



**EUROPEAN COMMISSION**  
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate E - Food Safety: plant health, animal health and welfare, international questions  
**E1 - Plant health**

**Sanco/221/2000 –rev.10**  
**25 February 2003**

**DRAFT**  
**WORKING DOCUMENT**

**GUIDANCE DOCUMENT**  
**ON THE ASSESSMENT OF THE RELEVANCE OF**  
**METABOLITES IN GROUNDWATER OF SUBSTANCES**  
**REGULATED UNDER COUNCIL DIRECTIVE 91/414/EEC**

This document has been conceived as a working document of the Commission Services, which was elaborated in co-operation with the Member States. It does not intend to produce legally binding effects and by its nature does not prejudice any measure taken by a Member State within the implementation prerogatives under Annex II, III and VI of Council Directive 91/414/EEC, nor any case law developed with regard to this provision. This document also does not preclude the possibility that the European Court of Justice may give one or another provision direct effect in Member States.

# Contents

<b>1. Introduction</b> .....	<b>3</b>
<b>2. Context and general approach</b> .....	<b>4</b>
<b>3. Definitions</b> .....	<b>5</b>
<b>4. Sequential assessment of the relevance of metabolites</b> .....	<b>6</b>
<i>Step 1: Exclusion of degradation products of no concern</i> .....	<i>6</i>
<i>Step 2: Quantification of potential groundwater contamination</i> .....	<i>7</i>
<i>Step 3: Hazard Assessment: Identification of relevant metabolites</i> .....	<i>8</i>
a. Stage 1 of Step 3: Screening for biological activity: .....	<i>8</i>
b. Stage 2 of Step 3: Screening for genotoxicity: .....	<i>9</i>
c. Stage 3 of Step 3: Screening for toxicity .....	<i>9</i>
<i>Step 4: Exposure assessment - threshold of concern approach</i> .....	<i>10</i>
<i>Step 5: Refined risk assessments for non-relevant relevant metabolites</i> .....	<i>11</i>
<b>5. References</b> .....	<b>13</b>
<b>6. Decision Tree</b> .....	<b>14</b>

1.

## Introduction

This document, on the assessment of the relevance of metabolites in groundwater, is intended to provide guidance for notifiers and Member States in the context of the review of active substances under Council Directive 91/414/EEC concerning the placing of plant protection products on the market. The document intends to identify a consensus approach in regulatory decision-making concerning the inclusion of active substances in Annex I of the Directive. It does not prejudice the authority of Member States in national authorisations, nor does it prejudice the application of other Community legislation in force. Nonetheless, the document still provides some recommendations, which might be helpful in maintaining harmonised assessment schemes and decision making in Member States.

Metabolites and breakdown products of active substances may occur in many environmental compartments (in particular in soil, surface waters, groundwater and air), in animal feed or in food for human consumers. It is the intention of the Commission Services to cover all of these aspects in guidance documents, which are to be continuously revised to keep the guidance in line with scientific and technical progress as well as regulatory changes. This guidance document focuses on groundwater, though the general approach may also be applicable for the regional management of surface water resources intended for the abstraction of drinking water in Member States.

Separate guidance documents on terrestrial and aquatic ecotoxicology have been produced and will be continuously adapted to scientific and regulatory progress to address the protection of non-target organisms in these environmental compartments<sup>1</sup>. These guidance documents address aspects of the ecotoxicology assessment not only for the active substances but also for metabolites or breakdown products, which are formed after their application and include the assessment of groundwater as an ecosystem.

Council Directive 91/414/EEC refers to "*relevant metabolites*" in its Annex VI (Annex VI, point C 2.5.1.2<sup>2</sup>), where the acceptable concentrations of "active substances or of relevant metabolites" in groundwater are restricted to the maximum permissible concentration laid down by the Drinking Water Directive (Council Directive 98/83/EC regulating the quality of water intended for human consumption)<sup>3</sup> or a lower concentration, if necessary due to its toxicological properties.

In turn, the term "*relevant metabolites*" is also used in the Drinking Water Directive, where it is provided that concentrations of pesticides and their relevant metabolites in drinking water must not exceed 0.1 µg/L.

Neither of the two Directives defines the term "*relevant metabolite*" and this has led to uncertainty for regulators and notifiers. It is the goal of this document to lay down an operational definition of the term insofar as this is necessary for the review of active substances under Council Directive 91/414/EEC and to identify a consensus approach towards its application in regulatory decision-making concerning the inclusion of active substances in Annex I of the Directive.

In explicitly mentioning the term "relevant metabolites" in the texts of the two Directives the legislator acknowledges that there may be metabolites that are not relevant. Therefore, the provisions of both Directives are intended to regulate or place limits on a "relevant" subset of breakdown products in the same way as is done for active substances. Different provisions should apply for "non-relevant" substances.

---

1 References at the date of this document are:

(i) Guidance document on aquatic ecotoxicology: SANCO/3268/2001 rev 4 (final) dated 17 October 2002 and  
(ii) Guidance document on terrestrial ecotoxicology: SANCO/10329/2002 rev 2 final dated 17 October 2002.

<sup>2</sup> OJ L 265, 27 September 1997; p. 87-109

<sup>3</sup> OJ L 330, 5 December 1998; p. 32-54

This document describes a stepwise scheme, of increasing complexity, to identify “relevant metabolites” for which the above provision of Annex VI and thus the limit value of the Drinking Water directive should apply. The document further describes a scheme for the assessment of those metabolites, which are not identified as relevant, but which have to be evaluated previous to a decision on the inclusion of an active substance in Annex I to Directive 91/414/EEC.

## 2. Context and general approach

This guidance document focuses exclusively on the assessment, under Council Directive 91/414/EEC, of metabolites and breakdown products of active substances in groundwater, because the term "relevant metabolites" is used for this compartment in a unique legislative context. Issues related to the ecotoxicological aspects of metabolites and breakdown products in groundwater (under the scenario that non target organisms are dwelling in groundwater and that groundwater may eventually become surface water and thus an environment for aquatic organisms) and all ecotoxicological questions related to other environmental compartments such as soil, surface water and air, are treated in separate guidance documents for terrestrial and aquatic ecotoxicology. A guidance document for the compartment "air" will be developed at a future stage.

Following the precautionary principle laid down in the Water Framework Directive<sup>4</sup>, Groundwater must be regarded as a natural resource, which should be protected in its own right. In consideration of this principle, the limit value provided in Annex VI of Directive 91/414/EEC (and Directive 98/83/EC) for active substances and their relevant metabolites is not solely based on toxicological criteria. A risk assessment on human toxicology therefore cannot be the exclusive basis for a decision as to whether a metabolite has to be considered relevant or not. Furthermore, also for non-relevant metabolites it is considered appropriate that an adequate level of protection is established for groundwater, which takes into account the unique properties of this environmental compartment.

Consequently, this document describes a scheme to determine whether a metabolite is relevant (and thus subject to the 0.1 µg/L limit) or not relevant using criteria of biological activity, genotoxicity and toxicological hazard but also other, pragmatic administrative criteria to allow efficient and transparent regulatory decision-making. If a metabolite is not relevant, it is still subject to other limits, as outlined in detail in this document, and to further case-by-case assessments in-line with the above principle of precaution.

As noted above, this document is intended to provide guidance for the inclusion of active substances in Annex I of Directive 91/414/EEC. According to Art. 5 of the Directive “... an active substance shall be included in Annex I ... if it may be expected that plant protection products containing the active substance ... do not have any harmful effects ... on groundwater...”. This possibility of potential groundwater - or drinking water - contamination is investigated generally on the basis of the convention that a soil layer of approximately 1 m is used to represent the “groundwater” aquifer. Such an assumption is far from representative for all regions of Europe but it is considered to provide a realistic worst case on the European scale, in compliance with Art. 5 of the Directive. Should, at a future stage, more realistic assessment schemes and models become available for refined assessments at the European scale (e.g. probabilistic assessments based on real groundwater distribution data), this Guidance document will be revised to reflect such a progress.

This document does not prejudice the authority of Member States to grant national authorisations. It is recommended that Member States develop their own national and regional scenarios for the assessment of groundwater contamination to ensure that the limit values provided by Community legislation are respected at the points of abstraction of groundwater. It may also be considered that Member States use

---

<sup>4</sup>Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy - OJ L 327, 22. December 2000, p.1

the guidance herein in conjunction with monitoring data where available as an orientation where regional or local schemes of resource management are developed to protect surface waters used for the abstraction of drinking water.

The hazard and risk assessment of active substances under Directive 91/414/EEC is highly developed and is supplemented by several guidance documents developed at Community level. The scientific assessment of metabolites and degradation products of these active substances should be of comparable transparency, scientific validity and degree of regulatory scrutiny as for the active substances themselves. The scheme described in this document for the evaluation of metabolites is aimed at achieving this goal and is aligned closely with that of the evaluation of active substances. The guiding principle of the assessment is that a metabolite or degradation product is considered relevant, if there is reason to assume that it has comparable intrinsic properties as the active substance in terms of its biological target activity, or that it has certain toxicological properties that are considered severe (i.e. genotoxic, toxic to reproduction, carcinogenic, toxic or very toxic), unless demonstrated to the contrary.

A stepwise procedure is used which aims in the first instance to select those cases which need further consideration (Steps 1 and 2). It then provides guidance on how metabolites should be treated in further, more complex, steps ranging from screening in a hazard assessment to (using further experimental data) a full risk assessment. A decision-tree to visualise the general approach is provided on page 14.

Much of the data required for metabolites of individual active substances under the scheme may already be available. According to Council Directive 91/414/EEC, several studies have to be performed by the registrant on the metabolism of the active substance in the different environmental compartments where metabolites, degradation and reaction products may be formed (c.f. Annex II to the Directive). Data requirements concerning soil, which are of particular importance for the assessment of groundwater, are found in Section 7.1 of its Annex II.

Consequently, for all compartments, at least some information on the metabolism, rate, route, and kinetics is available for use in the risk assessment of the active substance and its metabolites and breakdown products. Before performing additional tests, notifiers should therefore examine existing studies and check whether metabolites or breakdown products under consideration have already been covered by studies required for the active substance or “major” metabolites (according to Annex II of Directive 91/414/EEC), considering the use pattern and the fate of the compounds investigated. Based on existing knowledge on related compounds, some fate and effects characteristics of metabolites may also be anticipated and used to extrapolate the required information.

### 3. Definitions

The following definitions are used in this guidance document:

1. **Metabolite:** for the purpose of this document, the term is used for all reaction or breakdown products of an active substance of a plant protection product, which are formed in the environment after the application, be it by biotic (microbials, other taxa) or abiotic processes (hydrolysis, photolysis). The terms “metabolite”, “breakdown product” and “degradation product” are used interchangeably throughout this document.
2. **Relevant metabolite:** a metabolite for which there is reason to assume that it has comparable intrinsic properties as the active substance in terms of its biological target activity, or that it has certain toxicological properties that are considered severe and unacceptable with regard to the decision-making criteria described in the text. Such a metabolite is therefore treated like the parent active substance in the assessment according to Annex VI, point C.2.5.1.2 of Directive 91/414/EEC. Where such a metabolite exceeds the maximum permissible concentration (0.1 µg/l) for groundwater, a non-inclusion

decision would be triggered at Community level for the active substance or a non-authorisation decision would be triggered at national level for specific uses of products containing that substance;

3. Metabolite of no concern: A metabolite which meets the criteria outlined in Step 1 of Part 4 below and is therefore deemed to be not relevant in the assessment according to Annex VI, point C.2.5.1.2 of Directive 91/414/EEC.
4. Non-relevant metabolite: a metabolite which does not meet the criteria provided for “relevant metabolites” and “metabolites of no concern”. A non-relevant metabolite may be subject, on a case-by-case basis, to an individual groundwater limit concentration, as outlined in detail in this document.

#### **4. Sequential assessment of the relevance of metabolites**

As a general rule, all metabolites which are expected to occur in soil under normal use conditions on the basis of results from soil degradation studies should be subject to further assessments of their structure and environmental fate with the aim of quantitatively assessing their ability to contaminate groundwater. The same assessment should be done for all metabolites found in lysimeter studies, where such studies have been conducted. It is recognised that, for practical reasons and reasons of technical feasibility, it might not be possible to identify those minor metabolites (< 10% of total applied on a molar basis) which occur transiently in soil, or metabolites which are found in very low amounts (< 5 % of total applied on a molar basis) and with no tendency to accumulate. Similar limitations apply to lysimeter studies, where characterisation of metabolites found in small amounts in leachates is also not always feasible.

Therefore, as a minimum, degradation products must be characterised and identified by the notifiers to the extent that is technically feasible and their relevance must be assessed, if one of the following conditions applies:

- a) Metabolites, which account for more than 10 % of the amount of active substance added in soil at any time during the studies; or
- b) which account for more than 5 % of the amount of active substance added in soil in at least two sequential measurements during the studies; or
- c) for which at the end of soil degradation studies the maximum of formation is not yet reached.

Moreover, all metabolites found in lysimeter studies at annual average concentrations exceeding 0.1 µg/l in the leachate should be identified and subject to further assessment.

##### ***Step 1: Exclusion of degradation products of no concern***

This step applies to all metabolites. A degradation product which may be expected to occur in groundwater as a result of a soil degradation study or a lysimeter study will require further assessment unless one of the following conditions apply:

- a) it is CO<sub>2</sub> or an inorganic compound, not containing a heavy metal; or,
- b) it is an organic compound of aliphatic structure, with a chain length of 4 or less, which consists only of C, H, N or O atoms and which has no "alerting structures" such as epoxide, nitrosamine, nitrile or other functional groups of known toxicological concern.
- c) it is a substance, which is known to be of no toxicological or ecotoxicological concern, and which is naturally occurring at much higher concentrations in the respective compartment.

If condition a), b) or c) is met, the degradation product is considered to be a degradation product of no concern and no additional data are required.

## ***Step 2: Quantification of potential groundwater contamination***

All metabolites not excluded in Step 1 that are found in soil degradation and/or available lysimeter or field leaching studies should in principle be characterised and identified by the notifiers to the extent that is technically feasible, as outlined above in the introductory remarks to this chapter. This is particularly the case for those metabolites which are predicted to be present in the leachate leaving the upper soil layer at an annual to triannual average flux (as defined by FOCUS<sup>5</sup>) concentration exceeding 0.1 µg/L. For these metabolites the predicted environmental concentration in groundwater needs to be estimated with the highest feasible accuracy and validity.

To quantitatively assess the fate of these metabolites with the FOCUS groundwater models and scenarios, data on degradation and sorption are required as input. As the required input depends on the intended uses of the active substance under investigation, the FOCUS guidance document should be consulted for further information on extent and quality of input parameters needed. Also expert judgement may be used to estimate the necessary model input parameters on degradation and sorption in cases where experimental data cannot easily be provided<sup>6</sup>. In these cases, a sensitivity analysis should be conducted to allow a judgement to be made on the level of confidence, which can be attributed to the calculations. However, experimental data should preferably be used.

For metabolites found in the leachate of lysimeter studies with annual average concentrations above 0.1 µg/L an attempt should be made to assess their leaching behaviour in other European regions with different soil and climatic conditions with the goal to extrapolate the experimental findings to other representative regions of European agriculture. All efforts should be made to quantitatively assess and identify individual compounds in the leachate fractions, as far as technically feasible. Since some Member States consider lysimeter studies as higher tier compared to model calculations, these provisions will not prejudice decision making on Member State level.

As far as valid and representative data are available for existing active substances, also monitoring data can be used to predict environmental concentrations of metabolites in groundwater. Monitoring data from regions with well-documented use of the active substance in question may provide a useful additional tool to supplement model calculations and lysimeter experiments to improve the accuracy and validity of estimates of potential groundwater contamination.

If, on the basis of these calculations and assessments, representative use-scenarios can be identified which predict no contamination of groundwater by the active substance or individual metabolites in excess of the limit values provided by the Drinking Water Directive or provision C. 2.5.1.1 of the Uniform Principles, then the active substance is eligible for further consideration of inclusion in Annex I of Directive 91/414/EEC if at least one Member State indicates an interest in granting an authorisation.

Nonetheless, consideration should be given to the fact that groundwater is also an ecosystem containing non-target organisms and that surface water bodies may be supplied from groundwater resources and that there are substances which may give reason for ecotoxicological concern at levels even below the default limit value provided for drinking water. This aspect should be considered in the context of the ecotoxicological assessment of the active substance, which is outside the scope of this document.

---

<sup>5</sup> FOCUS groundwater scenarios in the EU review of active substances - Report of the FOCUS Groundwater Scenarios Workgroup, Document SANCO/321/2000 rev.2, November 2000.

<sup>6</sup> Besides the OECD Test Guidelines, valuable guidance may also be found in the Opinion of the Scientific Committee on Plants on methods for the determination of the organic carbon adsorption coefficient (koc) for a plant protection product active substance in the context of Council Directive 91/414/EEC – SCP/KOC/002-final adopted by the SCP, 18 July 2002

Active substances, for which not all uses and use conditions reviewed have resulted in acceptable predicted groundwater contamination need to be assessed further by Member States when granting national authorisations. The Review Reports for these substances will highlight this area of potential concern in such cases.

All metabolites, which might be expected to exceed the limits laid down in Annex VI, point C.2.5.1.2 of Directive 91/414/EEC should be further assessed in Step 3. Again, also in these cases the environmental concentration in groundwater needs to be estimated with the highest feasible accuracy and validity, following the principles outlined above.

### ***Step 3: Hazard Assessment: Identification of relevant metabolites***

Step 3 provides a pragmatic scheme for the regulatory decision-making concerning the “relevance” of a certain metabolite. It is a 3-stage assessment involving (i) biological activity screening, (ii) genotoxicity hazard screening, and (iii) toxicity hazard screening. Any metabolite that does not pass all three stages is considered as “relevant” under regulatory aspects and thus unacceptable at groundwater contamination levels exceeding 0.1 µg/L. Passing the three stages does not imply non-relevance – it simply means that further assessment in Step 4 is required.

#### **a. Stage 1 of Step 3: Screening for biological activity:**

Active substances of plant protection products are defined according to Art. 2 of the Directive on the basis of their biological activity against plants or harmful organisms (in the context of this document defined as the “biological activity”). The same criterion is used here to identify those breakdown products, which – from a regulatory perspective - should be treated in the same way as active substances with respect to groundwater protection.

The goal is to identify metabolites, which have a comparable target activity as the parent active ingredient, and to deal with cases where the parent molecule is a precursor of the active substance. Efficacy testing should be focused on this question of comparing the activity against the biological target. However, for parent compounds with a known range of activities, or for a compound belonging to a totally new group, it may be necessary to test a metabolite in a more extensive screening battery.

Structure-activity relationships may be considered on the basis of the mode of activity of the parent molecule (i.e. usually the active substance). In many cases for compounds belonging to a well defined group of active substances (e.g. sulfonyl thiourea herbicides) this may already provide useful and sufficient information for the assessment of this question in the absence of experimental data.

In cases where the above considerations do not lead to clear results, the metabolite should be evaluated in biological screening assays using standard methods comparing weight equivalents of the parent substance and the metabolites in question. As a possible refinement and if necessary, comparative testing may be done at the maximum application rate and based on a molar equivalent compared to the active substance. The maximum test rate then would be calculated by:

$$\text{Rate}_{\text{metabolite}} = M/A \cdot \text{Rate}_{\text{a.s.}}$$

in which:

$\text{Rate}_{\text{metabolite}}$	= application rate at which metabolite should be tested in screen (kg/ha)
$\text{Rate}_{\text{a.s.}}$	= use rate of active ingredient (kg/ha)
$M$	= molar mass of metabolite

A = molar mass of active substance

On the basis of this maximum level, the effect of the metabolite against a range of target organisms should be compared to the activity of the parent compound. Metabolites of unknown structure (e.g. fractions from a lysimeter experiment) should be subject to a similar assessment, insofar as this is technically feasible. A case-by-case approach should be followed in this event, which should be developed in close collaboration between the notifier and the Rapporteur Member State. The metabolite(s) in question should be characterised as far as possible to allow an expert judgement on its activity.

In screening assays it will often not be possible to determine and compare the biological activity of a parent molecule and its metabolites with great precision, and this will also not be necessary in most cases. As a line of orientation, it should be sufficient to demonstrate that the biological activity of a metabolite is clearly less than 50% of the activity of the parent molecule. Otherwise the biological activity should be considered as “comparable”.

From a regulatory perspective, metabolites with a comparable or higher biological activity than the parent are considered as relevant and must, therefore, not exceed a level of 0.1 µg/L in groundwater as determined according to Step 2.

All other products passing this stage should be further screened in Stage 2.

**b. Stage 2 of Step 3: Screening for genotoxicity:**

All metabolites that have passed step 1, step 2 and stage 1 of step 3 should be screened for their genotoxic activity by at least the following package of *in vitro* genotoxicity studies: Ames test, gene mutation test with mammalian cells, and chromosome aberration test. Equivocal results in *in vitro* studies should be substantiated by *in vivo* experiments. Mutagenic metabolites (any category) are considered relevant.

**c. Stage 3 of Step 3: Screening for toxicity**

Stage 3 of Step 3 is aimed at the question of whether a metabolite has certain toxicological properties, which - from a regulatory perspective - qualify for considering it “relevant”. A metabolite is considered “relevant” if its toxicological properties lead to a classification as toxic or very toxic (T or T+) according to Directive 67/548/EEC. Reflecting the general concept of this document, the toxicity classification of the parent active substance as determined according to Directive 67/548/EEC is used for pragmatic reasons as a starting point to focus the screening activity. The Step 3 screening is applied as follows:

For parent active substances, which are classified as acutely or chronically toxic or very toxic (T followed by R25, R24, R23 or R48, or T+ followed by R28, R27, R26 or R39) the acute or chronic toxicity of the metabolite must be determined. Metabolites, which on the basis of an appropriate test qualify as toxic or very toxic (T or T+) are considered “relevant”.

For parent active substances, which are classified for reproductive toxicity (any category with R60 R61, R62 or R63), it must be show by an appropriate test or convincing other evidence that the metabolite does not qualify for the same classification. Metabolites, which qualify for a classification of their reproductive toxicity (any category with R60 R61, R62 or R63) are considered to be “relevant”.

For parent active substances classified as category 1 or category 2 carcinogens (Carc. Cat. 1; R 45) or (Carc. Cat. 2; R 45) all metabolites are considered to be “relevant”. For parent active substances classified as category 3 carcinogens (Carc. Cat. 3; R 40), convincing evidence must be provided that the metabolite will not lead to any risk of carcinogenicity. This may be done by appropriate carcinogenicity testing, by the provision of mechanistic evidence (e.g. absence of the likely mechanistic effect leading to carcinogenicity with the parent molecule, such as target organ pathology, peroxisome proliferation, cytochrome P450 induction or metabolism of thyroid hormones) or by a convincing toxicological assessment taking into consideration all available data.

However, independent of the classification of the parent active substance, if there is reason to expect that a certain degradation product may be toxic or highly toxic, a targeted testing may be necessary.

All metabolites passing stage 3 of step 3 and are not considered as “relevant” are subject to an exposure and/or risk assessment as outlined in the steps below:

#### ***Step 4: Exposure assessment - threshold of concern approach***

Metabolites which have not been identified as being relevant according to the hazard screening outlined in Step 3, should be further tested in an exposure assessment to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via their drinking water.

Such an assessment, if done in isolation, would require, in principle, a full set of toxicological data according to Annex II of the Directive to ultimately establish an Acceptable Daily Intake value for these substances and is not excluded in Step 5 below. However, as a pragmatic alternative in cases where a full quantitative risk assessment cannot be provided, an approach following a "threshold of concern" should be followed. The approach is based on a statistical evaluation of lifetime carcinogenicity studies for more than 500 substances, which were originally compiled by Gold *et al.* 1989<sup>7</sup> and later supplemented and refined by other authors. Both, the Scientific Committee on Plants<sup>8</sup> and the Scientific Committee on Food<sup>9</sup> have discussed this concept and found that the available scientific information base is sufficiently large to consider an application of a threshold of toxicological concern as a concept, which is rational, pragmatic and scientifically valid.

Following this concept, for substances of unknown structure the Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day<sup>10</sup>, which is in line with the threshold developed by the US-FDA. Assuming a consumption of 2 liters of water per day<sup>11</sup>, all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L.

When carrying out this assessment, it must be checked whether there is potential exposure for consumers via other sources but drinking water, e.g. if the metabolite in question is also found among the residues on treated commodities. Such a potential exposure from other sources should be taken into account in order to ensure that total exposure of consumers to the metabolite will not exceed the acceptable overall threshold of concern of 0.02 µg/kg body weight/day.

Such a threshold can only be considered acceptable if the metabolite in question  
- does not exceed 0.75 µg/L (or a lower level, if consumers are exposed also via other routes)

---

<sup>7</sup> Gold *et al.* 1989

<sup>8</sup> SCP 2000

<sup>9</sup> SCF, 1996;

<sup>10</sup> Munro *et al.*, 1996; Munro *et al.*, 1999.

<sup>11</sup> Which is a conservative value also recommended by WHO (1994).

and has passed Step 3 i.e.

- has a lower biological activity than the parent,
- is not genotoxic and
- is not defined as toxic.

Substances for which all metabolites meet all these criteria can be further considered for Annex I inclusion. Where there is insufficient information to do a satisfactory assessment at this Step, then a refinement is necessary and further data will be required in Step 5.

### ***Step 5: Refined risk assessments for non-relevant metabolites***

Metabolites which have passed steps 1 to 3 and for which levels of estimated concentrations of metabolites in groundwater (as defined in Step 2) lie between 0.75 µg/L (from Step 4) and 10 µg/L<sup>12</sup> will require a refined assessment of their potential toxicological significance for consumers. All such metabolites, which are estimated to occur at levels exceeding the toxicological threshold for unknown substances, must be fully identified and also synthesised by the notifier, if necessary to allow their further testing.

The appropriate strategy for the assessment of these cases has to be developed on a case-by-case basis in collaboration between the notifier and the Rapporteur Member State.

As a general principle, it should be understood that data requirements raised in this context do not always have to be addressed by experimental studies. Notifiers may, if possible, address open questions by using available information in support of a scientific and rational assessment. Valuable sources of information include, but are not limited to:

- consideration of molecular structure of the metabolite (active part intact?);
- the occurrence of metabolites in existing tests with the active substance;
- general knowledge on the relationship between the toxicity of metabolites and their parent substances;
- available knowledge on related compounds.

In such cases expert judgement may be used to determine the necessity of requiring additional information.

With regard to human toxicology it should be investigated in particular whether a metabolite was also identified in mammalian laboratory animals and, consequently, has been intrinsically subject to toxicity studies along with the active substance. The occurrence of metabolites, their quantification and the extrapolation of this information to humans should be based on expert judgement, taking into consideration known differences in phase one and two metabolism and assessments of biochemical plausibility. For example, a metabolite formed in soil, which may be present in the 1 m groundwater horizon may be a plausible metabolite in mammals, which is only transient and, therefore, not detectable in significant quantity in laboratory animals. Conjugates formed in biotic processes in the soil may be readily cleaved in the gastro-intestinal tract and may give rise to known metabolites in mammals.

If the metabolite is found in laboratory animals, the acceptable limit in groundwater for this compound may be defined on the basis of existing studies with the active substance.

---

<sup>12</sup> This limit value of 10 µg/L is selected for pragmatic reasons. It is also the current limit value defined in the Drinking Water Directive for chlorinated aliphatic hydrocarbons such as trichlorethene. Some degradation products of pesticides may belong into this chemical category. Note that some other products may also belong to other defined categories in Drinking Water Directive and are, therefore, subject to a different limit.

If a metabolite is not likely to be formed in laboratory animals upon exposure to the active substance, stepwise testing should be conducted to determine the full toxicological profile of the metabolite or to generate enough information to allow a comparison with the toxicology profile 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, but the investigation of potential genotoxicity will probably represent the first step in most cases. 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<sup>13</sup>), or toxicological information derived from structurally related chemicals.

For non-genotoxic substances, and in the absence of any particular alerting chemical structures in the metabolite, an extrapolation from subchronic to chronic study results will be possible in most cases. It is largely agreed in the scientific community<sup>14</sup> that an extra assessment factor of 10 will be adequate to cover the additional uncertainty when an acceptable daily intake for consumers is derived from a 90-day study result.

As provided above for step 4, also in step 5 the question must be addressed whether there are other sources of exposure for consumers but groundwater. The permissible exposure of consumers via water is calculated on the basis of a daily consumption of 2 L/day and taking into account exposure from all other routes, if appropriate.

Where actual or predicted concentrations of a non-relevant metabolite in groundwater exceed 10 µg/L, no general guidance can be provided in the context of this document. As outlined in the introduction, regulatory decisions must maintain a high level of protection for groundwater. Therefore, it is necessary to carefully evaluate case by case, whether the requirements of Article 5 (1) of the Directive are still fulfilled and the active substance can be included in Annex I to the Directive. Such an assessment must consider the overall profile and use pattern of the substance and it must be based on strict precaution.

---

<sup>13</sup> Structure-activity relationships.

<sup>14</sup> Lewis *et al.* 1990

## 5. References

1. SCP 2000: 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) scp/guide-metab/002final of 1 December 2000.
2. Guidance document on aquatic ecotoxicology in the frame of the Directive 91/414/EEC (Commission Document SANCO/3268/2001 rev 4 (final) dated 17 October 2002).
3. Guidance document on terrestrial ecotoxicology in the frame of the Directive 91/414/EEC (Commission Document SANCO/10329/2002 rev 2 final dated 17 October 2002).
4. Guidance document on persistence in soil (Commission Document 9188/VI/97. Current Revision 8 dated 12 July 2000).
5. 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.
6. 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.
7. 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.
8. WHO (1994). Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. *Environmental Health Criteria* 170; WHO, Geneva.
9. 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.
10. 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.
11. 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) scp/guide-metab/002 bis final of 16 December 2002.

6. Decision Tree

# Determination of relevance of metabolites in groundwater

2 February 2003

