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

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON COMMISSION DRAFT GUIDANCE DOCUMENT ON THE SETTING OF ACCEPTABLE OPERATOR EXPOSURE LEVELS (AOEL) (Doc. SANCO/7531/VI/95-rev 6 dated 10 September 2001)

(Opinion adopted by the Scientific Committee on Plants on 23 October 2002)

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A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON COMMISSION DRAFT GUIDANCE DOCUMENT ON GUIDANCE FOR THE SETTING OF ACCEPTABLE OPERATOR EXPOSURE LEVELS (AOELS)
(Doc. SANCO/7531/VI/95-rev6 dated 10 September 2001)
Opinion adopted by the Scientific Committee on Plants on 23 October 2002.

B. TERMS OF REFERENCE

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

C. OPINION OF THE COMMITTEE

Opinion

The SCP agrees with the general principles and structure of the draft guidance document, however, when the document deals with consolidated toxicological and risk assessment principles, it recommends wording consistency with other related documents of the Commission.
The SCP recommends to the Commission to reconsider the concept of bystander, its appropriate exposure scenarios and the adequacy of applying the AOEL to this sub-population.
The SCP substantially agrees with the approach taken on the assessment factors. The SCP is of the opinion that human data are most useful because they provide reassurance on the extrapolation process; however, apart from ethical issues, it is stressed that human data should be used in the context of the entire toxicological profile of the PPP under consideration. This also applies to human data obtained from monitoring operators and re-entry workers.
The SCP is of the opinion that a biological threshold of toxicity is always likely to exist even though we are unable to identify it. For genotoxic carcinogens the absence of threshold is a default assumption taken as a precaution in the absence of experimental evidence of a threshold.
The SCP recommends that the concept of margin of safety be clearly defined in the context of the document.
The SCP notes that the AOEL is protective for any one-day exposure. High exposures occurring within few minutes (which might be relevant for Cmax-dependent effects) can only occur as accidental conditions. As such these are not covered by operator exposure modelling under Good Agricultural Practice. Consequently the SCP does not see the need for having an acute AOEL.

A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON COMMISSION DRAFT GUIDANCE DOCUMENT ON GUIDANCE FOR THE SETTING OF ACCEPTABLE OPERATOR EXPOSURE LEVELS (AOELS)
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B. TABLE OF CONTENTS

C. BACKGROUND

In collaboration with experts from all Member States and the European Crop Protection Association (ECPA), the Commission has prepared a draft Guidance Documents on the Setting of Acceptable Operator Exposure Levels (AOELs). It has been largely based on the documents "Recommended method for the establishment of acceptable operator exposure levels (AOELs)" and "Criteria to establish health-based occupational exposure limits for pesticides". These documents have resulted from a research project sponsored by the European Commission to develop a harmonised procedure to set AOELs within the European Union (see EU Project Group, 2000).

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.

Source documents made available to the SCP:

1. Draft Guidance document for the setting of Acceptable Operator Exposure Level (AOEL): Terms of Reference, submitted by DG Health and Consumer Protection, 1 October 2001 (SCP/GUIDE-AOEL/001).

2. Draft Guidance document for the setting of Acceptable Operator Exposure Level (AOEL): Consolidation of Member States' (DK, FI, FR, NL, PT, SW, UK) and ECPA comments, submitted by DG Health and Consumer Protection, 1 October 2001, consolidated by the secretariat (SCP/GUIDE-AOEL/003)

Opinion

The SCP agrees with the general principles and structure of the draft guidance document, however, when the document deals with consolidated toxicological and risk assessment principles, it recommends wording consistency with other related documents of the Commission.
The SCP recommends to the Commission to reconsider the concept of bystander, its appropriate exposure scenarios and the adequacy of applying the AOEL to this sub-population.
The SCP substantially agrees with the approach taken on the assessment factors.
The SCP is of the opinion that human data are most useful because they provide reassurance on the extrapolation process; however, apart from ethical issues, it is stressed that human data should be used in the context of the entire toxicological profile of the PPP under consideration. This also applies to human data obtained from monitoring operators and re-entry workers.
The SCP is of the opinion that a biological threshold of toxicity is always likely to exist even though we are unable to identify it. For genotoxic carcinogens the absence of threshold is a default assumption taken as a precaution in the absence of experimental evidence of a threshold.
The SCP recommends that the concept of margin of safety be clearly defined in the context of the document.
The SCP notes that the AOEL is protective for any one-day exposure. High exposures occurring within few minutes (which might be relevant for Cmax-dependent effects) can only occur as accidental conditions. As such these are not covered by operator exposure modelling under Good Agricultural Practice. Consequently the SCP does not see the need for having an acute AOEL.

I. General comments

The SCP agrees with the general principles and structure of the draft guidance document. However, in several instances the document describes consolidated toxicological and risk assessment principles (e.g.: 2.3, 2.4, 2.6, 2.8, 4.1, 4.2, 4.3, 4.10, 4.13, 4.16). It is recommended to assure consistency with other related documents of the Commission.

The concept of AOEL has been developed to assess the acceptability of operator exposure to PPPs. As such, this can be applied also to another selected sub-group such as that represented by the re-entry workers. On the other hand, the SCP noted that there appears to be no clear definition of bystander. In addition, specific criteria to assess or estimate bystander exposure have not yet been developed. The SCP is of the opinion that a difference should be made between a subject who is at risk of being exposed during the application of the PPP because he is occasionally in the proximity of the field and a subject who lives or works near the field being treated. The first case should be considered under the Good Agricultural Practice principles (i.e.: no one should be present during field application of PPP, if not involved with the work) and, therefore be avoided with proper risk management procedures. For those who will "inevitably" be near the field (f.i. rural area dwellers), the AOEL could, in principle, be applied, although it should be noted that such bystanders include individuals from the general population and not a selected sub-group such as the operators. In conclusion the SCP recommends to the

Commission to reconsider the concept of bystander, their appropriate exposure scenarios and the adequacy of applying the AOEL to this sub-population.

The SCP substantially agrees with the approach taken on the assessment factors and notes that this subject has also been addressed in the Guidance Document on Acute Reference Dose. Assessment factors are used to take into account our lack of knowledge and/or uncertainties. The standard assessment factor of 100 is conventionally made up of 10 for animal-to-human (2.5 for toxicokinetic and 4.0 for toxicodynamic) and 10 for intra-human (3.16 for both toxicokinetic and toxicodynamic) variability (Renwick …). Mechanistic and/or kinetic data may allow the reduction of this factor, although rules to determine the extent of the reduction are not available.

The SCP is of the opinion that a biological threshold is always likely to exist even though we are unable to identify it. Therefore, the absence of threshold for genotoxic carcinogens is a default assumption, taken as a precaution in the absence of experimental evidence of a threshold, and it is not an experimentally proven finding. Therefore, modification of wording on this issue is recommended (e.g. paragraph 2.7).

II. Specific comments

II.1 Chapter 1 Introduction

1.1. Reference to the guidance document on micro-organisms might be given.

1.2. The last two sentences might be omitted here since the issue is discussed in detail below (chapter 4).

1.3 –1.4. Regarding the bystander see the general comments above.

1.5. The second sentence is unclear. An additive effect should be expected in the presence of exposure to more than one active ingredient when they have a common mechanism of action or the same target organ. In this case the sum of the ratios

$$\frac{\text{Exposure estimate}}{\text{AOEL}}$$

calculated for each active ingredient should be less than 1. Therefore, as correctly stated no “formulation specific AOEL” is required.

II.2 Chapter 2 Hazard Characterisation

Chapter 2 can be shortened and simplified, and repetitions avoided.

2.4. It is suggested that in the second sentence the reference to the statistical significance be softened. Biological significance even in the absence of statistical significance might be taken into account.

2.9. Human data are most useful because they provide reassurance on the extrapolation process. However, the SCP 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 SCP stresses that

human data should be used in the context of the entire toxicological profile of the PPP under consideration (see also the opinion on the draft guidance document on Acute Reference Dose). This also applies to human data obtained from monitoring operators and re-entry workers.

II.3 Chapter 3 Extrapolation issues

3.2., 3.3. and 3.4. The issue of the assessment factors is also addressed in the guidance document on Acute Reference Dose. Consistency is recommended. (See also the opinion on draft guidance document on Acute Reference Dose). Among the key factors indicated at point 3.4. exposure duration extrapolation and dependence of effects from peak concentration or area-under-the curve might also be taken into consideration.

3.8. The SCP recommends that the concept of margin of safety be clearly defined in this paragraph or in the document. Reference can be made to the opinion on iprovalicarb. The SCP is of the opinion that the usual assessment factor of 100 is acceptable in the presence of an adequate toxicological database. Additional factors on the basis of the characteristics of the effect are justified in the presence of severe effects where the NOAEL is close to the LOAEL. This would apply to all severe irreversible effects and not only to teratogenicity and cancerogenicity.

3.10. The SCP is of the opinion that issues such as animal welfare should be taken into account. Consequently, when the AOEL is based on a LOAEL with the use of additional assessment factor and comparison with estimated or measured exposure is reassuring, additional studies should be avoided.

3.11. The same comment as above applies to the request for additional studies (5^{th} line of the paragraph).

3.12. Time and route of exposure issues would be better discussed separately.

3.13. The SCP agrees with what is expressed in this paragraph and encourages any effort in the direction suggested.

3.15-3.17. The SCP is of the opinion that these paragraphs could benefit from an expansion with more details, as for example given in the EU FAIR document (FAIR, 2000). Incidentally, the SCP notes that many substances are “activated” in the liver, not necessarily inactivated (3.16).

II.4 Chapter 4 Recommended method for setting an AOEL

4.3. The reference to human data does not seem to be necessary, since they are discussed elsewhere.

4.4. The SCP strongly supports the idea of setting a single AOEL. However, it seems unlikely that targets or critical effects differ according to exposure period. Rather, NOAELs for the same effect may differ. This might be taken into account in specific instances.

4.5. See the guidance document on Dermal Absorption and the SCP's opinion on it.

4.6. Last sentence, see comments to point 3.8.

4.9. In general this paragraph deals with established criteria. Consistency in wording with other guidance documents is recommended.

4.14. The SCP notes that the AOEL is meant to be protective for any one-day working exposure. High exposures occurring within few minutes (which might be relevant for Cmax-dependent effects) can only occur as accidental conditions. As such these are not covered by operator exposure modelling under GAP. The SCP also notes that operator exposure is estimated or calculated on a single day work, as representative of every repeated daily exposure. Consequently the SCP does not see the need for having an acute AOEL

4.18. It should be stressed that differences in metabolism do not necessarily mean differences in toxicity. Moreover, attention to qualitative rather than quantitative differences in metabolism should be given. Inhalation should also be considered.

4.19. For sake of consistency, reference to the Guidance Document on dermal absorption is recommended.

4.22. The SCP noted that the AOEL is an occupational exposure limit. Therefore, the SCP is of the opinion that compounds causing the effects described in this paragraph should also be considered within the scope of the document. In fact, a No Observed Adverse Effect Concentration derived from experimental studies can be used to establish an acceptable exposure concentration. This can be then compared against the concentrations in air that are measured in the field or estimated by exposure models.

II.5 Chapter 5 Summary and conclusion

The opinions of the SCP on the contents of Chapter 5 have been already discussed above.

D. REFERENCES

No further documentation was used.

Acknowledgements

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Toxicology: Prof. M. Maroni (Chairman) and Committee Members: Dr. MP. Delcour-Firquet, Prof. A. Leszkowicz, Dr. O. Meyer, Dr. A. Moretto, Prof. E. Petzinger, Prof. K. Savolainen, Prof. A. Silva Fernandes, Dr. G. Speijers, and invited experts, Prof. CL. Galli, Dr. D. McGregor.