Relevant impurities

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 determinethe relevance of impurities

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.

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.

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 ist contribution to the overall hazard of the active ingredient, not potential for exposure to the impurity, which is dependent on the application and conditions.

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).

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.

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.

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.

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.

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 mosthazardous 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.

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.

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?

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**

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

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.

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)

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.

Relevant impurities identified in active ingredients in EU
~ 35 pesticides an 70 relevant impurities
(in German,extract)

Wirkstoff	BVL-Nr.	Verunreinigung	Höchstgehalt
Benthiavalicarb	1032	6,6'-Difluor-2,2'-dibenzothiazol	3,5 mg/kg
		Bis (2-amino-5-fluorphenyl)disulfid	14 mg/kg
Bifenox	0537	2,4-Dichloranisol	6 g/kg
		2,4-Dichlorphenol	3 g/kg
Captan	0012	Perchlormethylmercaptan	5 g/kg
		Folpet	10 g/kg
		Tetrachlorkohlenstoff	0,1 g/kg

FAO and WHO Specifications for pesticides: a training manual