Opinion on the general criteria for setting acute reference doses for plant protection products (opinion of the Scientific Committee on Plants expressed on 28 January 2000)

TERMS OF REFERENCE

The SCP at its third plenary meeting identified the risk assessment of plant protection product residues as an important priority for the Committee with respect to its work in the context of Directive 91/414/EEC concerning the placing of plant protection products on the market. The Committee subsequently issued several opinions in 1998 [1] relating to acute dietary risk assessment of pesticide residues in food and decided that it should return to the emerging issue of acute toxicological risk assessment and identified the following aspects which should be addressed in its opinion:

1. Which plant protection product active substances should be considered for the allocation of an Acute Reference Dose (ARfD).

2. Which studies and toxicological end-points should be used to derive an ARfD

The Committee consulted experts in the area and took their report into account when preparing the following opinion.

OPINION

General considerations

Life-time dietary exposures to residues of pesticides are considered to be without health risks for consumers when the Acceptable Daily Intakes (ADI) are not exceeded. Intakes are calculated as averages over a long period of time; this means that occasional (single meal/one day) intakes above the ADI may occur due to either variability in residue concentration or amount of food eaten. These intakes are considered to be without long-term risk if compensated by lower intakes on other occasions. It has been shown, however, that some active substances or residues may have acute toxicity or may be able to induce long-term effects, after a single dose. In this case, fluctuation of intake above the ADI may pose health risk. For this reason the allocation of an Acute Reference Dose (ARfD) might be required to estimate the extent, if any, of the intake fluctuation above the ADI which is unlikely to pose health risks.

The toxicological information provided by the Annex 2 to EC Directive 91/414 represents the basis for deriving the ARfD. The FAO/WHO 1997 Consultation defined acute reference dose as " An estimate of the amount of substance in food or drinking water, expressed on a body-weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable risk to the consumer on the basis of all the known facts at the time of evaluation. It is usually expressed in milligrams of the chemical per kilogram of body weight."

As a general principle, it is recommended that an ARfD be based on the most sensitive acute end-point of relevance to humans, in the most sensitive species. However, given the wide range of toxic end-points produced by pesticides, there will be instances where other pertinent issues should be considered. Therefore risk assessments should take into account the entire toxicological profile of the pesticide under evaluation.

Which pesticides should be allocated an ARfD?

As a general rule, all pesticides should be considered as requiring an ARfD. The likelihood that an ARfD would be necessary is particularly high when the mechanism of pesticide action is relevant to humans and is consistent with the production of toxic effects after a single exposure. (Examples include cholinesterase inhibition; direct action on the nervous system; disruption of oxidative phosphorylation / mitochondria). For some pesticides, an evaluation of the toxicological data will indicate that an ARfD is unnecessary. This decision should be reached only **after** considering all the data. The range of crops treated with a particular pesticide may vary over time and any decision on whether to set an ARfD should be based solely on toxicology and be independent of the current patterns of use and estimated intakes. If an evaluator concludes that an ARfD is unnecessary, the facts which support this conclusion should be described in detail. This description should make reference, but not be limited to the issues dealt with below.

In determining whether or not an active ingredient should be allocated an ARfD the following issues in particular should be considered:

1. **Findings in acute toxicity studies**. Does the pesticide produce mortality, overt clinical signs, changes in behaviour or relevant pathological lesions after a single dose of < 2000 mg/kg bw? Care should be taken in interpreting findings that may be due to the dosing procedure or gastrointestinal lesions that might be due to a local irritant response. Care should also be taken in the assessment of possible delayed effects.

2. **Findings in teratogenicity studies**. Are there increases in specific, foetal abnormalities in teratology studies? If present, in the absence of data to the contrary, these should be considered as being related to a single exposure at the critical period of organogenesis. Care should be exercised in the interpretation of general fetotoxicity, such as, reduced body weight and delayed ossification as these effects may be secondary to repeated exposure.

Apart from effects on the foetus, evidence of clear maternal toxicity early in the dosing period in itself indicates an ARfD should be considered.

3. **Repeated-dose studies**. Most repeated-dose toxicity studies include regular investigations such as clinical signs, behaviour, body weight and food consumption. Changes in these parameters during the first few days of dosing might indicate that an ARfD should be allocated. Effects from interim or terminal investigations may be produced by either a single dose or repeated doses and expert judgement must be used in deciding whether a finding is relevant to an assessment of acute exposure in humans.

Which studies and end-points should be used to derive an ARfD?

It is not possible to identify specific studies that would be appropriate for use in all circumstances. The entire toxicity database should be considered and the most appropriate

study determined on a case-by-case basis. If this study involves repeated dosing, expert judgement must be used to ensure that the end-point chosen is one that is likely to result from a single exposure.

If a specific additional study is required to refine an ARfD, this should be chosen after reviewing the available data to identify the most sensitive acute end-point of relevance to humans, in the most sensitive species.

CONCLUSIONS

1. The setting of an ARfD should be considered for all pesticides, though in many instances it will be unnecessary to set one. If a pesticide is not acutely toxic and an ARfD is considered unnecessary, the reasons supporting this conclusion must be described in detail.

2. The entire toxicity database should be considered in determining the most appropriate species and end-point for deriving an ARfD. The critical end-point should be one that is relevant to a single exposure in humans.

3. Available data might be insufficient to set an accurate ARfD. This must be clearly indicated for the benefit of risk managers who might or might not require further refinement.

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[1] http://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scp_out14_en.pdf

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