Opinion of the Scientific Committee on Plants regarding the Draft guidance document on relevant metabolites (Document SANCO/221/2000-Rev.2 of October 1999) (opinion adopted by the Scientific Committee on Plants on 30 November 2000)

1. TITLE

Opinion of the Scientific Committee on Plants regarding the DRAFT GUIDANCE DOCUMENT ON RELEVANT METABOLITES (Document SANCO/221/2000-Rev.2 of October 1999)

(Opinion adopted by the Scientific Committee on Plants on 30 November 2000)

2. TERMS OF REFERENCE

The draft guidance document on relevant metabolites, together with comments from seven Member States and from ECPA [1] , has been referred by the Commission to the Scientific Committee on Plants (SCP) without specific questions but with a request for an overall assessment of the document.

3. BACKGROUND

The current legislation (Directive 91/414/EEC [2] and its annexes) provides a common framework for all Member States for the authorisation of plant protection products (PPPs). It distinguishes between:

- the evaluation and authorisation of PPP's at Member State level, including setting the specific conditions of use and appropriate risk mitigation measures. Data requirements and decision-making criteria are harmonised and laid down in Annexes III and VI, respectively;

- the joint evaluation of an active substance (including metabolites, degradation or reaction products which are " *relevant"* or, respectively, " *of significance from the toxicological, ecotoxicological or environmental point of view"*) by Member States, culminating in a Community Decision on whether the active substance should be included in Annex I to Directive 91/414/EEC (i.e., the list of active substances which are authorised for incorporation in PPPs). For the evaluation at EU level (which is where the SCP provides advice to the Commission), the Directive provides for common data requirements (Annex II) and evaluation principles.

Hence, it is required both at Member State and at Community level to distinguish between metabolites, which are relevant and/or of significance from the toxicological, ecotoxicological or environmental point of view and those which are not. Only for relevant/significant metabolites is it required to perform an evaluation (which may require specific studies) and to apply the Uniform Principles as established in Annex VI to Directive 91/414/EEC for decision-making. However, the Directive does not define when a given metabolite should be considered relevant/significant. This absence of guidance causes considerable difficulties in

the evaluation and decision-making process. Therefore, the "draft Guidance Document on Relevant Metabolites" has been developed as a working document by the Commission, with the purpose to provide such guidance to Member States and notifiers.

Hereafter, the Committee discusses general aspects of the draft guidance document (in section 4.1) and provides detailed comments on some of the sections of the document (in section 4.2) and on the figures of the document (in section 4.3). Section 5 provides a summary of the conclusions.

4. OPINION

4.1 Principles of the document

The authors of the guidance document appear to have followed a number of basic principles, which are briefly summarised below together with the stated views of the SCP:

1. Interpretation of different wording of the Directive 91/414/EEC and its annexes: 'the terms 'relevant metabolites' and 'metabolites of toxicological, ecotoxicological and/or environmental significance' are interpreted as synonyms in the guidance document, i.e. 'relevant' can be translated as 'being of toxicological, ecotoxicological and/or environmental significance'.

The SCP supports this view. It should be clarified, however, that the draft guidance document is intended to cover not only metabolites but also any other breakdown or reaction product (terms which are mentioned in the same context in the annexes of the Directive). In this opinion, the SCP also uses the term metabolite to apply to any transformation product occurring in fate and/or metabolism studies, irrespective of the mechanism by which it is produced (biotic, abiotic).

2. Metabolites have only to be evaluated and assessed for those compartments where they occur as a direct or indirect consequence of the intended use, and for those non-target organisms which may be exposed.

The SCP supports this view but wishes to emphasise that all the possible routes of exposure should be considered. For example, metabolites occurring only in soil fate studies may well require an assessment with regard to aquatic relevance where they can be expected to be transported into surface water (e.g., by runoff, drain flow or leaching from treated fields; see FOCUS [3] reports for modelling transport to groundwater [4]) . Therefore, definition 6 in section 3 of the document is considered to be too restrictive, as it defines the compartment of concern solely as the compartment where a metabolite occurs in a fate study, thus disregarding transport into other compartments. The draft guidance document should be clarified accordingly. Transport via air should be included as soon as the assessment scheme currently under development by EPPO [5] /CoE [6] is available.

3. The document proposes a stepwise procedure to decide on the relevance of a given metabolite. A set of criteria and definitions are used to describe the different tiers (see summary of tiered approach in section 4.2 of this opinion, in the comments on useful definitions).

The SCP acknowledges the effort to limit testing of metabolites to the minimum necessary and agrees with the second tier of the criteria (see section 5 items a) and b) and section 6 items a) and b) of the draft guidance document). The SCP disagrees with the rigid use of the 10% trigger value (tier 1) and recommends amendments/clarifications to other (tier 3) criteria like the proposed toxicological and ecotoxicological tests (see below, comments on the respective sections).

4. Once a metabolite is identified as relevant, the evaluation and risk assessment must follow the same rules (e.g., apply the same trigger values and TER's [7]) as for the active substance, as provided for in Annexes II and VI of Directive 91/414/EEC.

The SCP supports this view since there is no scientific reason to use different criteria when performing risk assessments for active substances, metabolites, or formulated plant protection products (all of which are chemical substances or mixtures thereof to be intentionally applied to the environment). As indicated above, there are practical limitations to testing all metabolites, and a selection should be made of those considered potentially "relevant". However, the SCP considers some of the set of toxicological and ecotoxicological tests which are proposed in the draft guidance document for the assessment of metabolites to be insufficient to allow an adequate risk assessment (see specific comments and proposals further down in this opinion).

5. For the assessment of toxicological and ecotoxicological relevance, the draft guidance document proposes hazard-based approaches first (fixed limit values of toxicity), which are followed by risk-based assessment steps.

The SCP is of the opinion that exposure estimates (however crude or conservative) should be possible in all cases, and therefore risk-based approaches be equally possible and preferable.

4.2 Comments on individual sections of the document

re: 1. of the draft guidance document "Introduction"

The introduction refers to the other three guidance documents [8] , but the relation between the one under consideration and the other three remains unclear. While it is stated that this guidance document does not provide the full details of a metabolite assessment, it does so in fairly great detail for toxicology, soil ecotoxicology and aquatic ecotoxicology, which includes the potential for groundwater to become surface water. For surface water, a separate section (8) is provided which refers to the Guidance Document on Aquatic Ecotoxicology. However, it appears that the approaches taken for metabolites in the Aquatic Guidance Document and in this document differ. Furthermore, there is no cross-reference between the Terrestrial Guidance document and the section 7.3 dealing with soil ecotoxicology. This last comment applies to Figure 1 of the document as well (see below).

re 3. of the draft guidance document "Useful definitions"

The document proposes a stepwise procedure to decide on the relevance of a given metabolite. A set of definitions is used to describe the state on each step.

Summary of tiered approach in the draft guidance document:

1. major or minor metabolite? (TIER 1)
major metabolite: ³ 10% at any time of a degradation/metabolism study; è 2
minor metabolite: < 10% at any time of a degradation/metabolism study è 4

2. if major metabolite, or minor one with reason for concern, then check criteria a) or b) in sections 5 and 6 (TIER 2). If at least one of those is met, the metabolite is non-relevant.
If none of those are met è potentially relevant è 3

3. criteria in section 7 (TIER 3): pesticidal activity; toxicology; aquatic ecotoxicology; soil ecotoxicology; surface water (reference only to aquatic ecotox guidance document)
If all criteria are met è non-relevant
If one or more are not met è relevant è to be assessed as the active substance (includes applying the 0.1 mg/l criterion for groundwater)

4. if there are reasons for concern for minor metabolites è potentially relevant; è 2

The authors state in section 4 that the trigger value of 10% is an arbitrary value. The SCP is aware that this value was derived taking into account practical considerations, like standard laboratory practice at that time and detection limits for unlabelled substances in field trials, rather than for the needs of the risk assessment. In the experience of the SCP, metabolites where they have been tested, have often been found to be less toxic than the parent substance. However, there are no reliable rules to identify with confidence which metabolites would be more toxic than the parent substance. Hence, the 10% trigger should only be used as a pragmatic screening criterion [9] , above which further testing and assessment would be more or less automatically required. For metabolites below the trigger, the notifiers should at least be required to justify the absence of further testing and assessment. Therefore, in the view of the SCP, all metabolites have to be considered as potentially relevant until a further assessment (testing and/or scientifically documented justification; using amended tiers 2 and 3 but not 1; see summary of tiered approach above) indicates that they are non-relevant. The distinction between 'major' and 'minor' metabolites should be abandoned. The definitions in section 3 of the draft guidance document should be amended accordingly.

The SCP is aware that this may have consequences for the conduct of fate/metabolism studies. While the SCP recognises that there are (ever changing) practical/technical limits for analytical methods and the identification of *all* metabolites occurring, the use of a single value like 10% (below which identification would not be performed) is not supported by the SCP. Metabolites should be identified as technically feasible, or down to a level which corresponds to a threshold of (eco-)toxicological concern (see below, comments on *re: 6* and on *re: 7.2*).

As mentioned above (4.1; # 2), definition 6 (*Compartment of concern*) [10] of section 3 is too restrictive. Compartments of concern are not only those where a given metabolite is produced but also those into which it may be transported by various routes.

re 4. of the draft guidance document "Identification of major metabolites"

Here, the guidance document also acknowledges that minor metabolites may also be relevant, as was stated above as the opinion of the SCP. The other parts of the document should reflect this more explicitly, with the burden of proof of non-relevance clearly being assigned to notifiers. The SCP has already commented above that the distinction between major and minor metabolites be removed.

re 5. of the draft guidance document "Soil"

The SCP supports the criteria listed in items a) and b) in this section of the guidance document. There are however inconsistencies between section 5 and the flow diagram (see below; comment on figure 2).

re 6. of the draft guidance document "Groundwater"

In this section, the value of 0.1 mg/l is mentioned as a trigger for further evaluations, as described in the following sections on pesticidal activity, toxicology and ecotoxicology. For clarification, it should be noted that this value has two roles which need to be distinguished in the discussion:

a. as a trigger for further evaluation;

b. as a decision-making criterion which requires that a metabolite which has been identified as relevant may not exceed 0.1 mg/l (Annex VI).

The SCP, in the following paragraphs, offers comments on both roles:

a) *0.1 mg/l as trigger value:*

The SCP supports in general the criteria listed in items a) and b) and the proposed assessment procedure which requires further evaluation for metabolites occurring at levels above 0.1 mg/l. However, the SCP wishes to point out that there are active substances which are ecotoxicologically active at levels well below the trigger value of 0.1 mg/l (e.g., pyrethroids, insect growth regulators, sulfonylurea herbicides). This trigger value can therefore not be regarded as a level which is generally safe to non-target organisms in surface water. In mammalian toxicology, it can be regarded as a reasonably safe trigger, although exceptions can occur. Hence, where exposure to metabolites cannot be excluded, and where there is cause for concern, e.g. for metabolites structurally very similar to active substances which exhibit effects at such low levels, further toxicological and/or ecotoxicological evaluations should also be required for metabolites occurring at levels below 0.1 mg/l. The notifier should be required to provide scientifically documented justification when no further testing is performed. Such justifications may make use of, e.g.,

- - exposure estimates for groundwater and subsequently surface water;
- - consideration of molecular structure of the metabolite (active part intact?);
- - the (eco-)toxicological profiles of the active substance and other metabolites (is there a consistent detoxification? change of sensitivity among species?);
- - the occurrence of metabolites in existing tests (e.g., long-term tests with the a.s.; see also comment under "General" at the end of section 4.2);
- - general knowledge on the relationship between the toxicity of metabolites and their parent substances; etc.

(The SCP has, to some extent, used and published similar considerations in its opinions on several active substances and on the ecotoxicological guidance documents [11]) .

Metabolites of concern as described above should also be included in the residue definition of the respective environmental compartment/matrix for monitoring purposes. The draft guidance document should be amended accordingly.

The SCP is also aware that some Member States have introduced ecotoxicological screening tests with the complete leachate, in order to assess the combined toxicity of all metabolites.

The SCP suggests that consideration be given to replacing the trigger value of 0.1 mg/l (as the entry trigger for further toxicological and ecotoxicological testing) by a trigger value which takes the distribution of the existing toxicity data into account. For example, in toxicology, a "threshold value of toxicological concern" (0.02 mg/kg bw [12] /day) has been derived by the US-FDA [13]. A similar ecotoxicological trigger, based on a certain percentile of the overall distribution, could be used to predict whether a new substance is likely to be more toxic at the estimated concentration (e.g. in the leachate).

b) ***0.1 mg/l as decision-making criterion:***

Some Member States argued in their comments that the value of 0.1 mg/l (in the sense of a cut-off value rather than as a trigger for further assessment) should consistently be applied not only to the parent (active) substance but also to all of its metabolites, regardless of their properties. As was stated in some comments, this criterion has been selected under a zero-contamination approach, regardless of the toxicological properties of the substance concerned. Other considerations may have included the extremely long-term nature of groundwater contamination: degradation and dilution processes in groundwater may take decades; and a contamination exceeding a chosen limit value is likely to have long-term consequences for the use of the groundwater resource or the use of the arable land above the aquifer. There could also be cases where a toxicological limit value must be lowered because of new toxicological data or progress of science, thus causing a groundwater reservoir to exceed the new limit value.

However the SCP observes that applying the limit value of 0.1 mg/l to all metabolites (except those mentioned in the first paragraph of Section 6 of the document) would require a re-assessment of evaluation procedures in the EU. Currently, laboratory data and modelling are used in a tiered system to decide on the necessity of lysimeter testing. Since the laboratory tests on metabolism in soil and leaching are necessarily much shorter than lysimeter studies, metabolites which occur in lysimeters may not yet be formed in the lower-tier studies. In addition, analytical methods are more powerful in the lysimeter studies. Hence, many metabolites that might eventually leach at such low levels cannot be detected in the current lower-tier studies.

The following example may serve to illustrate the order of magnitude of the occurrence necessary for such metabolites: assuming a dose of 1 kg a.s./ha, and a reasonably wet climate, the limit value of 0.1 mg/l corresponds with the leaching of one single metabolite at a level in the order of 0.01% of the applied dose. Given the complexicity both of the molecular structure of PPPs and of the soil metabolic pathways, it is likely that at least one of the many resulting metabolites would exceed this level.

Therefore, if the limit value of 0.1 mg/l is applied to all metabolites, more lysimeter testing would be necessary, and many, if not the majority, of currently used active substances would exceed (with at least one of their metabolites) the limit value.

Hence, while the likelihood, extent and duration of groundwater contamination can be assessed more or less accurately by applying the respective (current) state of the scientific knowledge, and while such assessments become increasingly sophisticated, uncertainties do remain and cannot be avoided. The same applies for effect assessments, and the more quantitative description of the remaining uncertainties is currently a very important research topic (e.g., probabilistic risk assessment approaches).

Those observations apply to both, the active substances and their metabolites. From a scientific point of view, the assessment of groundwater contamination and the possible resultant (eco)toxicological effects of active substances and of metabolites should follow the same principles. However, it is the SCP view that the final decision whether to use a risk-based criterion or an otherwise derived limit value (e.g., 0.1 mg/l) is a political one.

re 7. of the draft guidance document "Decision making on soil and groundwater metabolites"

re: 7.1 Pesticidal activity :

The definition and role of this criterion could be worded more clearly and consistently. Two aspects are mentioned in the guidance document.

In section 2 (second to last paragraph), pesticidal activity is mentioned in the context of parent substances which degrade so fast (e.g., in the spraying tank) that the metabolite is really the active chemical. In this case, the SCP recommends to amend/extend the definition of the active substance, since - at least from the environmental point of view - the substance to be assessed is not the chemical that is included in the commercial product but the "active metabolite" (for other criteria, this may not apply). The SCP supports the draft guidance document's statement that such metabolites require the same evaluation and assessment as the active substance (including the application of the uniform principles established in Annex VI to Directive 91/414/EEC).

Elsewhere, in section 7.1, pesticidal activity is discussed in a wider context. The SCP supports the wide view taken here, and the testing proposed in this section.

Section 7 (introductory paragraph) also states that metabolites with a pesticide mode of action (as defined by the testing described in 7.1) should be treated like an active substance. From figures 2 and 3 it becomes clear that this includes applying the uniform principles of Directive 91/414/EEC. The SCP supports this view.

re: 7.2 Toxicology :

The SCP considers the proposed test scheme for a risk-based toxicological assessment as insufficient. In a tiered approach, the following steps should be used:

- was the metabolite present in animal studies? If yes, can an assessment be made based on the existing data? To answer the above questions, expert judgement is needed case-by-case;

- if no, stepwise testing should be considered to determine the full toxicological profile of the metabolite or to generate enough information to allow a comparison with the toxicology profile/data of the active substance to be made. The extent of the toxicology testing should be

determined by expert judgement on a case-by-case basis. The notifier should always be required to provide justification when a full toxicological profile is not produced. Possible reasons for avoiding unnecessary testing include the use of existing information on alerting structures (SAR's [14]) , an expected exposure below the toxicological threshold of concern (that could be indicatively set at 1.5 mg/person/day or 0.02 mg/kg bw [15] /day [16]) and useful toxicological information derived from structurally related chemicals.

The section also states that a NOAEL [17] of 50 mg/kg bw/day is considered sufficient for a hazard-based approach (i.e., to rule out risk and stop testing if the value is exceeded). A justification for such a value is missing, as was noted by some Member States in their comments, and the SCP doubts whether cases exist where no exposure assessment can be made. On the contrary, the SCP is of the opinion that an exposure assessment can always be provided and the hazard-based approach should be excluded.

re: 7.3 Ecotoxicology

Water :
As stated above (Section 4.2, re: 1), the three tests proposed for water organisms appear not to be fully consistent with either the aquatic ecotoxicology guidance document or the respective SCP opinion. Acute tests are not reliable predictors of long-term toxicity, and if they were to be used for such predictions, they should be applied with larger uncertainty factors than normal. The authors were clearly aware of this since they mentioned that the proposed trigger values are " *indicative"*. The SCP agrees with this position. Considering the fact that those values are proposed to assess the relevance of metabolites reaching surface waters *via* groundwater, the SCP observes that those values can be regarded as conservative [18] , in view of the low concentrations to be expected (for metabolites entering surface waters *directly*, e.g. via runoff; the SCP assumes that the Guidance Document on Aquatic Ecotoxicology, which provides different triggers, would be followed). However, the SCP considers it a disadvantage (and unequal treatment of different substances) if - as is proposed in the draft guidance document - a decision is taken based on hazard figures alone. The SCP recommends to include exposure estimates in the assessment, and to decide on the relevance based on TER values. Such TER values should be at least the same as required for the active substance for surface water, and could be justified to be more severe due to the uncertain prediction of long-term effects by the proposed acute/short-term tests and to take account of the possible long-term nature of groundwater contamination. Hence, the hazard-based first step should be abandoned, and the assessment be carried out using a risk-based approach.

At any rate, the array of test species should be extended to include *Lemna* (or, appropriate data on herbicidal activity across several taxa), as it was proposed by several Member States. Other tests (e.g., long-term) should be required based on consideration of exposure and persistence of the metabolite. The draft guidance document should reflect such additional considerations and flexibility for the test selection.

Soil :
For soil organisms, some Member States proposed to expand the array of tests (two, in the guidance) by at least the addition of a chronic study on earthworms and possibly on soil-dwelling arthropods, as well as to consider the fate (persistence) of a given metabolite when deciding on a set of ecotoxicological tests. The SCP supports those comments and recommends that the guidance document be revised accordingly.

As for water organisms, the SCP recommends to include exposure estimates in the assessment, and to decide on the relevance of metabolites based on TER values; i.e. to abandon the hazard-based step.

General :
Before performing additional tests, the notifiers should examine existing studies and check whether metabolites have not been already sufficiently covered, considering the use pattern and the fate of the metabolites. It may be worth planning for analytical identification of the metabolites as part of the standard ecotoxicological tests for the active substance, or at least take and store samples from which metabolites could be analysed later, if the need arises. At any rate, such studies (especially where a metabolite analysis has not been performed) need to be conducted at dose rates in the range of the intended application and of the existing fate studies. Limit tests at excessive doses carry the risk that especially microbial degradation might be different from the one at normal use rates, thus rendering such studies difficult to use.

QSAR's [19] may also exist, especially for metabolites, which are likely to have only a non-specific (narcotic) mode of action.

4.3 Comments on the figures of the draft guidance document

re: Figure 1 "Compartments in which relevant metabolites may occur"

As pointed out in the comments on the introduction, the relation between other guidance documents (aquatic, terrestrial ecotoxicology) and the "relevant metabolites" document requires further clarification.

re: Figures 2 to 4

As stated above, the SCP does not support the automatic conclusion that " *minor metabolites*" are " *not relevant*". It does also not support the use of the 10% trigger as the apparently sole decision making criterion to discriminate metabolites, which require further assessment, from those which do not. All flow diagrams should be amended accordingly.

re: Figure 2: Metabolites in soil

The figure contains, unlike section 7.3, an additional criterion for further ecotoxicological testing (DT50 [20] > 60 days). While the SCP supports the use of additional (fate) data for the decision on further testing in principle, such decision should be based on all available data and expert judgement (like in the existing Annexes II, III and VI) rather than on one specific value.

re: Figure 3: Metabolites in groundwater

As outlined above (comments on section 6), the trigger value of 0.1 mg/l cannot be considered safe for non-target organisms in all cases. Flexibility (testing also if PEC [21] < 0.1 mg/l) should be incorporated into the scheme.

re: Figure 4: Metabolites in surface water

Contrary to the soil compartment scheme, this one does not consider the fate of the metabolite as a trigger for further (or different) testing.

Figure 4 is the only diagram, which correctly includes expert judgement as a criterion of the assessment.

5. SUMMARY OF CONCLUSIONS

- - The term 'metabolite' should be clarified to cover any transformation product occurring in fate and/or metabolism studies, no matter by which mechanism it is produced (biotic, abiotic).
- - Compartment of concern: Metabolites have to be evaluated and assessed not only for those compartments where they originate but also for those into which they can be transported as a direct or indirect consequence of the intended use.
- - Tiered approach to assess metabolites: While the SCP supports a stepwise approach in principle, it disagrees with the rigid use of the 10% trigger value and recommends amendments/clarifications to other criteria like the proposed toxicological and ecotoxicological tests. The proposed hazard-based steps are also not supported by the SCP, since exposure estimates (however crude or conservative) are possible in all cases, and therefore risk-based approaches are equally possible and preferable.
- - Major/minor metabolites: The SCP does not support those definitions which are solely based on the 10% trigger. Rather, all metabolites have to be considered as potentially relevant until a further assessment (testing and/or scientifically documented justification) indicates that they are non-relevant. Identification of metabolites in fate studies should be done as far as technically feasible.
- - The evaluation and risk assessment for relevant metabolites should follow the same rules (e.g., apply the same trigger values and TERs as for the active substance) .
- - Other guidance documents: The relation between the draft guidance document on relevant metabolites and those on persistence, aquatic and terrestrial ecotoxicology requires more clarification.
- **- 0.1 mg/l** : As a *trigger* for further evaluation, this value is reasonably 'safe' for many substances, but exceptions (toxicity at lower levels) exist for both toxicology and ecotoxicology, and the need for further testing should be scientifically assessed also for substances at lower levels at least where cause for concern (including exposure) exists. Further consideration should be given to investigate existing (eco)toxicity data, in order to derive (a) new trigger value(s) for which the position on the distribution of toxicity values is known.
- **- 0.1 mg/l:** As to its proposed use as a *decision-making criterion* for all metabolites, the SCP is of the opinion that this is a political decision which involves consideration of uncertainties in exposure and effects assessments, of possible long-term consequences of groundwater contamination, of possible consequences for the use PPPs in agriculture, and of societies' values and perceptions.
- - Pesticidal activity: The SCP supports the proposed evaluation.
- - Toxicology: The SCP does not support the hazard-based step and recommends changes to the other assessment steps.
- - Ecotoxicology: The SCP does not support the hazard-based steps and recommends changes to the other assessment steps.

6. REFERENCES

- 1. Guidance Document on Aquatic Ecotoxicology; document 8075/VI/97 rev 7 of 8 July 2000
- 2. Guidance Document on Terrestrial Ecotoxicology; document 2021/VI/98 rev 7 of 8 July 2000
- 3. Guidance Document on Persistence in Soil; document 9188/VI/97 rev 7 of 29 June 2000
- 4. Opinion of the Scientific Committee on Plants on the Draft Guidance Document on Terrestrial Ecotoxicology (DG VI - 2021/VI/97 -Rev. 4 of 21.12.1998) - (Opinion expressed by the SCP on 24 September 1999)
- 5. Opinion of the Scientific Committee on Plants on the Draft Guidance Document on Aquatic Ecotoxicology (DG VI - 8075/VI/97-Rev.4 of 12.1998) (Opinion expressed by the SCP on 24 September 1999)
- 6. Opinion of the Scientific Committee on Plants on the Draft Guidance Document on Persistence in Soil (DG VI - 9188/VI/97-Rev.5 of 20.12.1998) - (Opinion expressed by the SCP on 24 September 1999)
- 7. Rulis AM (1986). De Minimis and the threshold of regulation. In: Food Protection Technology. CW Felix Ed. Lewis Publishers Inc., Chelsea, MI, 29-37.
- 8. Gold LS, Slone TH, Bernstein L (1989). Summary of carcinogenic potency and positivity for 492 rodent carcinogens in the carcinogenic potency database. Environ. Health Perspect. 79, 259-272.
- 9. Lewis SC, Lynch JR, Nikiforov AI (1990). A new approach to deriving community exposure guidelines from "no-observed-adverse-effect-levels". Regul. Toxicol. Pharmacol. 11, 314-330
- 10. Munro IC, Ford RA, Kennepohl E, Sprenger JG (1996). Correlation of structural class with No-Observed-Effect-Levels: a proposal for establishing a threshold of concern. Food Chem. Toxicol. 34, 829-867
- 11. SCF (Scientific Committee on Food) (1996). Opinion on Response to Request from the Commission for SCF Opinion on the Scientific Basis of the Concept of Threshold of Regulation in Relation to Food Contact Materials. Annex VII to Document III/5557/96. European Commission, Brussels.
- 12. Munro IC, Kennepohl E, Kroes R (1999). Application of a threshold of toxicological concern in the safety evaluation of certain flavouring substances. Food Chem. Toxicol. 37, 207-232.

7. DOCUMENTS MADE AVAILABLE TO THE COMMITTEE

- 1. Note from the Secretariat, 3 April 2000 (Doc. SCP/GUIDE-METAB/1).
- 2. Draft Guidance Document on Relevant Metabolites - October 1999 (Working document prepared by the Netherlands) (Doc. SCP/GUIDE-METAB/3).
- 3. Austrian comments on the draft guidance document on relevant metabolites, 10 March 2000 (Doc. SCP/GUIDE-METAB/004).
- 4. Danish comments on the draft guidance document on relevant metabolites, 15 March 2000 (Doc. SCP/GUIDE-METAB/005).
- 5. Belgian comments on the draft guidance document on relevant metabolites, March 2000 (Doc. SCP/GUIDE-METAB/006).
- 6. UK comments on the draft guidance document on relevant metabolites, 9 March 2000 (Doc. SCP/GUIDE-METAB/007).
- 7. Swedish comments on the draft guidance document on relevant metabolites, 14 March 2000 (Doc. SCP/GUIDE-METAB/008).

- 8. Danish comments on the draft guidance document on relevant metabolites, 15 March 2000 (Doc. SCP/GUIDE-METAB/009).
- 9. ECPA comments on the draft guidance document on relevant metabolites, 13 March 2000 (Doc. SCP/GUIDE-METAB/10).
- 10. German comments on the draft guidance document on relevant metabolites, 25 February 2000 (Doc. SCP/GUIDE-METAB/11).
- 11. French comments on the draft guidance document on relevant metabolites, 3 April 2000 (Doc. SCP/GUIDE-METAB/12).
- 12. Portuguese comments on the draft guidance document on relevant metabolites, 3 May 2000 (Doc. SCP/GUIDE-METAB/13).
- 13. Finnish comments on the draft guidance document on relevant metabolites, 17 May 2000 (Doc. SCP/GUIDE-METAB/14).
- 14. Greek comments on the draft guidance document on relevant metabolites, 3 April 2000 (Doc. SCP/GUIDE-METAB/15).

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Joint Environmental assessment/Toxicology WG: Prof. Hardy (Chairman), Committee Members: Dr. Delcour-Firquet, Mr. Koepp, Prof. Maroni, Dr. Moretto, Dr. Nolting, Prof. Savolainen, Prof. Silva Fernandes, Dr. Sherratt and invited experts, Dr. Boesten, Dr. Carter, Prof. Dybing, Dr. Forbes, Dr. Lambré, Dr. Luttik, Prof. Rueff, Prof. Slakinoja-Salonen, Dr. Tarazona, Prof. Vighi.

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[1] European Crop Protection Association.

[2] OJ N° L 230 of 19.08.1991 p. 1.

[3] Forum for the Co-ordination of pesticide fate models and their Use.

[4] FOCUS groundwater scenarios in the EU plant protection product review process. Report of the work of the groundwater scenario Workgroup of FOCUS, final version April 2000. Work on surface water models and scenarios is ongoing.

[5] European and Mediterranean plant protection organisation.

[6] Council of Europe.

[7] Toxicity over exposure ratio's.

[8] See references 1 to 3 in Section 6.

[9] See SCP Opinion on the draft Aquatic Ecotoxicology Guidance Document.

[10] Definition 6 defines compartment of concern as: "the environmental compartment (i.e. soil, water or sediment) that reveals amounts of metabolites greater than 10% of applied amount of

active substance at any time during the metabolism study is denoted as compartment of concern".

[11] See (Opinions of the SCP on PPPs.

[12] Body weight.

[13] See Section 6 ref. 7 to 12: Rulis, 1986; Lewis et al., 1990; Munro et al., 1996; SCF, 1996; Munro et al., 1999.

[14] Structure-activity relationships.

[15] Body weight.

[16] See references 7 - 12: Rulis, 1986; Lewis et al., 1990; Munro et al., 1996; SCG, 1996; Munro et al., 1999.

[17] No observed adverse effect level.

[18] See following crude worst-case scenario: application rate 1 kg a.s./ha; if 100% of it turned into a leaching metabolite (no known example), then the groundwater PEC would be approximately 0.33 mg/l. The draft guidance document proposes limit values of 1 mg/l (algae, NOEC) and 100 mg/l (daphnia, fish: LC50).

[19] Quantitative structure-activity relationships

[20] Period required for 50 percent dissipation.

[21] Predicted environmental concentration.