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SCIENTIFIC COMMITTEE ON PLANTS **SCP/GUIDE-METAB-bis/002 Final**

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE DRAFT GUIDANCE DOCUMENT ON RELEVANT METABOLITES (Document SANCO/221/2000-Rev. 7b of 3 July 2002)

(Opinion adopted by the Scientific Committee on Plants on 17 December 2002)

A. TITLE

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B. TERMS OF REFERENCE

In collaboration with experts from all Member States and from DG ENV the services of DG SANCO E1 have prepared a further revision of a draft Guidance Document (Sanco/221/2000–rev.7b; 3 July 2002), an earlier version of which was already commented by the Scientific Committee on Plants[1] (SCP).

The Scientific Committee on Plants is kindly asked again for an opinion on the revised document. Without any intention to limit the consideration of the document by the Committee, SANCO E1 would like to draw the Committee's attention to the following points, which should be addressed in particular:

1. What is the Committee's opinion with regard to the overall level of protection for consumers, which is achieved by the proposed approach?
2. Could the Committee comment on the appropriateness of the proposed cut-off limit to all non-relevant metabolites in groundwater?
3. Can the Committee comment on the introductory remarks for "Step 4" and provide its opinion about the alternative approach proposed by Germany (see comments)?

C. OPINION OF THE COMMITTEE

Opinion 1

The SCP is of the opinion that, in general terms, the envisaged level of protection for consumers achieved by the proposed approach is adequate and in line with the level of protection required by the Council Directive 91/414/EEC.
Moreover the Committee notes that the criteria adopted to assess the relevance of metabolites are not only toxicological, but also include policy or administrative criteria. For the sake of clarity and transparency, the Committee recommends the distinction between toxicological and non-toxicological regulatory decisions to be addressed and spelled out in the document.
The SCP after examining all the steps of the assessment procedure set by the guidance document in details, based on toxicological considerations, suggests some clarifications or modifications of them as follows:
- **Step 1 sub b): more precise definition of the "pesticidal activity" criterion;**
- **Step 1 sub c): re-consideration of the point in terms of applying a case-by-case assessment;**

[1] SCP/GUIDE-METAB/002FINAL of 1 December 2000.

- **Step 3 stage 1: the entire stage 1 of step 3 could be omitted; if retained, the legal and technical criterion of "having pesticidal activity" should be more precisely defined;**
- **Step 3 stage 2: eliminate the given examples of in vivo experiments or provide a more complete and appropriate list of tests;**
- **Step 3 stage 3: the entire stage 3 of assessment should be eliminated.**

Opinion 2

The SCP is of the opinion that posing a limit of 10 μg/L for all the substances in groundwater has not a toxicological justification and therefore such a limit cannot be proposed having regard to the protection of the population against the toxicological risk.
It is recognised that the European Commission might have other reasons that motivate setting an overall limit of concentration of chemicals in water; however, being based on non-scientific criteria, these reasons do not fall in the field of competence of the Committee and are not discussed here.
For the sake of clarity and transparency, the Committee recommends the distinction between toxicologically-based and non-toxicologically-based regulatory decisions to be clearly evidenced in the document. The non-toxicological reasons for the limit of 10 μg/L as a ceiling value for all the substances ought to be explained.

Opinion 3

Concerning the figure of daily water consumption to be used in risk assessment, the SCP believes that the value of 1.5 litres/day is the best estimate of the real water consumption of the population, 2 litres/day is a more conservative value that however has been conventionally used also by the World Health Organisation to assess the risk posed by chemicals in drinking water, and 3 litres/day is a clearly unrealistic, excessive value, that would introduce an artificial conservatism in the estimate.
Therefore the SCP recommends the use of the 2 litres/day value. This water consumption, when related to the suggested threshold of toxicological concern of 1.5 μg/person/day, would correspond to a chemical concentration in groundwater of 0.75 μg/L.

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B. TABLE OF CONTENTS

C. BACKGROUND

In collaboration with experts from all Member States and from DG ENV the services of DG SANCO E1 have prepared a further revision of a draft Guidance Document (Sanco/221/2000– rev.7b; 3 July 2002), an earlier version of which was already commented by the Scientific Committee on Plants[2] (SCP).

As background information for the Committee, comments received on a previous version of the document (rev.7a) are provided as well. The current revision was drafted accordingly. 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 Committee:

1. Draft Guidance document on the assessment of the toxicological relevance of metabolites in groundwater of active substances: Terms of Reference, submitted by DG Health and Consumer Protection, 4/7/2002 (SCP/GUIDE-METAB-bis/001).

2. Draft Guidance document on the assessment of the toxicological relevance of metabolites in groundwater of active substances: Consolidation of Member States' (DE, DK, IT, PT, SE, SF, UK) comments, submitted by DG Health and Consumer Protection, 4/7/2002, consolidated by the secretariat (SCP/GUIDE-METAB-bis/003)

3. Draft Guidance document on the assessment of the toxicological relevance of metabolites in groundwater of active substances: ECPA comments, incl. attachment 2 (8 April 2002), submitted by DG Health and Consumer Protection, 4/7/2002 (SCP/GUIDE-METAB-bis/004)

[2] SCP/GUIDE-METAB/002FINAL of 1 December 2000.

4. Draft Guidance document on the assessment of the toxicological relevance of metabolites in groundwater of active substances: Attachment 1 (publications Munro, 1996 and 1999) to ECPA comments (8 April 2002), submitted by DG Health and Consumer Protection, 4/7/2002 (SCP/GUIDE-METAB-bis/005)

5. Draft Guidance document on the assessment of the toxicological relevance of metabolites in groundwater of active substances: Comments of the Drinking Water Committee (no date), submitted by DG Health and Consumer Protection, 4/7/2002 (SCP/GUIDE-METAB-bis/006)

D. SCIENTIFIC BACKGROUND ON WHICH THE OPINION IS BASED

I. General Comments

The Committee, examining the guidance document and all the comments made by Member States and other stakeholders, recognises that this document intends to identify a consensus approach in decision making on a difficult subject on which contrasting and sometimes opposing views have been expressed. The Committee in the following text will address some of the key issues expressing its scientific advise on some general points before answering the specific questions asked by the Commission.

The title of the document expressively indicates the term "toxicological relevance of metabolites in groundwater", however the Committee notes that the criteria adopted to assess such relevance are not only toxicological, but also include policy or administrative criteria. Among these, the most important is the decision that the predicted concentration of the metabolite in groundwater greater or lower than 0.1 μg/L determines a different assessment procedure for the metabolite. The Committee underlines that such an approach is not a "toxicological approach" as it does not consider the properties of each individual chemical and, using the same figure for every compound, assumes that all metabolites are equivalent from the toxicological point of view. As such this approach does not fall in the field of competence of the Committee. Therefore for the sake of clarity and transparency, the Committee recommends the distinction between regulatory decisions based on toxicology and those based on other criteria to be addressed and spelled out in the document.

Another general point concerns the meaning of the word "relevance" in this new version of the guidelines. In the current version of the guideline the term relevance is used to indicate those compounds that would be subjected to a regulatory level (0.1 μg/L) after an assessment process that is carried out only when their predicted concentrations exceed 0.1 μg/L. Such a definition of relevance mixes concepts of "toxicological relevance" with "regulatory relevance". While the reasons for the adoption of such definition are understandable and legitimate, the Committee notes that it would be preferable to use different words to express different concepts, i.e. "toxicological relevance" and "regulatory relevance". This ought to be considered also in the definitions section of the document, where it would be preferable to separate the definition of relevance from the regulatory consequences of being defined relevant.

The final part of the Guidance document suggests that a screening for ecotoxicity with regard to groundwater organisms be performed and makes reference to another guidance document (Guidance document on aquatic ecotoxicology). The Committee is of the opinion that this aspect should be considered separately and not included in this Guidance document as it is not homogeneous to the subject dealt here.

II. Comments on the sequential assessment of the relevance of metabolites

Step 1

The Committee agrees with the general principle that there are breakdown products that should be excluded from assessment as they are considered to be "of no concern" as far as it regards toxicology. When examining the conditions through which these products are identified, the Committee notes that the condition of not having "any inherent activity as pesticide" (point b) is not a toxicological condition and should be distinct from the other conditions listed in the same point. In addition the Committee notes that the concept of "any inherent activity as pesticide" is not defined neither quantitatively nor qualitatively. It is not clear how this condition should be assessed and what criteria would be used to consider this condition satisfied. In particular it is not defined whether a testing of the product should be made, on which targets, and what would be the extent of activity taken into consideration to consider a substance a pesticide.

As the condition c) is concerned, the Committee is of the opinion that such a condition is hardly acceptable, at least in the form in which it is formulated. In fact, admitting the release of toxic metabolites in groundwater on the basis of their natural presence seems to set a policy that soil and groundwater can be polluted as long as they already contain such toxins. The Committee is of the opinion that what is "natural" is not necessarily non-toxic and adding man-made toxins to natural toxins is not an acceptable principle in a process of toxicological risk assessment. Rather, it would seem to be more appropriate to establish a case-by-case assessment rule for such conditions.

Step 2

This step becomes of fundamental importance in the way the assessment process has been set. The Committee notes that the compliance with the 0.1 μg/L limit is <u>not</u> a toxicological criterion.
In toxicological terms, considering the paper published by Munro et al. in 1999, on the threshold of toxicological concern and assuming an intake of 2 litres of water per day, such a limit would offer a cancer risk less than 10^{-6} with 99% probability assuming that 10% of the unknown metabolites are carcinogenic.

Step 3

This step includes three stages: screening for pesticidal activity, screening for genotoxicity, and screening for toxicity.

As to stage 1, the Committee is of the opinion that the criterion of assessment is <u>not</u> toxicologically relevant. This criterion evaluates biological (pesticidal) activity with comparison to the parent compound and aims at identifying those metabolites that are

equally or more active pesticides. The intent of this assessment is that when a substance meets this criterion, it becomes "relevant", i.e. subjected to the 0.1 μg/L limit, independently from its toxicological properties. Again, the Committee sees here a mix of regulatory criteria with toxicological criteria.

In addition, the Committee notes that the pesticidal criterion would benefit of more precise details concerning which targets are considered (the same as the parent or any other possible target) and how to treat metabolites that for example are 50% active: would they still be considered having pesticidal activity or not? It is obvious that there is some relationship between toxicity of a chemical and its pesticidal activity: in fact the pesticidal action is a toxic action against a biological target; the fact that this action is called "pesticidal" is merely due to the nature and desirability of the affected target.

The Committee is of the opinion that the entire stage 1 of step 3 could be omitted if the interest is to make a toxicological assessment. If instead the reason is of regulatory nature, this must be clearly spelled out, not be confused with the toxicological properties, and the legal and technical criterion of "having pesticidal activity" more precisely defined.

Concerning the stage 2 (Screening for genotoxicity) the SCP is of the opinion that the examples of *in vivo* experiments given in brackets may not be appropriate, in particular for the mentioned in vivo-in vitro UDS assay. Therefore it is recommended to eliminate the examples in brackets or to provide a more complete and appropriate list of tests.

As to the stage 3, the Committee has strong reservations on the proposed approach. The overall idea behind the proposed approach is that the toxicity of the metabolite should be somewhat predicted by the classification of the parent and, even more important, a metabolite becomes relevant when its toxicological properties lead to a classification "equal or more severe" than that of the parent compound.

The implicit assumptions of such a scheme are that:

- classification of a chemical according to Directive 67/548/EEC for any risk phrases sets a limit for that chemical at 0.1 μg/L and the limit is extended to all metabolites with the same classification
- the toxicity of a metabolite of a non-classified chemical is disregarded, at least in this stage
- a metabolite without toxicological classification can proceed to further assessment.

The Committee is of the opinion that the toxicological risk assessment should be based on qualitative and quantitative toxicological data. Classification by hazard is an administrative procedure that should not replace a careful consideration of type of effects, NOAELs, exposures, and related margins of safety.

The above mentioned assumptions would introduce a generalised regulatory limit that, by definition, does not consider the individual toxicological properties of the chemicals and even less considers the toxicological risk. Such a limit, that could be justified based on other considerations, is not justified from the toxicological standpoint.

The toxicity of a metabolite cannot be predicted from the toxicity of the parent compound. There are plenty of examples in the toxicological literature that a non-toxic chemical may originate active metabolites that in the end are responsible for its toxicity and also the reverse is true. Therefore the Committee concludes that the entire stage 3 of

assessment should be eliminated. A correct toxicological risk assessment should be done at a later stage of the process – which is what the guideline document identifies as step 5.

Step 4

As already discussed in its previous opinion on this matter, the Committee strongly supports the use of the concept of threshold of toxicological concern (TTC) for screening those chemicals that would need a more complete toxicological evaluation.
The Committee remarks that the figure proposed as a threshold (1.5 μg/person/day) was originally meant to be applied to unknown chemicals that can include both carcinogens and non-carcinogens. This figure, according to Munro et al. 1999, indicates a cancer risk less than 10^{-6} with 96% probability when 10% of the new untested chemicals are carcinogenic. The fact that such a figure is used for substances that have already been screened for genotoxicity, are of known structure, and derive from chemicals for which an entire toxicological dossier is available, would introduce a further margin of safety.
In fact, the human exposure threshold calculated by multiplying the 5th centile of animal NOEL distribution for non-carcinogenic substances as mg/kg/day by 60 (assumed to be the body weight) and dividing by a safety factor of 100, would result in an intake of 90 μg/day, a value still 60 fold higher than the TTC.
The Committee therefore concludes that TTC is a valid tool to be used in the process of assessment of metabolites and, under the proposed conditions of use, can provide an adequate margin of protection and a reliable assessment of the need for a more complete risk assessment of metabolites.

Concerning the issue raised in question 3 that relates to the figure of daily water consumption to be used in risk assessment, the SCP believes that the value of 1.5 litres/day is the best estimate of the real water consumption of the population, 2 litres/day is a more conservative value that however has been conventionally used also by the World Health Organisation to assess the risk posed by chemicals in drinking water, and 3 litres/day is a clearly unrealistic, excessive value, that would introduce an artificial conservatism in the estimate. Therefore the SCP recommends the use of the 2 litres/day value. This water consumption, when related to the suggested threshold of toxicological concern of 1.5 μg/person/day, would correspond to a chemical concentration in groundwater of 0.75 μg/L.

Step 5

This step is proposed in the document to be a refined risk assessment, however assuming the elimination of stage 3 of step 3, it would become the risk assessment step.
The Committee agrees with the general concepts laid down in the document concerning the strategy for the assessment. As a general rule the assessment should be complete and permit a thorough appreciation of the toxicological risk posed by the metabolite. However, on the base of expert judgement and a case-by-case approach, an unnecessary testing could be avoided when a justified toxicological evidence is provided for it.

In the final stage of this process, the risk characterisation of the metabolite has to be achieved. When the metabolite is also present in the animal metabolism, the ADI of the parent compound can be used as reference for the assessment assigning in a first tier all the toxicity to the metabolite and thus deriving a conservative limit of exposure.

As a side comment, the SCP notes that the guidance document should avoid to discuss speculative aspects such as for example that concerning plausibility in mammals of metabolites found in soil. These elements are indeed part of the "expert judgement" and do not seem to be appropriately located in a guidance document.

An important and innovative aspect included in this step is the limit of 10 μg/L as a ceiling value for all the substances that have positively passed the risk assessment process. The SCP is of the opinion that posing such a limit for all the substances has not a toxicological justification and therefore such a limit cannot be proposed having regard to the protection of the toxicological risk for the population.
As above discussed for the 0.1 μg/L limit, it has to be recognised that the European Commission might have other reasons that motivate setting an overall limit of concentration of chemicals in water; however, being based on non-scientific criteria, these reasons do not fall in the field of competence of the Committee and are not discussed here.
For the sake of clarity and transparency, the Committee recommends the distinction between toxicologically-based and non-toxicologically-based regulatory decisions to be clearly evidenced in the document. The non-toxicological reasons for the limit of 10 μg/L as a ceiling value for all the substances ought to be explained.

III. Question 1

What is the Committee's opinion with regard to the overall level of protection for consumers, which is achieved by the proposed approach?

III.1 Opinion on question 1

The SCP is of the opinion that, in general terms, the envisaged level of protection for consumers achieved by the proposed approach is adequate and in line with the level of protection required by the Council Directive 91/414/EEC.
Moreover the Committee notes that the criteria adopted to assess the relevance of metabolites are not only toxicological, but also include policy or administrative criteria. For the sake of clarity and transparency, the Committee recommends the distinction between toxicological and non-toxicological regulatory decisions to be addressed and spelled out in the document.
The SCP after examining all the steps of the assessment procedure set by the guidance document in details, based on toxicological considerations, suggests some clarifications or modifications of them as follows:

- **Step 1 sub b): more precise definition of the "pesticidal activity" criterion;**
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- **Step 3 stage 2: eliminate the given examples of in vivo experiments or provide a more complete and appropriate list of tests;**
- **Step 3 stage 3: the entire stage 3 of assessment should be eliminated.**

IV. Question 2

Could the Committee comment on the appropriateness of the proposed cut-off limit to all non-relevant metabolites in groundwater?

IV.1 Opinion on question 2

The SCP is of the opinion that posing a limit of 10 μg/L for all the substances in groundwater has not a toxicological justification and therefore such a limit cannot be proposed having regard to the protection of the population against the toxicological risk.
It is recognised that the European Commission might have other reasons that motivate setting an overall limit of concentration of chemicals in water; however, being based on non-scientific criteria, these reasons do not fall in the field of competence of the Committee and are not discussed here.
For the sake of clarity and transparency, the Committee recommends the distinction between toxicologically-based and non-toxicologically-based regulatory decisions to be clearly evidenced in the document. The non-toxicological reasons for the limit of 10 μg/L as a ceiling value for all the substances ought to be explained.

V. Question 3

Can the Committee comment on the introductory remarks for "Step 4" and provide its opinion about the alternative approach proposed by Germany (see comments)?

V.1 Opinion on question 3

Concerning the figure of daily water consumption to be used in risk assessment, the SCP believes that the value of 1.5 litres/day is the best estimate of the real water consumption of the population, 2 litres/day is a more conservative value that however has been conventionally used also by the World Health Organisation to assess the risk posed by chemicals in drinking water, and 3 litres/day is a clearly unrealistic, excessive value, that would introduce an artificial conservatism in the estimate.
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D. REFERENCES

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.

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