriate and sufficiently clear and robust, a decision should be made. It is impossible to give guidance on how to deal with every possible scenario, but the evaluation team must record the basis for conclusions.

Slide F-15

Validity of test methods

Specification should already be supported by suitably validated analytical and physical test methods but are the methods suitable for use with M2 products? Were they used to generate the M2 data?

Have the analytical methods for non-relevant impurities been appropriately validated by M2? Are they considered appropriate by analysts in the evaluation team?

Hazard tests should be conducted according to widely accepted and published protocols. If not, are the tests considered appropriate by toxicologists and/or ecotoxicologists in the evaluation team?

Slide F-16

Validity of analytical data

How were "unknowns" quantified in batch analyses?

"Unknowns" data from GC-FID or TIC from GC-EIMS are fairly reliable.

"Unknowns" data from HPLC-UV, LC-MS and LC-MS/MS tend to be unreliable.

Distinguish between "unknowns" and the unaccountable fraction.

Slide F-16 **Note that...**

(i) "Unknowns" are unidentified components, not fully characterized and difficult to quantify with certainty. Components such as "ash", which are also not fully characterized, are quantifiable with reasonable certainty. "Unknowns" should not be confused with the "unaccountable fraction", which is simply an arithmetic value.

(ii) GC-FID = gas chromatography with a flame-ionization detector; TIC = total ion (current) chromatogram; GC-EI/MS = coupled gas chromatography-mass spectrometry with electron (impact) ionization; HPLC-UV = high-performance liquid chromatography with detection by ultraviolet light absorption; LC-MS = coupled (high-performance) liquid chromatography-mass spectrometry; LC-MS/MS = coupled (high-performance) liquid chromatography-tandem mass spectrometry.

(iii) The "unaccountable fraction" is the difference between 1000 g/kg and the "mass balance" (also known as the material accountability and representing the sum of all measured components), when the mass balance is less than 1000 g/kg. Values reported as "... less than ..." must not be included in the mass balance.

Slide F-17

Validity of analytical data

Are mass balance data acceptable?

A few sums slightly >1000 g/kg can arise from analytical uncertainty but, if all values exceed 1000 g/kg, or any values greatly exceed it, the analytical method(s) may provide poor accuracy.

Mass balances <980 g/kg generally should be investigated, to ensure that significant components were not undetected.

A sum of the manufacturing limits is meaningless and should not be calculated.

Slide F-18

Validity of analytical data

What do reports of "not detected" or "not measurable" mean?

These should be expressed as "<x g/kg".

Data on "ash", "particulates", inorganics, volatiles, etc., may be included in mass balance.

But it is important to avoid double-counting, so particular care is required with data for acidity/alkalinity, for example.

Slide F-18 **Note that ...**

(i) Values for "acidity/alkalinity" should be considered very carefully, as they may be expressed as "H_2SO_4" or "NaOH", which does not necessarily mean that these compounds are present. The acidity/alkalinity may be due to identified acidic or basic components already accounted for in the mass balance.

Slide F-19

Validity of hazard data

Qualitative assessments can vary according to the protocol used.

In all cases where the data or assessments appear questionable, they should be checked in the study reports.

Data reported as identical to those in published literature should be checked in study reports, especially if the study details and/or several hazard characteristics appear to be identical to published data.

Finally, **note that** assessment of whether or not an equivalent (or non-equivalent) product is acceptable for the proposed application(s) is beyond the scope of this training course.

LEARNING UNIT G

Team exercises, introduction

Slide G-01

Learning objectives
After completing this *Learning unit*, you should: have some practical experience in assessment of relevant impurities and in the determination of equivalence; understand the importance of teamwork in these tasks.

Slide G-02

Team exercises
Participants will be grouped into teams. Teams will work in parallel on the exercises. Teams should ask facilitators for help them with problems they cannot resolve. At the end of the period allocated for work on each exercise, teams will present their overall conclusions in a plenary discussion session.

Slide G-02 **Note that ...**

(i) Each team should appoint a moderator, to co-ordinate discussions and present the team's conclusions in plenary sessions, and a rapporteur, to record team decisions and conclusions. Teams may appoint a different moderator and rapporteur for each exercise.

Lists of the participants allocated to each team will be distributed by the facilitator or local organizer.

Slide G-03

Time available for exercises
Exercise 1, **relevant impurities**, ¼ hour introduction, 1½ hours teamwork, 1 hour presentations and discussion Exercise 2, **equivalence**, ¼ hour introduction, 1 hour teamwork, 1¼ hours presentations and discussion Exercise 3, **equivalence**, ¼ hour introduction, 1½ hours teamwork, 1½ hours presentations and discussion Exercise 4, **equivalence**, 1¼ hours teamwork, 1 hour presentations and discussion

Slide G-04

Exercises
Exercise data are fictional but present typical problems in assessment of impurity relevance or product equivalence. To simplify these exercises, it is assumed that some (or all) test methods and data have already been checked as valid. If a gap in the information provided prevents your team from making a decision, **question the facilitators** to help to resolve it. Provide a brief explanation of each decision, so that you can show how and why the team reached its conclusions.

Slide G-05

Exercises
A blank *Relevant impurities evaluation table* or *Equivalence evaluation table* will be distributed at the start of each exercise, to help you assemble the data quickly and to simplify decision-making by the evaluation team. After teams have presented their evaluations at the end of each exercise, a corresponding completed *Evaluation table* will be distributed for general discussion. All of these tables may be inserted into the *Participant's guide*, to assemble a complete reference volume. The blank *Evaluation table*s could be adapted for use in your work, to help with decision-making and record-keeping.

Slides G-04 and G-05 **Note that ...**

(i) Before starting each exercise, it will be described briefly and the corresponding data and blank *Evaluation table*s will be distributed.

(ii) The exercises have logical conclusions but, as in real-life, the conclusion may depend upon the information available and the opinions of the evaluation team. Any gaps or problems remaining unresolved, preventing the team from reaching what its members collectively consider to be a sound conclusion, should be recorded by the team and identified during the plenary discussion session.

(iii) Ask facilitators for help with information gaps and problems in these exercises. This simulates normal working practice, where additional information is likely to be required from the manufacturer or other sources in some cases (such as published literature or independent experts). Remember the essential need to protect commercial confidentiality. Maintenance of commercial confidentiality may be simulated in the exercises if team members do not reveal, to other teams, their own team's additional information, conclusions and rationales until presented in the subsequent plenary discussion session.

LEARNING UNIT G, EXERCISE 1

Zappacarb relevant impurities

Slide G-06

Exercise 1, background

Zappacarb is a carbamate insecticide.

Manufacturing limits for purity/impurities have been provided for zappacarb TC.

Hazard data have been provided for zappacarb TC and two impurities.

Some information is provided on zappacarb formulations and storage stability.

To simplify the exercise, all test methods and data have already been checked as valid (✅) in the blank *Relevant impurities evaluation table* provided.

Note that ...

(i) You are not asked to evaluate the validity of test methods and data, although this is an essential first step in real-life cases, because the exercise would become too complex.

Slide G-07

Exercise 1, workplan

Using the blank *Relevant impurities evaluation table* provided, designate impurities as relevant or non-relevant.

If you cannot resolve a problem, question the facilitator (in lieu of the manufacturer and other sources of information) to elicit the information you need.

Explain your decisions in the table provided. If you designate an impurity as relevant, what limit do you suggest and why?

Refer to the Appendix of the *Participant's guide*, if required.

If you have time, also consider relevant impurities in formulations.

LEARNING UNIT G, EXERCISE 1 (i)

Data on Zappacarb and its impurities (from manufacturer except where indicated)

Characteristic	Value
Physico-chemical characteristics of the pure active ingredient	
zappacarb molecular weight	257
water solubility at 25 ºC	95 mg/l
hydrolysis, half-life at 25 ºC	pH 4 >60 days; pH 7 = 34 days; pH 9 = 1.2 days
dissociation characteristics	no acidic or basic characteristics in the range pH 1-13
Active ingredient content of TC, minimum	
zappacarb	940 g/kg
Impurity content of TC, maximum	
impurity A	5 g/kg
impurity B	2 g/kg
impurity C	30 g/kg
impurity D	7 g/kg
impurity E	2 g/kg
alkalinity, as NaOH	1 g/kg
water	<1 g/kg
acetone insolubles	5 g/kg
Formulation characteristics	
formulation types	WG, GR, 100–250 g/kg range
stability of zappacarb in formulations at 54 ºC for 14 days	minimum 95%
impurity A in formulations at 54 ºC for 14 days	maximum 0.5% of initial zappacarb content
impurity B in formulations at 54 ºC for 14 days	maximum 0.2% of initial zappacarb content
impurity C in formulations at 54 ºC for 14 days	maximum 5% of initial zappacarb content
Toxicology of TC	
rat acute oral LD_{50}	90 mg/kg bw
rat acute dermal LD_{50}	600 mg/kg bw
rabbit acute inhalation LC_{50}	>0.1 g/l
rabbit skin irritation	slight irritant
rabbit eye irritation	irritant
guinea-pig skin sensitization	non-sensitizer
Toxicology of impurities	
impurity A, rat acute oral LD_{50}	12 mg/kg bw (from published literature)
impurity B, rat acute oral LD_{50}	80 mg/kg bw (from published literature)

LEARNING UNIT G, EXERCISE 1 (ii)

Relevant impurities evaluation table Evaluation team: ..... Date: ..... Document No: .....

Zappacarb (manufacturing data from .....)

Component	Manufacturing limit, g/kg	Hazard information considered (indicate source)	Methods and test data valid?	Relevant?	Maximum acceptable limit	Proposed limits		Rationale
						pre-storage test, g/kg of TC or TK	post-storage test, % of a.i.	
zappacarb			☑					
impurity A			☑					
impurity B			☑					
impurity C			☑					
impurity D			☑					
impurity E			☑					
water			☑					

Relevant impurities evaluation table Evaluation team: ..... Date: ..... Document No: .....

Zappacarb (manufacturing data from .....)

Component	Manufacturing limit, g/kg	Hazard information considered (indicate source)	Methods and test data valid?	Relevant?	Maximum acceptable limit	Proposed limits		Rationale
						pre-storage test, g/kg of TC or TK	post-storage test, % of a.i.	
acetone insolubles			☑					
Other characteristics, not strictly impurities but amenable to similar assessment (e.g. alkalinity, pH). Entries for limits to include units, if different from column heading								
alkalinity, as NaOH			☑					

Notes.

Column 4: ☑ assessments are provided to simplify the exercise. In real-life cases, the evaluation team makes these assessments.

Column 5: enter **yes**, no, or ? (questionable or uncertain).

LEARNING UNIT G, EXERCISE 1 (iii)

Relevant impurities evaluation table Evaluation team: ..... Date: ..... Document No: .....

Zappacarb (manufacturing data from .....)

Component	Manufacturing limit, g/kg	Hazard information considered (indicate source)	Methods and test data valid?	Relevant?	Maximum acceptable limit	Proposed limits		Rationale
						pre-storage test, g/kg of TC or TK	post-storage test, % of a.i.	
zappacarb	940 g/kg	rat acute oral LD_{50} = 90 mg/kg bw (ex manufacturer)	☑			940 g/kg	95%	
impurity A	5 g/kg (5 g/kg post-storage)	rat acute oral LD_{50} = 12 mg/kg bw (ex literature) active ingredient content of WG and GR formulations: 100–250 g/kg	☑	**yes**	12.5 g/kg	**5 g/kg**	–	Supplementary information (i) The structure of impurity A suggests that its mode of action is similar to that of the active ingredient and their effects can be considered additive. This information provided to team: At a theoretical maximum impurity A content of 60 g/kg (1000–940), active ingredient hazard is increased by 48% (more than 10% increase) Impurity A relative hazard = 90/12 = 7.5 Maximum theoretical increase in hazard = ((94 x 1)+((100–94) x 7.5)/94 = 1.48 (48%, relevant) Maximum acceptable limit for impurity A = ((1.1 x 94 x 1)–(94 x 1))/7.5 = 1.25% (12.5 g/kg) Limit: (i) 5 g/kg limit is below 12.5 g/kg, the concentration required for 10% increase in hazard; (ii) impurity A does not increase in storage, so a 5 g/kg limit is both acceptable and appropriate. No increase in storage, so no post-storage limit required Supplementary information (i) Analytical LOQ = 0.1 g/kg product in 100-250 g/kg formulations. This information provided to team: A corresponding limit of 0.5% of the zappacarb content is therefore practicable for formulations

Relevant impurities evaluation table Evaluation team: ..... Date: ..... Document No: .....

Zappacarb (manufacturing data from .....)

Component	Manufacturing limit, g/kg	Hazard information considered (indicate source)	Methods and test data valid?	Relevant?	Maximum acceptable limit	Proposed limits		Rationale
						pre-storage test, g/kg of TC or TK	post-storage test, % of a.i.	
impurity B	2 g/kg (2 g/kg post-storage)	rat acute oral LD_{50} = 80 mg/kg bw (ex literature)	☑	no	–	–	–	Supplementary information (i) The structure of impurity B suggests that its mode of action is similar to that of the active ingredient and their effects can be considered additive. This information provided to team: At a theoretical maximum impurity B content of 60 g/kg (1000 minus 940), active ingredient hazard increased by 7% (less than 10% increase) so, even in the worst case imaginable, the hazard contribution is negligible. Impurity B relative hazard = 90/80 = 1.125 Maximum theoretical increase in hazard = ((94 x 1)+((100-94) x 1.125)/94 = 1.07 (7%, not relevant)
impurity C	30 g/kg (47 g/kg post-storage)	no information	☑	no	–	–	–	Not known to pose increased or additional hazards, so potential increase in storage does not change the assessment
impurity D	7 g/kg	no information	☑	no	–	–	–	Not known to pose increased or additional hazards
impurity E	2 g/kg	no information	☑	no	–	–	–	Not known to pose increased or additional hazards
water	<1 g/kg	hydrolysis, half-life at 25 ºC = pH 4 >60 days pH 7 = 34 days pH 9 = 1.2 days (ex manufacturer)	☑	no	–	–	–	Not measurable in practice (note: if ≥1 g/kg, water might be relevant due to potential for alkaline hydrolysis but probably not in zappacarb if alkali is controlled)

Relevant impurities evaluation table Evaluation team: ..... Date: ..... Document No: .....

Zappacarb (manufacturing data from .....)

Component	Manufacturing limit, g/kg	Hazard information considered (indicate source)	Methods and test data valid?	Relevant?	Maximum acceptable limit	Proposed limits		Rationale
						pre-storage test, g/kg of TC or TK	post-storage test, % of a.i.	
acetone insolubles	5 g/kg	formulations: WG, GR	☑	no	–	–	–	Insoluble/particulate material is unlikely to pose problems in production or use of WG or GR (note: could be relevant in TC used to prepare UL, SL, EC, etc.)
Other characteristics, not strictly impurities but amenable to similar assessment (e.g. alkalinity, pH). Entries for limits to include units, if different from column heading								
alkalinity, as NaOH	1 g/kg	hydrolysis, half-life at 25 ºC = pH 4 >60 days pH 7 = 34 days pH 9 = 1.2 days (ex manufacturer)	☑	**yes**	?	**1 g/kg**	–	Classified as a physical property in FAO/WHO specifications because it is not a chemical or physical entity that can be isolated as such. Nonetheless, in effect it is a relevant impurity. Alkaline hydrolysis is rapid and, although the water content is minimal (<1 g/kg), water is capable of degrading about 14 times its own weight of zappacarb in the presence of alkali. A 1 g/kg limit is probably appropriate unless the manufacturer has data to show that higher levels can be tolerated without significant degradation of zappacarb. In formulations, control of pH range may be simpler and more sensitive than measurement of alkalinity, if control is necessary in such products. Cannot increase in storage, so no post-storage limit required.

Notes.

Column 4: ☑ assessments are provided to simplify the exercise. In real-life cases, the evaluation team makes these assessments.

Column 5: enter **yes**, no, or ? (questionable or uncertain).

LEARNING UNIT G, EXERCISE 1 (iv)

Plenary presentations and discussion.

Note that ...

(i) The toxic hazard contribution of an impurity can only be estimated where comparable data exist for both the active ingredient and the impurity, and where it is known (or can be assumed) how to calculate the cumulative hazard (by addition in the impurity A and B examples given).

(ii) The theoretical maximum of 60 g/kg for impurity concentration in this case is derived from 1000 minus 940 g/kg, which is the minimum content of active ingredient subtracted from the whole TC. Assuming compliance with the minimum for active ingredient content and considering each impurity separately, its concentration cannot possibly exceed the consequential maximum for total impurities (60 g/kg). Of course, it is highly unlikely that only a single impurity will be present in a TC but there is no other rational basis for estimating its maximum theoretical concentration. If the impurity is assessed as non-relevant at its maximum theoretical concentration, a separate specification clause and limit are unnecessary because its concentration will be controlled by means of the clause and limit for active ingredient content.

(iii) The theoretical worst-case hazard contributions of impurities A and B cannot be summed to assess the impact of both, because it would be impossible for both to occur at 60 g/kg in a TC containing 940 g/kg zappacarb. Any theoretical estimate which takes into account both impurities leads to a calculated hazard contribution lower than that from impurity A alone, because A is more hazardous than B. Nonetheless, in cases where specification limits are developed for two or more impurities which increase the same hazard as the active ingredient, their total estimated maximum contribution (derived from the *proposed limit for each impurity*) should not increase the active ingredient hazard by >10%.

(iv) Impurities presenting different toxic hazards from those of the active ingredient should be considered case by case. Such impurities qualify as relevant if they occur in the TC or TK at ≥1 g/kg, or if they occur at quantifiable lower levels if they can be considered exceptionally hazardous. GHS guideline limits should be used as the maximum acceptable limit in all cases where a more refined assessment cannot be made.

(v) Impurities (or physical properties such as alkalinity) presenting non-toxic hazards should also be considered case by case. Worst-case hydrolysis hazards due to the presence of water may be calculated in simple cases, where the corresponding maximum theoretical loss of active ingredient may be calculated. In other cases, conservative limits may have to be adopted if the levels at which problems definitely occur are unknown. GHS guideline limits are not appropriate for non-toxic hazards.

(vi) Relevant impurities should also be considered in formulations. In most cases, limits for formulations should equate to those for the TC or TK. However, the limit for a formulation may have to be increased, relative to that applying to the TC or TK, if an increase in impurity levels during product storage is unavoidable. Alternatively, if the active ingredient content of the formulation is so low that either the impurity cannot be detected or its hazards cannot be manifested, there may be no value in attempting to control the impurity in such products.

LEARNING UNIT G, EXERCISE 2

Happyfos equivalence

Slide G-08

Exercise 2, background

Happyfos is an organophosphorus insecticide for which a TC specification was developed by manufacturer 1 (M1).

All data supporting the M1 product have been previously assessed for validity and accepted, so there is no special reason to reassess the M1 data.

Generic manufacturer (M2) of happyfos TC claims that its product is equivalent to that of M1 and has submitted data to support the claim.

The M2 manufacturing process involves a synthesis route similar to that of M1. The process details differ, especially in the isolation of happyfos TC.

Slide G-09

Exercise 2, workplan

Using the blank *Equivalence evaluation table* provided, tabulate the two manufacturers' data for the comparison.

To simplify the exercise, some M2 test methods and data have already been checked as valid (☑) in the table.

Check the reported mass balance data and calculate: (i) values for the unaccountable fraction; and (ii) the average plus or minus 3 s.d. values, for impurity and active ingredient content, respectively.

Note that ...

(i) You are only given the job of partly evaluating the validity of certain test methods and data because, although this is an essential first step in real-life cases, the complete job would introduce too much complexity into this short exercise.

(ii) Where validity is **not** already checked (☑) in the blank *Equivalence evaluation table*, you should consider carefully whether the data in question provide important support for conclusions. If so, validity should be checked. If not, you have limited time and should not waste it by investigating issues that are not really important.

Slide G-10

Exercise 2, workplan, continued

Are there any serious gaps in the M2 data?

Are any of the M2 data questionable or unacceptable?

If you cannot resolve a problem, ask the facilitator (in lieu of the manufacturer and other sources of information) for help.

Test each appropriate characteristic for equivalence.

Overall, is the M2 product equivalent or non-equivalent?

Briefly explain each decision in your *Equivalence evaluation table*.

LEARNING UNIT G, EXERCISE 2 (i)

Reference profile (manufacturer 1, M1)

Happyfos purity/impurity data from M1

Component	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Manufacturing limit
happyfos, g/kg	968.6	956.3	946.4	955.7	949.9	930 minimum
Impurities, g/kg						Maximum
A (relevant)	**0.8**	**2.3**	**3.4**	**1.9**	**2.5**	**5**
B	2.6	3.2	5.1	2.4	4.2	7
C	23	25	27	25	24	30
D	0.9	1.5	1.3	1.1	1.2	2
E	0.5	0.6	0.1	0.4	0.5	1
F	<1	<1	<1	<1	<1	<1
G	<1	<1	<1	<1	<1	<1
total*	996.4	988.9	983.3	986.5	982.3	

* Totals reported by the manufacturer should be checked, as one of the checks on validity of data.

Happyfos toxic hazard data from M1

(including only the data used for equivalence determination)

Test	Result	Purity of TC, %
rat, acute oral LD_{50}	120 mg/kg bw	94.5
rat, acute dermal LD_{50}	1500 mg/kg bw	95.6
rat, acute inhalation LD_{50}	0.7 mg/l	94.5
rabbit, eye irritation	slight irritant	94.5
rabbit, skin irritation	non-irritant	96.0
guinea-pig, skin sensitization	non-sensitizer	93.7

Happyfos physico-chemical characteristics data from M1

Characteristic	Result	Purity, %
vapour pressure	1.3×10^{-4} Pa at 25 °C	98.0
melting point	14 °C	98.0
solubility in water	4 mg/l at 25 °C (pH 7)	97.1
octanol/water partition coefficient	log K_{ow} = 2.9	98.4
hydrolysis characteristics	half life at 25 °C pH 5 = 17 days pH 7 = 120 days pH 9 = 0.5 days	>97.5 radio-purity
photolysis characteristics	stable to photolysis	>97.5 radio-purity
dissociation characteristics	does not dissociate	–

M1 Happyfos, physical description and other specified characteristics

Characteristic	Value
physical description	Colourless-to-pale brown viscous liquid
Other specified characteristics	
none	–

LEARNING UNIT G, EXERCISE 2 (ii)

Data to be tested for equivalence with reference profile (manufacturer 2, M2)

Happyfos purity/impurity data from M2

Component	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Manufacturing limits
happyfos, g/kg	961.1	958.2	967.5	963.3	964.8	950 minimum
Impurities, g/kg						Maximum
A (relevant)	**3.4**	**3.1**	**3.6**	**3.1**	**3.3**	**4**
B	2.6	3.2	2.1	2.4	4.0	5
C	16	18	14	15	16	20
D	<1	<1	<1	<1	<1	<1
E	<1	<1	<1	<1	<1	<1
F	<1	<1	<1	<1	<1	<1
G	<1	<1	<1	<1	<1	<1
total*	983.1	982.5	987.2	983.8	988.1	

* Totals reported by the manufacturer should be checked, as one of the checks on validity of data.

Happyfos toxic hazard data from M2

Test	Result	Purity of TC, %
rat, acute oral LD_{50}	150 mg/kg bw	96.4
rat, acute dermal LD_{50}	1200 mg/kg bw	96.4
rat, acute inhalation LD_{50}	800 mg/m^3	96.4
rabbit, eye irritation	non-irritant	96.4
rabbit, skin irritation	non-irritant	96.4
guinea-pig, skin sensitization	non-sensitizer	96.4

Happyfos physico-chemical characteristics data from M2

Characteristic	Result	Purity, %
vapour pressure	9×10^{-5} Pa at 25 °C	99.1
melting point	15.5 °C	99.1
solubility in water	2.5 mg/l at 25 °C (pH 7)	99.1
octanol/water partition coefficient	log K_{ow} = 3.1	99.1
hydrolysis characteristics	half life at 25 °C pH 5 = 24 days pH 7 = 145 days pH 9 = 7 hours	>99 radio-purity
photolysis characteristics	stable to photolysis	>99 radio-purity
dissociation characteristics	no information	–

M2 Happyfos, physical description and other specified characteristics

Characteristic	Value
physical description	colourless viscous liquid
Other specified characteristics	
none	–

LEARNING UNIT G, EXERCISE 2 (iii)

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Happyfos TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
Active ingredient minimum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average – 3 s.d. in parenthesis)					
happyfos	( )	( )	☑		
Impurity maximum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average + 3 s.d. in parenthesis)					
impurity A (**relevant**)	( )	( )	☑		
impurity B	( )	( )	☑		
impurity C	( )	( )	☑		
impurity D	( )	( )	☑		
impurity E	( )	( )	☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Happyfos TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
impurity F	( )	( )	☑		
impurity G	( )	( )	☑		
Range of unaccountable fractions in 5-batch analysis data, calculated as: 1000 – (measured components total)					
Physical description of the technical grade active ingredient					
Other specified properties of the technical grade active ingredient, if any					
none	–	–	–		
Hazard data for the technical grade active ingredient					
rat acute oral LD_{50}			☑		
rat acute dermal LD_{50}			☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Happyfos TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
rat acute inhalation LD_{50}			☑		
rabbit eye irritation			☑		
rabbit skin irritation			☑		
guinea-pig skin sensitization			☑		
Physico-chemical properties of the pure active ingredient					
vapour pressure			☑		
melting point			☑		
solubility in water			☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Happyfos TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
octanol/water partition coefficient			☑		
hydrolysis characteristics			☑		
photolysis characteristics			☑		
dissociation characteristics					
Notes. 1 M1 = manufacturer 1 (reference profile); M2 = manufacturer 2 (data to be tested for equivalence). 2 In columns 4 and 5, enter ✓ = yes, or ✗ = no, or ? = questionable or uncertain. In column 6, summarize the basis of assessment and/or problems. 3 Some ☑ assessments are provided to simplify the exercise. In real-life cases, the evaluation team makes all assessments.			Overall conclusions		

LEARNING UNIT G, EXERCISE 2 (iv)

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Happyfos TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and test data valid?	Equivalent?	Rationale and supplementary information
Active ingredient minimum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average – 3 s.d. in parenthesis)					
happyfos	930 g/kg (930.0)	950 g/kg (952.3)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **higher** than M1
Impurity maximum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average + 3 s.d. in parenthesis)					
impurity A (**relevant**)	**5** g/kg (5.0)	**4** g/kg (3.9)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **lower** than M1
impurity B	7 g/kg (6.9)	5 g/kg (5.1)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **lower** than M1
impurity C	30 g/kg (29)	20 g/kg (20)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **lower** than M1
impurity D	2 g/kg (1.9)	<1 g/kg (–)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **lower** than M1
impurity E	1 g/kg (1.0)	<1 g/kg (–)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **lower** than M1
impurity F	<1 g/kg (–)	<1 g/kg (–)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **not higher** than M1
impurity G	<1 g/kg (–)	<1 g/kg (–)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **not higher** than M1
Range of unaccountable fractions in 5-batch analysis data, calculated as: 1000 – (measured components total)					
	3.6 to 17.7 g/kg	11.9 to 17.5 g/kg		✓	Unaccountable fraction <20 g/kg in both M1 and M2
Physical description of the technical grade active ingredient					
	colourless to pale brown viscous liquid	colourless viscous oil		✓	M1 description encompasses M2
Other specified properties of the technical grade active ingredient, if any					
none	–	–	–	✓	M2, like M1, has no other properties to be controlled by the specification.

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Happyfos TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and test data valid?	Equivalent?	Rationale and supplementary information
Toxicology of the technical grade active ingredient					
rat, acute oral LD_{50}	120 mg/kg bw	150 mg/kg bw	✓	✓	M2 **not more** hazardous than M1
rat, acute dermal LD_{50}	1500 mg/kg bw	1200 mg/kg bw	✓	✓	M2 **not more** hazardous than M1 (M2 not less than half the LD_{50} of M1)
rat, acute inhalation LD_{50}	0.7 mg/l	800 mg/m^3 (0.8 mg/l)	✓	✓	M2 **not more** hazardous than M1
rabbit, eye irritation	slight irritant	non-irritant	✓	✓	M2 **not more** hazardous than M1
rabbit, skin irritation	non-irritant	non-irritant	✓	✓	M2 **not more** hazardous than M1
guinea-pig, skin sensitization	non-sensitizer	non-sensitizer	✓	✓	M2 **not more** hazardous than M1
Physico-chemical properties of the pure active ingredient					
vapour pressure	1.3 x 10^{-4} Pa at 25 °C	9 x 10^{-5} Pa at 25 °C	✓		–
melting point	14 °C	15.5 °C	✓		–
solubility in water	4 mg/l at 25 °C (pH 7)	2.5 mg/l at 25 °C (pH 7)	✓		–
octanol/water partition coefficient	log K_{ow} = 2.9	log K_{ow} = 3.1	✓		–
hydrolysis characteristics	half life at 25 °C pH 5 = 17 days pH 7 = 120 days pH 9 = 0.5 days	half life at 25 °C pH 5 = 24 days pH 7 = 145 days pH 9 = 7 hours	✓		–
photolysis characteristics	stable to photolysis	stable to photolysis	✓		–
dissociation characteristics	does not dissociate	no information	✗		Supplementary information (i) This is not an important gap, because happyfos has no acid/base characteristics This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Happyfos TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and test data valid?	Equivalent?	Rationale and supplementary information
Notes. M1 = manufacturer 1 (reference profile) M2 = manufacturer 2 (data to be tested for equivalence). ☑ = assessments provided to simplify the exercise.			Overall conclusions ✓	✓	No significant gaps in M2 data. No indication that M2 TC is worse than M1 TC and it is of higher purity

LEARNING UNIT G, EXERCISE 2 (v)

Plenary presentations and discussion

Note that ...

(i) Manufacturing limits may or may not be consistent with average ± 3 x s.d. of 5-batch data. They may be based on production history or some other criterion, but it is helpful for the evaluation team to know the basis.

(ii) One or two instances of unaccountable fractions exceeding 20 g/kg may be acceptable in special cases, for example if the analysis is unusually challenging. However, if the majority of data exceed this limit, they should be investigated in detail. Be aware that excellent mass balances based on peak areas from, for example, a GC-FID analysis ignore the possible presence of impurities such water and compounds of very low volatility. Similarly, certain low-volatility compounds in GC-FID chromatograms could be artefacts produced from the stationary phase, and high-volatility components could be hidden in the solvent peak. Unknowns should not be quantified by HPLC-UV, LC-MS or LC-MS/MS, because the response of such systems is compound-dependent.

(iii) Although the acceptability of M1 data must have been assessed before they were designated as reference profiles, it is possible that doubts could arise from consideration of M2 data. Such doubts should be recorded (and resolved if practicable) before concluding the determination of equivalence.

(iv) To simplify this exercise, most M2 test methods were already assessed as acceptable. Normally, however, all such checks must be made by the team assessing equivalence. Although the acceptability of M1 data is assessed before designating them as reference profiles, it is possible that doubts could arise from consideration of M2 data. Such doubts should be recorded (and resolved if practicable) before concluding the determination of equivalence.

(v) No entries are required in cells shaded grey in the *Equivalence evaluation table*. However, if the values for the characteristics involved, in columns 2 and 3, are conflicting or otherwise problematic, they may cast doubt upon the validity of other data and therefore these issues should be resolved or rationalized, to provide maximum support for the overall conclusions on equivalence.

LEARNING UNIT G, EXERCISE 3

Superthrin equivalence

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Exercise 3, background

Superthrin is a pyrethroid insecticide for which a TC specification was developed by manufacturer 1 (M1).

All data supporting the M1 product have been previously assessed for validity and accepted, so there is no special reason to reassess the M1 data.

Generic manufacturer (M2) of superthrin claims that its TC is equivalent to that of M1 and has submitted data to support the claim.

The M2 manufacturing process involves a synthesis route and isolation procedure which differ from those of M1.

"Unknowns" in M1 TC are high molecular weight materials and are not considered hazardous.

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Exercise 3, workplan

Using the blank *Equivalence evaluation table* provided, tabulate the two manufacturers' data for the comparison.

To simplify the exercise, some M2 test methods and data have already been checked as valid (☑) in the table.

Check the reported mass balance data and calculate: (i) values for the unaccountable fraction; and (ii) the average plus or minus 3 s.d. values, for impurity and active ingredient content, respectively.

Note that ...

(i) You are only given the job of partly evaluating the validity of certain test methods and data because, although this is an essential first step in real-life cases, the complete job would introduce too much complexity into this short exercise.

(ii) Where validity is **not** already checked (☑) in the blank *Equivalence evaluation table*, you should consider carefully whether the data in question provide important support for conclusions. If so, validity should be checked. If not, you have limited time and should not waste it by investigating issues that are not really important.

Slide G-13

Exercise 3, workplan, continued

Are there any serious gaps in the M2 data?

Are any of the M2 data questionable or unacceptable?

If you cannot resolve a problem, ask the facilitator (in lieu of the manufacturer and other sources of information) for help.

Test each appropriate characteristic for equivalence.

Overall, is the M2 product equivalent or non-equivalent?

Briefly explain each decision in your *Equivalence evaluation table*.

LEARNING UNIT G, EXERCISE 3 (i)

Reference profile (manufacturer 1, M1)

Superthrin purity/impurity data from M1

Component	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Manufacturing limits
superthrin, g/kg	859	887	883	872	881	860 minimum
Impurities, g/kg						Maximum
A	76.6	53.5	50.3	43.5	48.7	70
B (relevant)	**1.3**	**1.3**	**1.3**	**1.2**	**1.3**	**2**
C	1.9	1.9	1.8	1.9	2	3
D	1.1	1	1	1	1	2
E	1.4	1.9	<1	<1	1	5
F	1.8	1.7	1.7	1.5	1.6	3
G	1.2	<1	1.4	1	1.4	2
H	6.9	6.5	7.2	9.1	7.1	15
I	6.7	5.5	6.7	4.8	5.3	10
J	2.6	2.6	2.6	2.5	2.5	5
K	11.6	10.5	18.8	7.9	8.6	15
L	<1	<1	<1	<1	<1	1
M	1.4	1.5	1.7	1.8	1.8	3
N	2.3	2.1	2.2	4.7	2.2	10
O	1.9	<1	1.8	1.2	1.6	5
P	2.3	2.3	2.3	2.3	2.3	3
Q	1.4	<1	1.3	<1	1.3	2
R	1.1	<1	2	4.6	1.1	10
S	<1	<1	<1	5.7	<1	10
T	3.5	4.7	3.1	4.8	4.5	10
U	5.9	5.3	6.4	9.3	5.9	15
solvent 1	0.5	<1	2	2.4	2.1	5
solvent 2	0.2	0.4	0.5	<1	0.9	2
inorganics	<1	<1	<1	<1	<1	1
water	<1	<1	<1	<1	<1	1
unknowns	<1	<1	2.1	5.2	2.1	–
total*	992.6	989.7	1001.2	988.4	987.3	

* Totals reported by the manufacturer should be checked, as one of the checks on validity of data.

Superthrin toxic hazard data from M1

(including only the data used for equivalence determination)

Test	Result	Purity of TC, %
rat, acute oral LD_{50}	950 mg/kg bw	87.8
rat, acute dermal LD_{50}	>2500 mg/kg bw	88.2
rat, acute inhalation LD_{50}	>800 mg/m^3	87.2
rabbit, eye irritation	slight irritant	88.0
rabbit, skin irritation	slight irritant	87.0
guinea-pig, skin sensitization	slight sensitizer	87.0

Superthrin physico-chemical characteristics data from M1

Characteristic	Result	Purity, %
vapour pressure	5×10^{-7} Pa at 20 °C	90.3
melting point	52 °C	88.9
solubility in water	2 µg/l at 25 °C	91.2
octanol/water partition coefficient	log K_{ow} = 5.4	89.8
hydrolysis characteristics	at 25 °C pH 5 no degradation in 30 days pH 7 no degradation in 30 days pH 9 half-life = 10 days	95 (radio-purity)
photolysis characteristics	half-life = 21 days in natural summer sunlight at 46 ºN	95 (radio-purity)
dissociation characteristics	does not dissociate	–

M1 Superthrin, physical description and other specified characteristics

Characteristic	Value
physical description	yellowish viscous liquid or semi-solid
Other specified characteristics	
none	–

LEARNING UNIT G, EXERCISE 3 (ii)

Data to be tested for equivalence with reference profile (manufacturer 2, M2)

Superthrin purity/impurity data from M2

Component	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Manufacturing limits
superthrin, g/kg	961	972	956	978	982	930 minimum
Impurities, g/kg						Maximum
A	10.6	12.1	15.4	13.2	9.6	25
B	<1	<1	1.9	<1	<1	3
F	3.5	2.1	5.4	2.7	4.2	10
P	1.1	<1	1.6	2.4	2	5
V	<0.5	<0.5	<0.5	<0.5	<0.5	0.5
solvent 3	<1	<1	2.3	1.7	3.2	5
solvent 2	<1	<1	<1	<1	<1	1
inorganics	<1	<1	<1	<1	<1	1
water	<1	<1	<1	<1	<1	1
unknowns	9.6	1.2	4.3	2.1	2	15
total*	985.8	987.4	986.9	1000.1	1003.0	
acidity (H_2SO_4)**	<1	<1	<1	<1	<1	1

* Totals reported by the manufacturer should be checked, as one of the checks on validity of data.

** Acidity or alkalinity data are not included in the 5-batch sum unless the measurement is known to quantify appropriately a single identified component, not otherwise included in the sum.

Superthrin toxic hazard data from M2

Test	Result	Purity of TC, %
rat, acute oral LD_{50}	1100 mg/kg bw	96.4
rat, acute dermal LD_{50}	>3000 mg/kg bw	96.4
rat, acute inhalation LD_{50}	>500 mg/m^3	96.4
rabbit, eye irritation	non-irritant	96.4
rabbit, skin irritation	non-irritant	96.4
guinea-pig, skin sensitization	moderate-sensitizer	96.4

Superthrin physico-chemical characteristics data from M2

Characteristic	Result	Purity, %
vapour pressure	4 x 10^{-6} Pa at 20 °C	90.3
melting point	46–48 °C	88.9
solubility in water	5 µg/l at 25 °C	91.2
octanol/water partition coefficient	log K_{ow} = 4.7	89.8
hydrolysis characteristics	at 20 °C pH 5 =stable pH 7 = stable pH 9 = half-life = 22 days	98.5 (radio-purity)
photolysis characteristics	no information	–
dissociation characteristics	does not dissociate	–

M2 Superthrin, physical description and other specified characteristics

Characteristic	Value
physical description	colourless-to-pale yellow waxy solid
Other specified characteristics	
none	–

LEARNING UNIT G, EXERCISE 3 (iii)

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
Active ingredient minimum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average – 3 s.d. in parenthesis)					
superthrin	( )	( )	☑		
Impurity maximum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average + 3 s.d. in parenthesis)					
impurity A	( )	( )	☑		
impurity B (**relevant**)	( )	( )	☑		
impurity C	( )	( )			
impurity D	( )	( )			
impurity E	( )	( )			
impurity F	( )	( )	☑		
impurity G	( )	( )			

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
impurity H	( )	( )			
impurity I	( )	( )			
impurity J	( )	( )			
impurity K	( )	( )			
impurity L	( )	( )			
impurity M	( )	( )			
impurity N	( )	( )			
impurity O	( )	( )			
impurity P	( )	( )	☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
impurity Q	( )	( )			
impurity R	( )	( )			
impurity S	( )	( )			
impurity T	( )	( )			
impurity U	( )	( )			
Impurity V	( )	( )	☑		
solvent 1	( )	( )			
solvent 2	( )	( )	☑		
solvent 3	( )	( )	☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
inorganics	( )	( )			
water	( )	( )	☑		
unknowns	( )	( )			
Range of unaccountable fractions in 5-batch analysis data, calculated as: 1000 – (measured components total)					
Physical description of the technical grade active ingredient					
Other specified properties of the technical grade active ingredient, if any					
acidity (as H_2SO_4), maximum	( )	( )	☑		
Toxicology of the technical grade active ingredient					
rat acute oral LD_{50}			☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
rat acute dermal LD_{50}			☑		
rat acute inhalation LC_{50}			☑		
rabbit skin irritation			☑		
rabbit eye irritation			☑		
guinea-pig skin sensitization					
Physico-chemical properties of the pure active ingredient					
vapour pressure			☑		
melting point			☑		
solubility in water			☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 methods and data valid?	Equivalent?	Rationale/comment
octanol/water partition coefficient			☑		
hydrolysis characteristics			☑		
photolysis characteristics			☑		
dissociation characteristics			☑		
Notes. 1 M1 = manufacturer 1 (reference profile); M2 = manufacturer 2 (data to be tested for equivalence). 2 In columns 4 and 5, enter ✓ = yes, or ✘ = no, or ? = questionable or uncertain. In column 6, summarize the basis of assessment and/or problems. 3 Some ☑ assessments are provided to simplify the exercise. In real-life cases, the evaluation team makes all assessments.			Overall conclusions		

LEARNING UNIT G, EXERCISE 3 (iv)

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
Active ingredient minimum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average – 3 s.d. in parenthesis)					
superthrin	860 g/kg (842.9)	930 g/kg (936.6)	☑	✓	M2 limit **much higher** than M1. Note: limit not consistent with 5-batch data in M1. Supplementary information: (i) M1 limit was raised following improvements in manufacturing process. This information provided to team:
Impurity maximum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average + 3 s.d. in parenthesis)					
impurity A	70 g/kg (93.1)	25 g/kg (19.0)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 **lower** than M1.
impurity B (**relevant**)	**2** g/kg (1.4)	**3** g/kg (-)	☑	✖	M1 limit consistent with 5-batch data and impurity well-controlled. M2 limit consistent with data but impurity is apparently poorly-controlled. M2 limit **higher** than M1. Supplementary information: (i) Impurity B is more difficult to control in M2 process and the product cannot be guaranteed to comply with M1 limit of 2 g/kg. This information provided to team: (ii) The current limit of 2 g/kg is well below the 20 g/kg maximum acceptable for impurity B. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....
Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity C	3 g/kg (2.1)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity D	2 g/kg (1.2)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity E	5 g/kg (2.8)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity F	3 g/kg (2.0)	10 g/kg (7.5)	✓	✗	Limit consistent with 5-batch data in both M1 and M2. M2 limit is **more** than 3 g/kg **higher** than M1. Supplementary information: (i) There is no information to suggest that impurity F should be considered relevant. This information provided to team:
impurity G	2 g/kg (1.8)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity H	15 g/kg (10.4)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? M2 subsequently characterized the three unknowns occurring ≥0.1 g/kg in the 5 batches and showed that one was impurity H. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....
Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity I	10 g/kg (8.4)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity J	5 g/kg (2.7)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity K	15 g/kg (24.5)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? M2 subsequently characterized the three unknowns occurring ≥0.1 g/kg in the 5 batches and showed that one was impurity K. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....
Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity L	1 g/kg (-)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity M	3 g/kg (2.2)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity N	10 g/kg (6.1)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity O	5 g/kg (2.6)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity P	3 g/kg (2.3)	5 g/kg (3.4)	✓	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **less** than 3 g/kg higher than M1.
impurity Q	2 g/kg (1.5)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity R	10 g/kg (7.2)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....
Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity S	10 g/kg (–)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity T	10 g/kg (6.4)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? The analytical method had not been validated for this impurity by M2. Evaluator considered that the GC-FID method of M2 should have detected the impurity if present >1 g/kg. This information provided to team:
impurity U	15 g/kg (11.3)	–	? ✓	✓ ✓	Apparently occurs only in M1, so M2 limit apparently **lower** than M1. Supplementary information: (i) But was the impurity overlooked by M2? M2 subsequently characterized the three unknowns occurring ≥0.1 g/kg in the 5 batches and showed that one was impurity U. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity V	–	0.5 g/kg (–)	✓	? ✓	Impurity does not occur ≥1 g/kg in M2, which makes it non-relevant unless exceptionally hazardous. Supplementary information: (i) There is no evidence to suggest that impurity V is exceptionally hazardous. This information provided to team: The products are equivalent by this criterion (note that if impurity V had required control at <1g/kg, the products would be non-equivalent and it could be appropriate to assess the possibility of its undetected occurrence in M1 TC).
solvent 1	5 g/kg (4.3)	–	? ✓	✓ ✓	M2 TC **not analysed** for presence of this impurity Supplementary information: (i) Solvent not used in M2 process. This information provided to team:
solvent 2	2 g/kg (1.4)	1 g/kg (–)	✓	✓	Solvent used in both M1 and M2 processes. Limits consistent with 5-batch data in both. M2 limit **lower** than M1.
solvent 3	–	5 g/kg (4.7)	✓	✗ ✓	Solvent used only in M1 process. Limit consistent with 5-batch data. M2 limit **higher** than M1. Supplementary information: (i) Hazard data are readily available for most common solvents. Solvent 3 was assessed as non-relevant at the theoretical maximum concentration of 70 g/kg (1000 minus 930 g/kg). This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
inorganics	1 g/kg (–)	– (–)	✖	? ✓	M2 TC **not analysed** for presence of inorganics. Supplementary information: (i) M2 process unlikely to lead to measurable levels of inorganics. This information provided to team:
water	1 g/kg (–)	1 g/kg (–)	✓	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **equal** to M1.
unknowns	– (8.5)	15 g/kg (14.1)	? ✓	✖ ✓	Method validation for "unknowns" is always problematic and may be impossible. M1 data imply a limit of about 9 g/kg is required but M1 has no manufacturing limit for "unknowns". Supplementary information: (i) M1 limit for unknowns (of high MW) was reduced following improvements in manufacturing process, which reduced the content to <0.1 g/kg. This information provided to team: M2 5-batch data consistent with limit of 15 g/kg. Apparently non-equivalent. Supplementary information: (ii) M2 subsequently characterized the three unknowns occurring ≥0.1 g/kg in the 5 batches and showed that they were impurities H, K and U. This information provided to team: The supplementary information shows that the M2 limit for the sum of impurities H, K and U does not exceed the M1 limit for any one of them and therefore the M2 product is actually equivalent in this respect.

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
Range of unaccountable fractions in 5-batch analysis data, calculated as: 1000 – (measured components total)					
	–1.2 to 12.7 g/kg	–3.0 to 14.2 g/kg		✓	Unaccountable fraction <20 g/kg in both M1 and M2, therefore major impurities were not likely to have been missed in the analyses, assuming that the validation data indicate acceptable accuracy, precision and linearity of response.
Physical description of the technical grade active ingredient					
	yellowish viscous liquid or semi-solid	Colourless-to-pale yellow waxy solid		✓	M1 description encompasses M2
Other specified properties of the technical grade active ingredient, if any					
acidity (as H_2SO_4)	–	1 g/kg (–)	✓	✗ ✓	Limit consistent with 5-batch data in M2. Data cannot be added to mass balances. No data for M1. Supplementary information: (i) A small quantity of citric acid is used in both synthetic processes to prevent superthrin epimerization but, at its theoretical maximum concentration in M2 TC (70 g/kg, from 1000 minus 930 g/kg), it is considered to be non-hazardous and therefore it is not a relevant impurity. (ii) Citric acid is removed in the M1 process and is not responsible for the higher eye and skin irritation scores of M1. This information provided to team:
Toxicology of the technical grade active ingredient					
rat acute oral LD_{50}	950 mg/kg bw	1100 mg/kg bw	✓	✓	M2 **not more** hazardous than M1 TC.
rat acute dermal LD_{50}	>2500 mg/kg bw	>3000 mg/kg bw	✓	✓	M2 **not more** hazardous than M1 TC.
rat acute inhalation LC_{50}	>800 mg/m^3	>500 mg/m^3	✓	✓	M2 TC perhaps **not more** hazardous than M1 but obscured by difference in maximum levels tested, which is **less than a factor of 2.**
rabbit skin irritation	slight irritant	non-irritant	✓	✓	M2 **not more** hazardous than M1 TC.

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
rabbit eye irritation	slight irritant	non-irritant	✓	✓	M2 **not more** hazardous than M1 TC.
guinea-pig skin sensitization	slight sensitizer	moderate sensitizer	?	✗ ✓	M2 apparently **more** hazardous than M1 TC. Supplementary information: (i) The difference is not real but reflects different scoring methodology. (ii) None of the impurities is suspected of being a skin sensitizer. This information provided to team:
Physico-chemical properties of the pure active ingredient					
vapour pressure	5 x 10^{-7} Pa at 20 °C	4 x 10^{-6} Pa at 20 °C	✓		Supplementary information: (i) Higher volatility perhaps due to water impurity but probably unimportant. This information provided to team:
melting point	52 °C	46–48 °C	✓		Supplementary information: (i) Lower melting point due to water impurity but probably unimportant. This information provided to team:
solubility in water	2 µg/l at 25 °C	5 µg/l at 25 °C	✓		Supplementary information: (i) Apparently higher water solubility probably due to measurement error at this concentration. This information provided to team:
octanol/water partition coefficient	log K_{ow} = 5.4	log K_{ow} = 4.7	✓		Supplementary information: (i) Apparently lower octanol affinity probably due to measurement error. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Superthrin TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
hydrolysis characteristics	at 25 °C pH 5, <5% degradation in 30 days pH 7, <5% degradation in 30 days pH 9, half-life = 10 days	at 20 °C pH 5 =stable pH 7 = stable pH 9 = half-life = 22 days	☑		Supplementary information: (i) Apparently slower hydrolysis at pH 9 presumably due to lower temperature. This information provided to team:
photolysis characteristics	half-life = 21 days in natural summer sunlight at 46 ºN	?	☑		No data from M2 but **not** a serious data gap.
dissociation characteristics	does not dissociate	?	☑		No information on M2 but not necessary because acid/base characteristics not expected.
			Overall conclusions		
Notes. 1 M1 = manufacturer 1 (reference profile); M2 = manufacturer 2 (data to be tested for equivalence). 2 ☑ assessments are provided to simplify the exercise. In real-life cases, the evaluation team makes these assessments. 3 → indicates reconsideration of an initial assessment, taking into account supplementary information or technical issues.			✗ ✓	✗ ✓	(i) Doubts about the validity of methods and data were resolved and/or were not critical for decision-making. (ii) M2 TC is non-equivalent by several criteria. (iii) However, the M2 TC is of higher purity than M1 and, with the exception of impurity B, the supplementary information shows that it is not materially worse than M1 TC. (iv) The M2 limit for impurity B (3 g/kg) is well within the 20 g/kg maximum acceptable limit and therefore the existing specification limit of 2 g/kg could be raised to 3 g/kg to accommodate the M2 product. (v) The hazard data indicate equivalence and, by raising the limit for the relevant impurity (which would remain acceptable), the two products could share the same specification.

LEARNING UNIT G, EXERCISE 3 (v)

Plenary presentations and discussion

Note that ...

(i) Manufacturing limits may or may not be consistent with average ± 3 x s.d. of 5-batch data. They may be based on production history or some other criterion, but it is helpful for the evaluation team to know the basis.

(ii) One or two instances of unaccountable fractions exceeding 20 g/kg may be acceptable in special cases, for example if the analysis is unusually challenging. However, if the majority of data exceed this limit, they should be investigated in detail. Be aware that excellent mass balances based on peak areas from, for example, a GC-FID analysis ignore the possible presence of impurities such water and compounds of very low volatility. Similarly, certain low-volatility compounds in GC-FID chromatograms could be artefacts produced from the stationary phase, and high-volatility components could be hidden in a solvent peak. Unknowns should not be quantified by HPLC-UV, LC-MS or LC-MS/MS, because the response of such systems is compound-dependent.

(iii) Although the acceptability of M1 data must have been assessed before they were designated as reference profiles, it is possible that doubts could arise from consideration of M2 data. Such doubts should be recorded (and resolved if practicable) before concluding the determination of equivalence.

(iv) To simplify this exercise, certain M2 test methods were already assessed as acceptable. Normally, however, all such checks must be made by the team assessing equivalence. Although the acceptability of M1 data is assessed before designating them as reference profiles, it is possible that doubts could arise from consideration of M2 data. Such doubts should be recorded (and resolved if practicable) before concluding the determination of equivalence.

(v) No entries are required in cells shaded grey in the *Equivalence evaluation table*. However, if the values for the characteristics involved, in columns 2 and 3, are conflicting or otherwise problematic, they may cast doubt upon the validity of other data and therefore these issues should be resolved or rationalized, to provide maximum support for the overall conclusions on equivalence.

LEARNING UNIT G, EXERCISE 4

Fantasychlor equivalence

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Exercise 4, background

Fantasychlor is a herbicide for which a TC specification was developed by manufacturer 1 (M1).

All data supporting the M1 product have been previously assessed for validity and accepted, so there is no special reason to reassess the M1 data.

Generic manufacturer (M2) of fantasychlor TC claims that its product is equivalent to that of M1 and has submitted data to support the claim.

The M2 manufacturing process involves a synthesis route and isolation procedure which differ from those of M1.

Slide G-15

Exercise 4, workplan

Using the blank *Equivalence evaluation table* provided, tabulate the two manufacturers' data for the comparison.

To simplify the exercise, some M2 test methods and data have already been checked as valid (☑) in the table.

Check the reported mass balance data and calculate: (i) values for the unaccountable fraction; and (ii) the average plus or minus 3 s.d. values, for impurity and active ingredient content, respectively.

Note that...

(i) You are given the job of only partly evaluating the validity of certain test methods and data because, although this is an essential first step in real-life cases, the complete job would introduce too much complexity into this short exercise.

(ii) Where validity is **not** already checked (☑) in the blank *Equivalence evaluation table*, you should consider carefully whether the data in question provide important support for conclusions. If so, validity should be checked. If not, you have limited time and should not waste it by investigating issues that are not really important.

Slide G-16

Exercise 4, workplan, continued

Are there any serious gaps in the M2 data?

Are any of the M2 data questionable or unacceptable?

If a problem is identified, ask the facilitator (in lieu of M2) for help to resolve it.

Test each appropriate characteristic for equivalence.

Overall, is the M2 product equivalent or non-equivalent?

Briefly explain each decision in your *Equivalence evaluation table*.

LEARNING UNIT G, EXERCISE 4 (i)

Reference profile (manufacturer 1, M1)

Fantasychlor purity/impurity data from M1

Component	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Manufacturing limits
fantasyclor, g/kg	999.2	998.9	997.8	998.1	996.1	990 minimum
Impurities, g/kg						Maximum
A	0.12	0.14	0.17	0.14	0.15	1
B	0.056	0.063	0.064	0.052	0.056	4
C (relevant)	**0.00060**	**0.00017**	**0.00013**	**0.00014**	**0.00012**	**0.001**
D	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5
E	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
water	<1	<1	<1	<1	<1	<1
total*	999.4	999.1	998.0	998.3	996.3	

* Totals reported by the manufacturer should be checked, as one of the checks on validity of data.

Fantasychlor toxic hazard data from M1

(including only the data used for equivalence determination)

Test	Result	Purity of TC, %
rat, acute oral LD_{50}	>4000 mg/kg bw	98
rat, acute dermal LD_{50}	>10000 mg/kg bw	98
rat, acute inhalation LD_{50}	0.1 mg/l	98
rabbit, eye irritation	severe irritant	95
rabbit, skin irritation	slight irritant	95
guinea-pig, skin sensitization	slight sensitizer	95

Fantasychlor physico-chemical characteristics data from M1

Characteristic	Result	Purity, %
vapour pressure	8.7×10^{-3} Pa at 25 °C	95
melting point	86°C	99
solubility in water	230 mg/l at 25 °C	98
octanol/water partition coefficient	log K_{ow} = 2.5	99
hydrolysis characteristics	at 25 °C pH 5 stable pH 7 stable pH 9 stable	97% radio-purity
photolysis characteristics	half-life = 2 days in natural summer sunlight at 35 ºN	97% radio-purity
dissociation characteristics	does not dissociate	–

M1 fantasychlor, physical description and other specified characteristics

Characteristic	Value
physical description	white or cream crystalline powder
Other specified characteristics	
none	–

Fantasychlor formulations made by M1: WG, EC.

LEARNING UNIT G, EXERCISE 4 (ii)

Data to be tested for equivalence with reference profile (manufacturer 2, M2)

Fantasychlor purity/impurity data from M2

Component	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Manufacturing limits
fantasyclor, g/kg	975.2	980.4	982.5	977.9	977.5	970 minimum
Impurities, g/kg						Maximum
A	2.58	0.18	0.15	0.16	0.14	4
B	0.086	0.059	0.046	0.054	0.038	0.5
C (relevant)	**0.00014**	**0.00038**	**0.00020**	**0.00095**	**0.00044**	**0.001**
E	<1	<1	<1	<1	<1	<1
F	1.5	<1	<1	5.6	<1	10
G	3.9	1.4	2.2	4.1	2.9	6
water	9.0	11.4	9.9	12.5	10.7	15
total*	992.3	993.4	994.8	1000.3	991.3	

* Totals reported by the manufacturer should be checked, as one of the checks on validity of data.

Fantasychlor toxic hazard data from M2

Test	Result	Purity of TC, %
rat, acute oral LD_{50}	>3000 mg/kg bw	97.3
rat, acute dermal LD_{50}	>12000 mg/kg bw	98.2
rat, acute inhalation LD_{50}	>150 mg/m^3	97.3
rabbit, eye irritation	irritant	97.5
rabbit, skin irritation	non-irritant	97.5
guinea-pig, skin sensitization	moderate sensitizer	98.0

Fantasychlor physico-chemical characteristics data from M2

Characteristic	Result	Purity, %
vapour pressure	8.7 x 10^{-3} Pa at 25 °C	95
melting point	88°C	99
solubility in water	315 mg/l at 30 °C	98
octanol/water partition coefficient	log K_{ow} = 2.5	99
hydrolysis characteristics	at 25 °C pH 5 stable pH 7 stable pH 9 stable	97% radio-purity
photolysis characteristics	half-life = 2 days in natural summer sunlight at 35 ºN	97% radio-purity
dissociation characteristics	does not dissociate	–

M2 fantasychlor, physical description and other specified characteristics

Characteristic	Value
physical description	pale yellow small crystalline flakes
Other specified characteristics	
none	–

Fantasychlor formulations made by M2: WG only.

LEARNING UNIT G, EXERCISE 4 (iii)

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale/comment
Active ingredient minimum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average – 3 s.d. in parenthesis)					
fantasychlor	( )	( )	☑		
Impurity maximum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average + 3 s.d. in parenthesis)					
impurity A	( )	( )	☑		
impurity B	( )	( )	☑		
impurity C (**relevant**)	( )	( )	☑		
impurity D	( )	( )			
impurity E	( )	( )	☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale/comment
impurity F	( )	( )	☑		
impurity G	( )	( )	☑		
water	( )	( )	☑		
Range of unaccountable fractions in 5-batch analysis data, calculated as: 1000 – (measured components total)					
Physical description of the technical grade active ingredient					
Other specified properties of the technical grade active ingredient, if any					
None	–	–	–		
Toxicology of the technical grade active ingredient					
rat, acute oral LD_{50}			☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale/comment
rat, acute dermal LD_{50}			☑		
rat, acute inhalation LD_{50}			☑		
rabbit, eye irritation			☑		
rabbit, skin irritation			☑		
guinea-pig, skin sensitization			☑		
Physico-chemical properties of the pure active ingredient					
vapour pressure			☑		
melting point			☑		

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale/comment
solubility in water			☑		
octanol/water partition coefficient			☑		
hydrolysis characteristics			☑		
photolysis characteristics					
dissociation characteristics					
Notes. 1 M1 = manufacturer 1 (reference profile); M2 = manufacturer 2 (data to be tested for equivalence). 2 In columns 4 and 5, enter ✓ = yes, or ✘ = no, or ? = questionable or uncertain. In column 6, summarize the basis of assessment and/or problems. 3 Some ☑ assessments are provided to simplify the exercise. In real-life cases, the evaluation team makes all assessments.			Overall conclusions		

LEARNING UNIT G, EXERCISE 4 (iv)

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
Active ingredient minimum, manufacturing limit (note: columns 2 & 3, also insert calculated values for 5-batch average – 3 s.d. in parenthesis)					
fantasychlor	990 (994.4)	970 (970.3)	☑	✖	Limit consistent with 5-batch data in M1 and M2. M2 limit **lower** than M1 but the difference is mainly due to water. In many cases, the presence of slightly more water would be unimportant but, in this case, water is important.
Impurity maximum, manufacturing limit (note: columns 2 & 3, also insert calculated values for five-batch average + 3 s.d. in parenthesis)					
impurity A	1 (0.19)	4 (3.9)	☑	✓	Limit not very consistent with 5-batch data in M1. Limit consistent with 5-batch data in M2, in which impurity A is rather poorly controlled. M2 limit is **not** more than 3 g/kg higher than M1.
impurity B	4 (0.074)	0.5 (0.1)	☑	✓	Limit not consistent with 5-batch data in M1. Limit consistent with 5-batch data in M2. M2 limit **lower** than M1 and, being <1 g/kg, it is not formally considered to be part of the impurity profile.
impurity C (**relevant**)	**0.001** (0.0009)	**0.001** (0.0014)	☑	✓	Limit consistent with 5-batch data in both M1 and M2. M2 limit **equal** to M1.
impurity D	<0.5 (–)	–	?	✓ ✓	Limit consistent with 5-batch data in M1 but does not occur ≤1 g/kg and is **not** exceptionally hazardous, so is not formally considered to be part of the M1 profile. Supplementary information: (i) Consideration of the manufacturing process indicates that impurity D should not occur in M2. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
impurity E	<0.1 (–)	<1 (–)	☑	? ✓	Limit consistent with 5-batch data in both M1 and M2. Unclear whether or not M2 limit is higher than M1. Supplementary information: (i) Impurity E is not exceptionally hazardous, and M2 confirmed that impurity B is never <0.5 g/kg, so it is not formally considered to be part of the M2 impurity profile. This information provided to team:
impurity F	–	10 (–)	☑	✘	Limit consistent with 5-batch data in M2. Not found in M1, so M2 limit is >3 g/kg **higher** than M1. Supplementary information: (i) There is no evidence to suggest that impurity F at its theoretical maximum concentration of 30 g/kg should be considered hazardous in fantasychlor TC. This information provided to team:
impurity G	–	6 (–)	☑	✘	Limit consistent with 5-batch data in M2. Does not occur in M1, so M2 limit is >3 g/kg **higher** than M1. Supplementary information: (i) Impurity G has some characteristics which suggest that it could be a skin sensitizer. This information provided to team:

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
water	<1 (–)	15 (14.7)	☑	✘	Limit consistent with 5-batch data in M1 and M2. Occurs at <1 g/kg in M1, so it is not a relevant impurity in M1 TC by this criterion. M2 limit is >3 g/kg **higher** than M1. Fantasychlor is not subject to hydrolysis, so water should not affect active ingredient stability. M2 prepares only WG formulations, so water in the TC should not influence the quality or stability of this product. However, M1 also prepares EC and water at 15 g/kg could create problems with formulation quality or stability.
Range of unaccountable fractions in 5-batch analysis data, calculated as: 1000 – (measured components total)					
	0.6 to 3.7 g/kg	–0.3 to 8.7 g/kg		✓	Unaccountable fraction <20 g/kg in both reference and generic profiles.
Physical description of the technical grade active ingredient					
	white or cream crystalline powder	pale yellow small crystalline flakes		? ✓	M2 differs slightly from M1 but description clause could be amended to include "pale yellow" and "flakes" without significantly changing the specification.
Other specified properties of the technical grade active ingredient, if any					
None	–	–	–	✓	M2, like M1, has no other properties to be controlled by the specification.
Toxicology of the technical grade active ingredient					
rat, acute oral LD_{50}	>4000 mg/kg bw	>3000 mg/kg bw	☑	✓	Any difference between M2 and M1 obscured by difference in maximum levels tested, which is **less than a factor of 2**.
rat, acute dermal LD_{50}	>10000 mg/kg bw	>12000 mg/kg bw	☑	✓	M2 **not more** hazardous than M1.
rat, acute inhalation LD_{50}	0.1 mg/l	>150 mg/m^3 (>0.15 mg/l)	☑	✓	M2 **not more** hazardous than M1.
rabbit, eye irritation	severe irritant	irritant	☑	✓	M2 **not more** hazardous than M1.

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
rabbit, skin irritation	slight irritant	non-irritant	☑	✓	M2 **not more less** hazardous than M1.
guinea-pig, skin sensitization	slight sensitizer	moderate sensitizer	☑	✗	M2 apparently **more** hazardous than M1.
Physico-chemical properties of the pure active ingredient					
vapour pressure	8.7 x 10^{-3} Pa at 25 °C	8.7 x 10^{-3} Pa at 25 °C	☑		M2 result identical to M1. Unlikely and study report should be checked.
melting point	86 °C	88 °C	☑		–
solubility in water	230 mg/l at 25 °C	315 mg/l at 30 °C	☑		Apparently higher solubility of M2 pure fantasychlor due to higher temperature?
octanol/water partition coefficient	log K_{ow} = 2.5	log K_{ow} = 2.5	☑		M2 result identical to M1. Possible but study report should be checked.
hydrolysis characteristics at 25°C	pH 5 stable pH 7 stable pH 9 stable	pH 5–9 stable	☑		M2 results identical to M1. Probable but study report should be checked.
photolysis characteristics	half-life = 2 days in natural summer sunlight at 35 ºN	–	✗		M2: no data. Probably **not an important gap.**
dissociation characteristics	Does not dissociate	–	✗		M2: no data but **not an important gap** because acid/base characteristics not expected.

Equivalence evaluation table Evaluation team: ..... Date: ..... Document No: .....

Fantasychlor TC (manufacturing data from ..... [M1, reference profiles] and ..... [M2])

Criterion	M1 data	M2 data	M2 method and data valid?	Equivalent?	Rationale and supplementary information
			Overall conclusions		
Notes. 1 M1 = manufacturer 1 (reference profile); M2 = manufacturer 2 (data to be tested for equivalence). 2 Certain ☑ assessments are provided to simplify the exercise. In real-life cases, the evaluation team makes all assessments. 3 → indicates reconsideration of an initial assessment, taking into account supplementary information or technical issues.			✘	✘	(i) Doubts about the origins of some physico-chemical data from M2 should be resolved. (ii) M2 TC is lower purity than M1 but this is largely due to a higher water content, which is not a problem for M2 formulations (WG only). (iii) Water content up to 15 g/kg could create formulation quality problems for M1 (EC), so it is not acceptable to introduce a new clause and limit at this level for water in the reference specification. (iv) Impurity G, which occurs only in M2 TC, may be a skin sensitizer and is therefore probably a relevant impurity in M2. (v) Minor amendment of existing description clause, to encompass M2, would not be a significant change. (vi) Overall, M2 is clearly non-equivalent and cannot share the same specification as the reference. Before a new specification is considered, do its proposed uses pose unacceptable risks? Risks should be assessed before reconsidering the specification.

LEARNING UNIT G, EXERCISE 4 (v)

Plenary presentations and discussion

Note that ...

(i) Manufacturing limits may or may not be consistent with average ± 3 x s.d. of 5-batch data. They may be based on production history or some other criterion but it is helpful for the evaluation team to know the basis.

(ii) One or two instances of unaccountable fractions exceeding 20 g/kg may be acceptable in special cases, for example if the analysis is unusually challenging. However, if the majority of data exceed this limit, they should be investigated in detail. Be aware that excellent mass balances based on peak areas from, for example, a GC-FID analysis ignore the possible presence of impurities such water and compounds of very low volatility. Similarly, certain low-volatility compounds in GC-FID chromatograms could be artefacts produced from the stationary phase, and high-volatility components could be hidden in the solvent peak. Unknowns should not be quantified by HPLC-UV, LC-MS or LC-MS/MS, because the response of such systems is compound-dependent.

(iii) Although the acceptability of M1 data must have been assessed before they were designated as reference profiles, it is possible that doubts could arise from consideration of M2 data. Such doubts should be recorded (and resolved if practicable) before concluding the determination of equivalence.

(iv) To simplify this exercise, certain M2 test methods were already assessed as acceptable. Normally, however, all such checks must be made by the team assessing equivalence. Although the acceptability of M1 data is assessed before designating them as reference profiles, it is possible that doubts could arise from consideration of M2 data. Such doubts should be recorded (and resolved if practicable) before concluding the determination of equivalence.

(v) No entries are required in cells shaded grey in the *Equivalence evaluation table*. However, if the values for the characteristics involved, in columns 2 and 3, are conflicting or otherwise problematic, they may cast doubt upon the validity of other data and therefore these issues should be resolved or rationalized, to provide maximum support for the overall conclusions on equivalence.

APPENDIX

Calculations to estimate the relevance of certain impurities

(Reproduced from the *Manual on development and use of FAO and WHO specifications for pesticides*, March 2006 revision.)

Calculation of worst-case-possible contribution by an impurity to the toxic hazards of the active ingredient

Note:

These calculations apply only where:

(i) where the nature of the toxic hazard presented by active ingredient and impurity is considered to be similar;
(ii) the effects may be considered to be additive; and
(iii) the toxicity of the impurity is known or can be approximated from data on analogous compounds.

If requirements (i) and (iii) are fulfilled but the effects are not additive, an appropriate calculation may be possible if the mathematical nature of the interaction is known.

The calculations are presented here in full, for clarity, but can be simplified by omitting the term for relative hazard of the active ingredient (=1).

Calculations

(i) Calculate the relative hazard of the impurity ($RelHaz_{imp}$) from the hazard data for the impurity (Haz_{imp}) and active ingredient (Haz_{ai}).

$RelHaz_{imp} = (Haz_{ai}/Haz_{imp}$

The relative hazard of the active ingredient ($RelHaz_{ai}$) is consequently 1.

(ii) Calculate the maximum theoretical increase in hazard of the active ingredient/impurity mixture (MTIHaz), as a proportion of active ingredient hazard (Haz_{ai}), from the minimum purity (%) of the TC ($\%ai_{min}$) and the corresponding theoretical maximum content (%) of the impurity ($\%imp_{max}$).

$MTIHaz = (\%ai_{min} \times RelHaz_{ai}) + (\%imp_{max} \times RelHaz_{imp}))/(\%ai_{min} \times RelHaz_{ai})$

(iii) Calculate the maximum limit acceptable for the impurity concentration ($\%Imp_{maxaccept}$) by substituting a limit of 1.1 (i.e. +10%) for MTIHaz and $\%Imp_{maxacceptt}$ for $\%imp_{max}$, in equation (ii):

$1.1 = ((\%ai_{min} \times RelHaz_{ai}) + (\%Imp_{maxaccept} \times RelHaz_{imp}))/(\%ai_{min} \times RelHaz_{ai})$

and rearranging equation (iii):

$\%Imp_{maxaccept} = ((1.1 \times \%ai_{min} \times RelHaz_{ai}) – (\%ai_{min} \times RelHaz_{ai}))/RelHaz_{imp}$

Where:

Haz_{ai} = active ingredient hazard value;
Haz_{imp} = impurity hazard value;
$RelHaz_{imp}$ = relative hazard of impurity compared with active ingredient;
$RelHaz_{ai}$ = relative hazard of active ingredient (=1);
$\%ai_{min}$ = declared minimum active ingredient content;

$\%imp_{max}$ = maximum theoretical content of impurity;
MTIHaz = maximum theoretical increase in hazard due to impurity;
$\%imp_{maxaccept}$ = maximum acceptable content of impurity.

Example 1

The acute oral LD_{50} of an impurity is 100 mg/kg bw and that of the active ingredient is 1000 mg/kg bw. The minimum purity of the TC is 92%.

$RelHaz_{imp}$ = 1000/100 = 10

MTIHaz = ((92 x 1) + (8 x 10))/(92 x 1) = 1.87 (87% >10% increase, the impurity is **relevant**)

$\%Imp_{maxaccept}$ = ((1.1 x 92 x 1) – (92 x 1))/10 = **0.92%**

Rounding to 1 (or 1.5) significant figure, the maximum limit acceptable for the concentration of this relevant impurity is therefore 1% in the TC and 1% of the active ingredient concentration.

Example 2

A biological pesticide TK has a minimum purity of 20%. The acute oral LD_{50} of an impurity is 2000 mg/kg bw and that of the active ingredient is 1000 mg/kg bw. That is, the impurity is less hazardous than the active ingredient.

$RelHaz_{imp}$ = 1000/2000 = 0.5

MTIHaz = ((20 x 1) + (80 x 0.5))/(20 x 1) = 3.0 (200% >10% increase, the impurity is **relevant**)

$\%Imp_{maxaccept}$ = ((1.1 x 20 x 1) – (20 x 1))/0.5 = **4%**

The maximum limit acceptable for the concentration of this relevant impurity is therefore 4% in the TK or 20% of the active ingredient concentration.

Example 3

The acute oral LD_{50} of an impurity is 400 mg/g bw and that of the active ingredient is 600 mg/kg bw. The minimum purity of the TC is 98%.

$RelHaz_{imp}$ = 600/400 = 1.5

MTIHaz = ((98 x 1) + (2 x 1.5))/(98 x 1) = 1.03 (3% <10% increase, the impurity is **non-relevant**).
