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SCIENTIFIC COMMITTEE ON PLANTS **SCP/GUIDE-ARFD/002-Final**

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON THE DRAFT GUIDANCE DOCUMENT FOR THE SETTING OF AN ACUTE REFERENCE DOSE (ARFD)

(Opinion adopted by the Scientific Committee on Plants, 18 July 2002)

A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON THE DRAFT GUIDANCE DOCUMENT FOR THE SETTING OF AN ACUTE REFERENCE DOSE (ARFD)
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B. TERMS OF REFERENCE

In collaboration with Member State experts, the Commission has prepared a draft Guidance Documents on ARfD setting. The document is intended to facilitate the review and decision-making concerning inclusion of active substances in Annex I of Council Directive 91/414/EEC.

The Scientific Committee on Plants (SCP) is requested to provide an opinion on the consolidated document.

C. OPINION OF THE COMMITTEE

The Committee is of the opinion that in the Guidance Document a clear distinction should be made between the introductory remarks, the hazard identification process, and the actual recommendations for setting the ARfD, in order to avoid confusion and unnecessary duplications. The general philosophy of the Community harmonised approach for setting ARfD should be clearly spelled out.

The Committee recommends that the ARfD should be clearly defined on a one-day time frame and that its establishment should not be driven by considerations of the likely dietary intake.

The Committee reaffirms its previous position on the need to consider the establishment of an ARfD for all PPPs and that when this is considered unnecessary the justifications for this should be clearly stated. Moreover, the Committee would like to see clarification and specifications of the alerts which would trigger the setting of an ARfD.

The Committee agrees with the concept that the current toxicological data package might lead to the setting of a "conservative" ARfD and supports a stepwise approach providing for additional studies. Such studies would address the appropriate end-point(s) at the appropriate time-point(s) to refine the ARfD and should only be performed if the estimated acute intake is higher than the proposed ARfD.

The Committee is of the opinion that no single test guideline, as that reported in Annex 1 of the draft guidance document, should be provided for studies aimed at refining an ARfD. The Committee noted that the proposed test guideline for a single dose study might result in it not being flexible enough to provide a good understanding and characterisation of the relevant effect, while requiring the measurement of a number of end-points which might not be so relevant. In conclusion, dosing regimen, endpoints and timing will have to be chosen on a case-by-case basis, depending on the toxicological profile of the PPP under consideration.

The Committee agrees with the concept that only one ARfD should be derived to cover all sub-population groups. The Committee recognises that the setting of two different ARfDs might be sometimes toxicologically justifiable but would pose risk management and risk communication problems.

The Committee believes that the possibility for deviation from the default assessment factors should always be considered when toxicokinetic and toxicodynamic (e.g. mechanistic) data support it.

Human data are most useful because they provide reassurance on the extrapolation process. However, the Committee noted that, apart from ethical issues, studies conducted in humans may have limitations (e.g. reduced number of subjects, the use of only one sex, the possibility of studying only selected end-points). The Committee stresses that human data should be used in the context of the entire toxicological profile of the PPP under consideration.

The Committee recommends a decision tree to be included in the technical guidance document to facilitate understanding and application of the step-wise approach.

The Committee is also aware that WHO will convene shortly a Working Group on ARfD with participants from different institutions world-wide. This group will make an assessment of what has been done so far by different regulatory bodies or committees and address issues which include those discussed in the Guidance Draft Document and in this opinion. The Committee suggests that a definitive Guidance Document be issued after consideration of the outcome of the WHO working group.

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[1] OJ No L 230, 19.8.1991,p.1.

Source documents made available to the Committee:

1. Draft Guidance document for the setting of an Acute Reference Dose (ARfD) 7199/VI/99 rev. 5 date 5 July 2001

2. Terms of reference to the Scientific Committee on Plants, submitted by DG health and Consumer Protection, 9 July 2001 (SCP/GUIDE-ARfD/001).

D. SCIENTIFIC BACKGROUND ON WHICH THE OPINION WAS BASED

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The major issues identified by the Committee in the context of setting an ARfD will be discussed below. More specific comments and minor issues will be dealt with at the end of the document.

I. General comments

1. Overall editorial structure

The overall editorial structure of the document is somewhat confusing and should be refined. A clear distinction should be made between the introductory remarks, the hazard identification process, and the actual recommendations for setting the ARfD, with the intent to avoid confusion and unnecessary duplications. Specific suggestions for changes to individual chapters are reported at the end.

2. Definition of ARfD

A clear definition of ARfD is missing in the draft guidance document. Rather, reference is made to the FAO/WHO (1998) definition of ARfD, which seems to be implicitly accepted by the Commission (point 1.3). A definition of ARfD should be clearly stated in the introductory Chapter, defining a reference time frame of one-day intake (see also Specific comments). The definition of ARfD is relevant to both the way intake of residues is calculated and how the animal dosing is performed. The Committee noted that intake is generally assessed on a per day basis, without subdivision into single meals. A worst case exposure scenario would then be to assume that the daily intake occurs in a single meal. Therefore, the most appropriate animal dosing appears to be gavage, in particular when effects are C_{max}[2]-dependent and reversible (e.g. inhibition of acetylcholinesterase by carbamates). However, there may be instances where other means of dosing (e.g. dietary exposure in dogs) are adequate as well.

[2] peak blood concentration

The SCP also recognises that there might be specific cases in which repeated high intakes within a few days might lead to cumulative toxicity, if the compound is persistent or the effects are irreversible or slowly reversible. These cases would not be covered by the ARfD, as previously defined (one-day). In such cases, it is recommended that a careful evaluation of the probability of such intakes be made, in order to assess whether toxicological limits other than the defined ARfD are needed.

3. When setting an ARfD (section 4 of document).

As already stated in its previous opinion (SCP, 2000), the Committee believes that the setting of an ARfD should always be considered for all plant protection products. However this will be unnecessary in many cases, because the compound would not elicit effects relevant to a single one-day intake. In these cases, the arguments supporting this conclusion must be described in detail.

The Committee agrees with the idea that, in principle, certain PPPs might not require an ARfD when their use will not lead to residues in food. The most obvious examples are the rodenticides and soil fumigants.

The Committee also recommends that the ARfD should be established as a toxicological benchmark (health-hazard limit) to be used in the context of the risk assessment process, which is in principle independent of the exposure scenarios and specific PPPs. Therefore, setting of the ARfD should not be driven by considerations of the likely dietary exposure pattern, but should only be based on toxicological considerations.

4. Refinement of ARfD

The Committee agrees with the concept that the current toxicological data package does not provide a study specifically designed for setting an ARfD. This fact might lead to the setting of an ARfD on the basis of conservative assumptions (i.e. the numerical value will probably be lower than what could be obtained by an appropriate study). However, taking animal welfare and other considerations into account, the Committee strongly supports the concept of a stepwise approach. This would only require additional studies to be performed, addressing the appropriate end-point(s) at the appropriate time-point(s) to refine the ARfD, if the estimated acute intake is higher than the ARfD set on the basis of the available database.

The Committee is of the opinion that no single test guideline, as that reported in Annex 1 of the draft guidance document, should be provided for studies aimed at refining an ARfD; dosing regimen, endpoints and timing will have to be chosen on a case-by-case basis, depending on the toxicological profile of the PPP under consideration.

5. Different population sub-groups and the setting of different ARfD

The Committee agrees with the concept that only one ARfD should be derived to cover all sub-population groups. It was noted that an ARfD might be based e.g. on developmental end-points which could not be relevant to population sub-groups other than pregnant animals/women.[3] However, the Committee recognises that, while it is

[3] In particular, this occurred with dinocap for which the 1998 JMPR established an ARfD based on developmental effects. However, the estimated acute intake for children exceeded that ARfD. On these

toxicologically justifiable, the setting of two different ARfDs would pose risk management and risk communication problems.

6. Assessment factors

The Committee believes that the possibility for deviation from the default assessment factors should always be considered when toxicokinetic and toxicodynamic (e.g. mechanistic) data support it (IPCS 2001).

7. Use of human data (re 2.10, 2.33, 2.34, 2.35)

This issue refers mainly, although not exclusively, to single or short-term exposures. Human data are most useful because they provide reassurance on the extrapolation process. However, the Committee noted that, apart from ethical issues, studies conducted in humans may have limitations (e.g. reduced number of subjects, the use of only one sex, the possibility of studying only selected end-points). The Committee stresses that human data should be used in the context of the entire toxicological profile of the PPP under consideration.

II. Specific Comments:

Specific comments on individual chapters are reported below (the numbers refer to those in the draft document):

Foreword
Re, p 2 §4 last sentence (disclaimer on risk assessment): this statement is in principle acceptable. However, the Committee believes that the establishment of the ARfD necessarily implies considerations of the regulatory (risk assessment) framework.

Last part of Foreword (three bullets): The Committee assumes that this section refers to the SCPH (Standing Committee on Plant Health) and not to the SCP.

Chapter 1 Introduction
There is some confusion between background quotations and recommendations actually endorsed by the Commission. Chapter 1 should only provide relevant historical reference, and the definition of ARfD.

Re 1.1:Last line. The words "over a long period of time" are vague and may be misleading.

Re 1.2: The Committee agrees that the ARfD should be considered for all compounds, and noted that what is stated in this paragraph is in contradiction with the recommendations provided in par. 4.6 of the draft guidance document (see also comments on 4.6, and General comment 7.). The paragraph is unclear and requires an improvement in wording.

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bases, the 2000 JMPR established an ARfD for the general population, other than women of child-bearing age, as based on non-developmental end-points which was higher than the previously established one. The latter will be applied only to women of childbearing age (FAO/WHO, 1998, 2000).

Re 1.3: It is not clear whether the Commission endorses the definition given by a FAO/WHO consultation. In addition, this definition includes a vague time span. Should the Commission adopt this definition, the Committee believes that the establishment of a clear time frame (one day) would be more appropriate for risk assessment (see also General comment 2.)

Re 1.4: Confusion between recommendations of the Commission and FAO/WHO suggestions still remains. At the end of *ii* "following repeated dosing" should be added.

Chapter 2 Hazard characterisation

Re 2.5: The Committee suggests that the ARfD be based on the critical effect that is relevant to one single-day intake. This would be consistent with the definition of ARfD as given in General comment 2. (see also above comment Re 1.3).

Re 2.10 (and Re 2.35): See General comment 8. Last sentence of 2.10 should be removed (it is unclear how "the ethical status of human studies" could be "established"); the Committee also believes that all available human studies always deserve consideration.

Re 2.14: Last sentence seems too general and could be omitted – it seems to refer to the "model" of the studies, while in the previous sentence the limitation seems to be on the way studies are performed.

Re 2.15: Omit "in future" and link the paragraph to par. 2.14

Re 2.16: The conclusion is too negative. The Committee recommends softening it to give a more supportive comment on the applicability of these studies.

Re 2.17: The Committee underlines that the information provided by short-term studies is relevant to the ARfD and, in certain cases, consideration ought to be given also to studies not complying with OECD guidelines (e.g. max. dose studies, preliminary studies).

Re 2.21: Last sentence: it is not clear whether the limited number of endpoints refers to the genotoxic or to the non-genotoxic end-points, or both. The Committee recommends that this be clarified.

Re 2.23: The Committee recommends this paragraph be rewritten to remove the ambiguity. (word "especially" to be deleted).

Re 2.26: 1st sentence: modify according to new OECD guidelines (treatment up to 20 days) 3rd sentence, second part of the sentence needs to be clarified ("this is usually justified by standard studies").

Re 2.27: (See also General comment 4.). Although pregnant animals are a specific population, findings in these animals might drive the ARfD which is really applied to all population. For clarity, the Committee recommends to merge 2.27 and 2.28.

Re 2.29: For clarity the Committee recommends this paragraph be put under the heading "Neurotoxicity studies" subheading "Delayed neurotoxiciy studies" (incidentally the 2

headings have the same number). The delayed polyneuropathy is not the acute critical effects for any pesticides.

Re 2.31: The wording of this paragraph wrongly implies that neurotoxicity studies should also be performed with non-neurotoxic compounds.

Re 2.34: (See also General comment 8.). The questionable quality of older data applies also to certain animal studies.

Chapter 3 Extrapolation from toxicity data to an ARfD

Re 3.1 and 3.2: The Committee recognises that the 2 options exist (single vs. multiple gavage administrations). However, the Committee is not aware of examples where, in the case of acute effects, the administration of the dose as a single gavage would cause less severe affects than the administration of the same dose subdivided in more than one gavage. Consequently, administration of the dose in a single gavage would be the worst case. The only exception would be in the case of saturation of absorption at the NOAEL[4] for the relevant effect: in such a case subdivision of the dose might be necessary. In addition there might be technical reasons for dose subdivision (e.g. problems of solubility)**.**

Re 3.3 to 3.5: These 3 paragraphs should be combined with 3.1 and 3.2, since they discuss the same issues (gavage vs. diet, single shot vs multiple shots)

Re 3.4: The Committee is not aware of examples demonstrating a higher effect of dose fractionation of organophosphates. A referenced example must be included, otherwise the sentence should be deleted.

Re 3.5: The reasoning of the first sentence has some value, but it may not be always true.

Re 3.6 and 3.7: The Committee notes that the 2 paragraphs do not include a mention that the effect considered should be relevant for human as already indicated in 2.9 (amend: "most sensitive relevant species")

Re 3.7: The Committee considers that this paragraph is unclear and needs to be rewritten (e.g. what does "specific ARfD" mean?).

Re 3.8 – 3.9: See above section 4 Refinement of of ARfD

Re. 3.12: The Committee notes that the sentence reports default values for toxicokinetics and toxicodynamics of respectively 2.5 and 4, whereas in paragraph 3.16, Renwick's data provide for the reverse. The Committee is of the opinion that the guidance document should be more explicit in stating that, when compound-specific and validated data are available, these could be used to replace the assessment factor for toxicokinetics and toxicodynamics (to account for interspecies as well as intraspecies differences).

Re. 3.13: The emphasis on PBPK modelling should be removed, in favour of strong specific data. The Committee agrees that there might be cases where it is possible to

[4] No Observed Adverse Effect Level

deviate from the standard default value (assessment factor of 100) but in these cases, detailed case-by-case justification should be provided.

Chapter 4 Recommended determination of the ARfD.

This Chapter should clearly state the procedure for setting an ARfD (what should be done and how, e.g. for the selection of NOAEL, the choice of the assessment factors, etc.). The Committee noted that some of these recommendations are anticipated in the previous chapters. For the sake of clarity, it is essential to avoid duplications in different chapters, when setting criteria. The inclusion of a decision tree in Chapter 4 would help the understanding of the recommended procedure for ARfD setting.

Re 4.1: The Committee is of the opinion that, as a default approach, setting of an ARfD should be always considered for all plant protection products (see also General comments 3. and 7.).

Re 4.3: The Committee suggests to delete the last 2 sentences.

Re 4.4: The Committee would like to see clarification to identify and specify the alerts (some alerts are mentioned in the introduction, without making clear whether or not they are endorsed by the Commission).

Re 4.6: The Committee notes that use patterns of PPPs may change with time, and therefore recommends not to use data showing no residues in food /feed as an argued reason for not setting an ARfD. For uses of PPPs on non food/ feed commodities see general comment 3. With reference to the 4th bullet of the draft, it is not clear why an ARfD should not be allocated because of a large gap between its value and the estimated intake.

Re "*ii Determination of a specific ARfD*": The Committee wonders why "specific" – it seems to imply that there are unspecific ARfD.

Re 4.8: see above "specific ARfD". The Committee believes that the ARfD should be set in the case of acute hazard (without considerations on exposure), and wonders why the document considers cases where short-term intakes above the ADI[5] are likely (see also General comment 2.). The word "acute" should replace "short-term" when referring to intake.

Re 4.10 & 4.11: The word "one day" should replace "short-term" when referring to intake.

Re 4.12: The Committee considers that this recommendation should be removed, since the technical guidance document is addressed to the experts who set (or assess) the ARfD, not to the people who may raise the need of an OECD protocol.

Re 4.17: The Committee does not agree with the suggested wording. The scenario described in these paragraphs, does not have to be treated as a separate entity.

[5] Acceptable Daily Intake

The points 4.14 to 4.17 should be deleted.

Chapter 5. Summary and overall conclusion

The Committee feels that the summary and the conclusions need to be modified according to the suggested amendments.

Re 5.1 and Re 5.2: The Committee disagrees (see above).

Re 5.3: Ethical considerations and usefulness of human data are independent concepts. This sentence should be better formulated.

Re 5.4: The Committee notes that this paragraph clearly states (for the first time in the document) the overall philosophy that drives the guidance document. It is recommended that this paragraph be placed at the beginning of the Guidance document. The wording should be more accurate and not in contradiction with other sentences.

Re 5.5: The possibility also exists of deriving the ARfD from "not appropriate studies", but different from that (those) used to set the ADI .

Re Appendix 1

See section above.

III. Conclusion of the Committee

The Committee is of the opinion that in the Guidance Document a clear distinction should be made between the introductory remarks, the hazard identification process, and the actual recommendations for setting the ARfD, in order to avoid confusion and unnecessary duplications. The general philosophy of the Community harmonised approach for setting ARfD should be clearly spelled out.

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E. REFERENCES

FAO/WHO (1998). Report of the 1998 Joint Meeting on Pesticide Residues. FAO, Rome, Italy.

FAO/WHO (2000). Report of the 2000 Joint Meeting on Pesticide Residues. FAO, Rome, Italy.

IPCS (2001) Guidance document for the use of data in development of chemical-specific adjustment factors for interspecies difference and human variability. Available on line at http://www.ipcsharmonize.org/CSAFsummary.htm.

SCP, (2000): 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 (SCP/RESI/074-Final
http://europa.eu.int/comm/food/fs/sc/scp/out02_ppp_en.html

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