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SCIENTIFIC COMMITTEE ON PLANTS **SCP/ISOXAFLUTOLE-BIS/002 Final**

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON ADDITIONAL QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF ISOXAFLUTOLE IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC

(Opinion adopted by the Scientific Committee on Plants on 30/01/2003)

A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON ADDITIONAL QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF ISOXAFLUTOLE IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC
(Opinion adopted by the Scientific Committee on Plants on 30/01/2003.)

B. TERMS OF REFERENCE

QUESTION 1: Given the variability in the DT_{50}[1]/DT_{90}[2] from field and laboratory, can the SCP comment on the appropriate DT_{50}/DT_{90} to be used in the FOCUS model scenarios?

QUESTION 2: Would the newly submitted data on metabolite RPA203328 cause the Committee to change its conclusion expressed in its opinion adopted on 18 May 1999 with respect to the environmental and toxicological safety of the metabolite, also in the light of the last draft (revision 7b) of the relevant metabolite guidance document?

C. OPINION OF THE COMMITTEE

Opinion on question 1:
The Committee considers the DT_{50} of metabolite RPA203328 used for the FOCUS scenario calculations too short. These DT_{50} values were based on the mentioned four field persistence studies assuming that the dissipation in the field could be completely attributed to transformation in soil and that the formation percentage of RPA203328 out of its precursor RPA202248 was 100%. These assumptions lead to underestimation of the DT_{50} and were insufficiently justified. The Committee recognises that transformation rates in field soil may be faster than expected on the basis of laboratory results. However, when field results are used to demonstrate this, the procedure should be conservative with respect to the estimated field DT_{50} for transformation.

Opinion on question 2:
No new data were submitted, on ecotoxicological effects of metabolite RPA 203328. The SCP's ecotoxicological assessment from 1999 was done according to the same principles as outlined by the recent version of the respective Guidance document (on aquatic ecotoxicology). Hence, there is no need for the Committee to change its evaluation of the ecotoxicological properties of RPA 203328. The Committee can, however, not complete the risk assessment since the exposure estimate (PEC values) has to be revised in the light of the new data (see opinion on question 1, above).
The Committee has reassessed the toxicological risk of this metabolite in light of the available data and of the draft guidance document on relevant metabolites in

[1] DT 50: Period required for 50% dissipation

[2] DT 90: Period required for 90% dissipation

groundwater (rev 7b) and has concluded that this metabolite is not toxicologically relevant under the considered scenario of exposure (groundwater).
Therefore, the Committee does not see the need to change its conclusion expressed in the opinion adopted on 18 May 1999 (SCP/ISOXA/012 Final).

A. TITLE

REPORT OF THE SCIENTIFIC COMMITTEE ON PLANTS ON ADDITIONAL QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF ISOXAFLUTOLE IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC

B. TABLE OF CONTENTS

C. BACKGROUND

Isoxaflutole is a new herbicide for pre-planting and pre-emergence control of grasses and broadleaf weeds in corn (maize) to be used in spring. Isoxaflutole is a pigment photosynthesis inhibitor.
The draft proposed inclusion of isoxaflutole in Annex I to Directive 91/414/EEC had already been referred to the Scientific Committee on Plants for consultation on three questions, a first opinion was adopted on 18 May 1999.

The first question asked by DG Environment on 3 July 2002 on isoxaflutole was to clarify the results obtained on the 80 percentile concentrations for the metabolite RPA203328 (2-methanesulphonyl-4-trifluoromethylbenzoic acid) in the FOCUS (FOrum for the Co-ordination of pesticide fate models and their USe)[3] PEARL[4] model in the addendum to Vol. 3, of March 2002 presented by the rapporteur Member State (The Netherlands).
In the discussions in the Working Groups of the Standing Committee of the Food Chain and Animal Health, at least one Member State expressed doubts on the use of the mean of 22.5 days for half-life (DT_{50}) in the field when the mean laboratory DT_{50} found was 529 days (between 205 and 852 days). The credibility of the 4 field half-lives chosen in the report CX011033A by Adventis crop Science (Goch, Manningtree, Meneville, Bologna) seemed thus questionable. The rapporteur Member State could not convince in its explanations to justify theses differences.
Moreover, US EPA (1999-2001) found laboratory DT_{50} up to 977 days in a sandy loam soil. The results obtained from the model FOCUS PEARL (2 safe uses on Porto and Sevilla) could be totally different with a higher DT_{50} and consequently no safe use obtained, the conclusions of the RMS should have been different.

[3] FOCUS groundwater scenarios in the EU review of active substances

[4] PEARL: Pesticide Emission Assessment at Regional and Local scales

The second question on the relevance of the metabolite RPA203328 was asked to confirm the opinion adopted by the SCP (SCP-ISOXA 012-Final) on 18 May 1999 as the guidance document on relevant metabolite (SANCO/221/2000 presently revision 7b 3/7/2002) was substantially modified since 1999.

Source documents made available to the Committee:

1. SCP-ISOX-BIS 001 : Terms of Reference - Evaluation of isoxaflutole in the Context of Council Directive 91/414/EEC concerning the Placing of Plant Protection Products on the Market.
2. SCP-ISOX-BIS 003 : Isoxaflutole: consolidated comments of the notifier - 6 October 2002.
3. SCP-ISOX-BIS 002 to 007 : Isoxaflutole Kinetics Evaluation.
4. SCP-ISOX-BIS 008 and 009 : Consolidated comments of the rapporteur Member States) - 16 October 2002.
5. SCP-ISOX-BIS 010 : Summary of FY 2001 Water Quality Monitoring for Isoxaflutole in Nebraska - 16 October 2002.
6. SCP-ISOX-BIS 011 : Final Environmental Impact Statement for Use of Pesticides Containing Isoxaflutole in Wisconsin - 16 October 2002.
7. SCP-ISOX-BIS 012 : Proposed use of isoxaflutole pesticide in Wisconsin, Wisconsin Dept. of Agriculture, Trade and Consumer Protection - 30 October 2002.
8. SCP-ISOX-BIS 013 : Proposed Regulatory Decision Document, Canadian Pest Management Regulatory Agency, PRDD2001-03 - 31 October 2002.
9. SCP-ISOX-BIS 014/014 bis : Addendum, Volume 3, Annex B–March 2002/30 October 2002.
10. SCP-ISOX-BIS 015 : List of studies submitted after finalization of the draft review report. Extract of the review report (SANCO/3136/99 rev 6) - 31 October 2002.
11. SCP-ISOXA 012-Final : Opinion of the SCP regarding the inclusion of isoxaflutole in Annex I of Directive 91/414/EEC concerning the Placing of Plant Protection Products on the market – adopted 18 May 1999.

D. SCIENTIFIC BACKGROUND ON WHICH THE OPINION IS BASED

I. Question 1:

Given the variability in the DT_{50}/DT_{90} from field and laboratory, can the SCP comment on the appropriate DT_{50}/DT_{90} to be used in the FOCUS model scenarios?

Opinion on question 1:

The Committee considers the DT_{50} of metabolite RPA203328 used for the FOCUS scenario calculations too short. These DT_{50} values were based on the mentioned four field persistence studies assuming that the dissipation in the field could be completely attributed to transformation in soil and that the formation percentage of RPA203328 out of its precursor RPA202248 was 100%. These assumptions lead to underestimation of the DT_{50} and were insufficiently justified. The Committee recognises that transformation rates in field soil may be faster than expected on the basis of laboratory results. However, when field results are used to demonstrate this, the procedure should be conservative with respect to the estimated field DT_{50} for transformation.

Scientific background on which the opinion is based

I.1 Sorption

For an appropriate assessment of the field persistence experiments it is necessary to evaluate the sorption properties of RPA203328. The monograph (Draft Assessment Report) reports one adsorption study with four soils which resulted in K_{OC}[5] values ranging from 26 to 33 L/kg (assuming K_{OC}=1.72 K_{OM}). The organic matter contents of these soils ranged from 2 to 4% and their pH from 4 to 7. The Addendum of March 2002 to the monograph reports a second adsorption study with four soils and one sediment. The organic carbon content of the soils ranged from 0.3 to 1.2% and their pH from 6 to 7. The K_{OC} values for the four soils ranged from 47 to 100 L/kg. The sediment had an organic carbon content of 5 % and a pH of 5.6 and its K_{OC} was 23 L/kg.
The RPA203328 molecule contains a phenyl ring with a COOH-group. The pK_a[6] of this group was not reported but will probably be in the range 3-5. It may then be expected that the K_{OC} decrease with increasing pH in the range from 4 to 8.
Table 1 lists all K_{OC} values and corresponding pH values and the source of the study.

Table 1: K_{OC} values of soils and one sediment reported for RPA203328.

Source	pH	K_{OC} (L/kg)
monograph	4.3	33
monograph	4.7	26
monograph	5.5	31
addendum (sediment)	5.6	23
addendum	6.2	47
addendum	6.4	91
addendum	6.5	100

[5] Koc : Organic carbon adsorption coefficient

[6] pK_a : Negative value of the logarithm of the dissociation constant for describing a charge transition in a molecule

monograph	6.7	33
addendum	6.8	82

Table 1 shows that the K_{OC} is not a function of the pH. The K_{OC} seems to be rather a function of the study (small range in monograph and wide range in addendum). From the measured adsorption coefficients and the solid-liquid ratio it can be calculated that the decrease of the concentration in the liquid phase in all adsorption studies ranged between about 10 and 20% except for the study with the sediment where the decrease was about 30%. The OECD guideline 106 (OECD, 2000, p. 7) recommends that the decrease is above 20% (preferably even above 50%) to ensure a good accuracy of the measured sorption coefficients. The background of this is that a low percentage decrease leads to a large systematic error in the sorption coefficients. Based on the above considerations, the Committee considers only the measured sorption coefficient of RPA203328 for the sediment reliable. However, the sediment had a pH of 5.6. As described before, the sorption of RPA203328 will probably decrease with increasing pH. So there is no reasonable certainty that the K_{OC} exceeds 0 for soils with pH values above 6.

I.2 Metabolism of isoxaflutole and transformation rate of RPA203328 in laboratory studies

The monograph reports a number of laboratory studies on the metabolism of isoxaflutole and its metabolites in aerobic soils. In all studies ^{14}C-labelled isoxaflutole (label in phenyl ring) was applied to soil. Isoxaflutole transformed rapidly into the RPA202248 metabolite which was further transformed into RPA203328. Table 2 summarises the results for RPA203328.

Table 2: Summary of results for RPA203328 in soil metabolism studies.

Soil texture	pH	Temp. (^oC)	Maximum % of radioactivity	Time of maximum (d)	% of radioactivity at end	Time at end (d)	Estimated half-life (d) #
sandy loam	6	20-22	62	30	47	365	853
clay	5	20-22	31	60	10	365	205
sandy loam	5	20	83	120	77	181	>>100
clay loam	8	20	7	7	1	120	<<100
loam	4	20	64	120	64	120	>100
loamy sand	7	20	90	91	90	120	>>100
loam	4	10	52	100	51	120	>>100

'>>' means 'much longer than' and '<<' means 'much shorter than'

The half-lives from the first two studies were calculated by the rapporteur and included a temperature correction to 20^{o}C. The rapporteur did not correct for the moisture (moisture contents were reported to be at 75% of field capacity). The Committee calculated these half-lives back to a matric suction of 10 kPa using the reported moisture contents and Table 5.2 of FOCUS (2000). This resulted in half-lives of 446 days for the sandy loam and of 156 days for the clay.

The other half-lives in the above table are rough guesses that the Committee made by expert judgement.

Pest Management Regulatory Agency (2001) described results of laboratory studies on the soil metabolism of isoxaflutole with two soils (sandy loam and clay). Soil pH and

temperature were not reported. The maximum percentages of RPA203328 were 55% for the sandy loam and 34% for the clay. The time at which these were reached and the duration of the study were not reported. The report states that the registrant reported half-lives of 977 days for the sandy loam and 289 days for the clay (no further details). These studies are not included in Table 2 because the report contained insufficient details as described above.

I.3 Estimation of DT_{50} of RPA203328 from field dissipation studies

The monograph reports four field studies on the persistence of isoxaflutole and its metabolites in soil. Plot sizes were between 1000 and 1600 m^2 and they were grown with maize. Table 3 describes soil properties, application rates and dates together with the range of monthly air temperatures of the first three or four months.

Table 3: Characteristics of the field persistence studies (soil properties are from top 10 cm).

Site	Soil texture	Organic matter (%)	pH	Application rate (g/ha)	Application date (1994)	Average monthly air temperature (^oC)
Bologna	loam	2	8	158	11 May	18-26
Goch	silt loam	3	6	156	27 May	13-17
Manningtree	loam	2	7	214	7 June	15-19
Mereville	silty clay loam	2	8	155	5 May	14-22

Rainfall was supplemented with irrigation water and total precipitation exceeded usually the monthly historical rainfall. However, the monograph did not report amounts of rainfall at the sites.
Soil samples were taken up to 1.2 m depth. The detection limit of RPA203328 was 5 µg/kg. This resulted in recovered amounts of RPA203328 as shown in Table 4.

Table 4: Recovered amounts of RPA203328 in the field persistence experiments.

Site	Bologna		Goch		Manningtree		Mereville	
	Time (d)	Amount (g/ha)	Time (d)	Amount (g/ha)	Time (d)	Amount (g/ha)	Time (d)	Amount (g/ha)
First detection	4	13	7	25	7	21	6	13
Maximum	14	33	28	61	121	178	14	27
Not detectable anymore	61		186		275		131	

The molar mass of RPA203328 is 0.74 times the molar mass of isoxaflutole. Thus the maximum amounts in the table correspond with 28, 53, 112 and 24 % of the isoxaflutole dose for Bologna, Goch, Manningtree and Mereville, respectively.

At the Bologna and Goch fields RPA203328 was not detected below 10 cm depth. Results for the other two fields are shown in Table 5.

Table 5: Contents of RPA203328 in soil (µg/kg) reported for the Manningtree and Mereville fields.

Depth (cm)	Manningtree (4 months)	Manningtree (6 months)	Mereville (0.5 month)	Mereville (1 month)
0-10				

10-20	100		5	9
20-30	41	8		6
30-60		5		

For the empty cells in the above table no values were reported but it is clear from the monograph that all deeper layers were below the detection limit of 5 μg/kg. This detection limit corresponds with an amount of 7 g/ha for a 10-cm thick layer and with 22 g/ha for a 30-cm thick layer (assuming a dry bulk density of 1.5 kg/L).

The notifier used the results of this experiment to fit half-lives of RPA203328. These were reported by Hardy (2001) and summarized in Addendum to Annex B of the monograph of March 2002. The procedure was based on the following assumptions:
1. RPA203328 is formed from isoxaflutole and the first metabolite RPA202248 via a sequential reaction scheme in which 100% conversion is assumed for formation of RPA20228 from isoxaflutole and also for formation of RPA203328 from RPA202248.
2. The decline of the total recovered amount in the field is only the result of transformation in soil.
3. If the soil residue of one of the three compounds was below the detection limit at a certain sampling date, a value of 4.5 g/ha was assumed for this compound at that date. This is the amount corresponding to a content of half the detection limit of 5 μg/kg present in a 10 cm layer.
4. A number of data were excluded because they were considered as statistical outliers. For RPA203328 the measurements after 99 and 121 days at Manningtree were excluded.

The rapporteur repeated the fitting procedure using another software package and without adding the 4.5 g/ha for dates with no detections.. The resulting half-lives are given in Table 6.

Table 6: Field half-lives (days) of RPA203328.

Site	Notifier	Rapporteur
Bologna	30	37
Goch	39	51
Manningtree	11	14
Mereville	10	12

So the rapporteur obtained half-lives that were about 20% longer than those of the notifier although the rapporteur seemed to have followed a slightlyless conservative approach. This indicates that the resulting half-lives are sensitive to subtle differences in the procedure (e.g. the selected software package).

The Committee finds the assumption of 100% formation of RPA203328 from RPA202248 not acceptable for Bologna and Mereville in view of the maximum percentages of 28 and 24% that were recovered from these sites. Hardy (2001) justified the 100% formation by stating that this formation percentage optimises close to 100% in most cases (referring to laboratory studies). However, the report of this optimisation procedure (Ref. 7 from Hardy, 2001) was not made available to the Committee. It would had been more appropriate if the full range of formation percentages had been reported by Hardy (2001): information about “most cases” is not enough when conservative assumptions are needed. The document “isoxaflutole: consolidated comments from the rapporteur Member State (NL)” pointed out that the fitting procedure does not converge

if this percentage formation would have been a fitting parameter and that a lower percentage formation leads to a longer half-life. The Committee accepts this statement but the consequence is that a more conservative estimate of the formation percentage should have been used for the Bologna and Mereville sites.

The decline of the total recovered amount of RPA203328 in the field may not only be the result of transformation in soil but also of 1) volatilisation, 2) phototransformation, 3) leaching and 4) plant uptake. The Committee accepts that losses resulting from volatilisation are ignored because RPA203328 is a weak acid. It accepts also that losses resulting from phototransformation are ignored because the available laboratory study on soil phototransformation did not show a fast transformation of RPA203328.

The possible significance of leaching losses may differ from site to site. Information on rainfall and irrigation amounts would have been helpfull to the Committee but these were not available. The notifier calculated total amount in the soil profile at each sampling time as the sum of the amounts in the layers that had detectable residues. An indication of the error resulting from leaching may thus be obtained by calculating the amount that would have been present in the shallowest residue-free soil layer if its RPA203328 content would have been equal to the detection limit. This is done for a number of sampling points in Table 7 (assuming a dry bulk density of 1.5 kg/L).

Table 7: Comparison of total recovered amounts of RPA203328 with amounts corresponding to the detection limit.

Site	Time	Soil layer considered in calculation of total amount	Total recovered amount (g/ha) (= Y)	Amount in shallowest soil layer corresponding to detection limit (g/ha) (=X)	X/Y
Bologna	14 d	0-10 cm	33	7	0.2
Goch	28 d	0-10 cm	61	7	0.1
Manningtree	121 d	10-30 cm	178	22	0.1
Manningtree	6 months	20-30 cm	13*	22	1.7
Mereville	1 month	10-30 cm	22	22	1.0

* This 13 g/ha was used by Hardy (2001) for estimating the half-life and is consistent with the 8 µg/kg reported in the monograph for the 20-30 cm layer. The monograph reports that additionally 5.2 µg/kg was present in the 30-60 cm layer (see bottom of p.176). Probably Hardy (2001) interpreted this 5.2 µg/kg as being below the detection limit.

These results indicate that the error in the recovered amounts resulting from leaching may have been 10-20% for Bologna and Goch. However, for Manningtree and Mereville it may have been 100-170%. Ignoring such possible losses for the latter two sites seems not justifiable.

As described before, the notifier assumed a total amount of 4.5 g/ha if no detectable soil residues were found for a given compound at a certain sampling date. Table 7 suggests that this is a non-conservative assumption because the detection limit in the shallowest residue free layer may correspond to values as high as 22 g/ha.
To assess the possible significance of plant uptake the Committee made calculations with FOCUS PEARL v1.1.1 and one FOCUS groundwater scenario (Okehampton) based on the following assumptions:

1. a total amount of RPA203328 of 50 g/ha is applied on 1 July,
2. uniform distribution of this total amount over the top 30 cm,
3. a half-life of RPA203328 in the top soil layer at 20°C and a matric suction of 10 kPa of 300 d (i.e. the average of the half-lives of 446 and 156 days reported earlier),
4. a transpiration stream concentration factor (i.e. the parameter describing the plant uptake rate of RPA203328) of 0.5 (i.e. the default value used in the FOCUS scenarios),
5. a K_{OC} of 25 L/kg (see the section on sorption) and a Freundlich[7] exponent of 0.90 (default value in FOCUS scenarios),
6. maize crop.

The total annual plant uptake of RPA203328 ranged from 13 to 16% of the amount of RPA203328 introduced into the soil system (the range results from a time series of 20 years). If the K_{OC} was set to zero (which can not be excluded as discussed before), the range was from 26 to 44%. Although these scenario calculations are very rough, they indicate that also plant uptake losses may have been significant. Admittedly, scenario calculations with site-specific meteorological data, rooting depths etc… may show that the plant uptake was only a few percent. However, the Committee could not find a justification for ignoring losses resulting from plant uptake.

As described before, Hardy (2001) excluded the RPA203328 measurements after 99 and 121 days at Manningtree in the derivation of its half-life. The only argument provided was that these were outliers. The Manningtree time series consisted of seven times with measurable amounts (starting at day 7 and ending at day 174) and the residues measured after 99 and 121 days were higher than any of the remaining five measurements: the recovered amounts were 107 g/ha after 99 days and 178 g/ha after 121 days, whereas the range for the other five times was 13-100 g/ha. It seems difficult to defend to omit these highest two values as outliers without a detailed justification. Thus the Commission considers omission of these outliers as a non-conservative assumption which was insufficiently justified and which may have led to a considerable underestimation of the half-life.

The Committee concludes with respect to RPA203328 that:
- the DT_{50} estimated from the Bologna site may have been underestimated considerably by assuming 100% formation from RPA202248,
- the DT_{50} estimated from the Goch site may have been underestimated by assuming 100% formation from RPA202248 and by ignoring plant uptake and leaching losses,
- the DT_{50} estimated from the Manningtree site may have been underestimated considerably by removing the amounts recovered after 99 and 121 days from the data and by ignoring leaching losses for the measuring point after 6 months,
- the DT_{50} estimated from the Mereville site may have been underestimated considerably by assuming 100% formation from RPA202248 and by ignoring leaching losses for the measuring point after 1 month.

Pest Management Regulatory Agency (2001) reported three field dissipation studies from the following Canadian sites: clay loam soil in Springbank (Ontario), clay soil in Selkirk (Ontario), sandy loam soil in Carman (Manitoba). Maize was grown on all sites. Information on soil properties, application rate and time, meteorological conditions and on plot sizes was not reported. Residues of RPA203328 were detected almost exclusively

[7] The Freundlich exponent describes the curvature of the sorption isotherm.

in the top 15 cm (detection limit was 5 μg/kg). DT50 values of RPA203328 were estimated to be 12 days for Springbank, 73 days for Selkirk and 9 days for Carman but the procedure that was used was not reported. Thus these results cannot be assessed by the Committee.

I.4 DT_{50} values of RPA203328 used for FOCUS scenario calculations

The notifier made FOCUS scenario calculations with PRZM[8] 2.3.1 for 8 sites (Chateaudun, Hamburg, Kremsmünster, Okehampton, Piacenza, Porto, Sevilla and Thiva). The half-life for the first four northern scenarios was assumed to be equal to the average field half-lives as determined by the notifier for Goch, Manningtree and Mereville. The half-life for the last four southern scenarios was assumed to be equal to the Bologna field half-life as determined by the notifier. The moisture and temperature dependencies of the transformation rate in PRZM were switched off.

The rapporteur made FOCUS scenario calculations with PEARL 1.1.1 for the same sites but using its own half-lives as a basis but calculated back to 20°C and a matric suction of -10 kPa. This resulted in DT50 values for RPA202228 of 12 days for Bologna, 29 days for Goch, 38 days for Manningtree and 11 days for Mereville.

The Committee considers the approach followed by the notifier inappropriate because the field half-lives were based on observed declines in the period May-September. By using these values and switching off the temperature dependency of the transformation rates in PRZM, it is assumed that the transformation rates in soil in winter are equal to those in May-September. This is a non-conservative assumption that was not justified and that is likely to have a large effect on the calculated leaching concentrations. The approach followed by the Rapporteur is preferable because it avoids this non-conservative assumption.

II QUESTION 2:

Would the newly submitted data on metabolite RPA203328 cause the Committee to change its conclusion expressed in its opinion adopted on 18 May 1999 with respect to the environmental and toxicological safety of the metabolite, also in the light of the last draft (revision 7b) of the relevant metabolite guidance document?

Opinion on question 2:

No new data were submitted, on ecotoxicological effects of metabolite RPA 203328. The SCP's ecotoxicological assessment from 1999 was done according to the same principles as outlined by the recent version of the respective Guidance document (on aquatic ecotoxicology). Hence, there is no need for the Committee to change its evaluation of the ecotoxicological properties of RPA 203328. The Committee can, however, not complete the risk assessment since the exposure estimate (PEC values) has to be revised in the light of the new data (see opinion on question 1, above).

The Committee has reassessed the toxicological risk of this metabolite in light of the available data and of the draft guidance document on relevant metabolites in

[8] PRZM: Pesticide Root Zone Model

groundwater (rev 7b) and has concluded that this metabolite is not toxicologically relevant under the considered scenario of exposure (groundwater).
Therefore, the Committee does not see the need to change its conclusion expressed in the opinion adopted on 18 May 1999 (SCP/ISOXA/012 Final).

Scientific background on which the opinion is based:

II. 1 Background for Ecological effects

In its opinion of 1999, the Committee concluded that the metabolite was less toxic than the parent molecule for all species, and that resulting TER[9] values for the most sensitive species (algae and duckweed) of 2000 to 3000 did not raise specific ecotoxicological concern. This assessment was based on available toxicity studies with algae, duckweed, Daphnia and fish and an estimated worst case exposure of 3 µg/L.

No new data were submitted on ecotoxicological effects of RPA 203328.
In addition, the recent revision of the guidance document on relevant metabolite SANCO/221/2000 (rev 7b 3/7/2002) does not any more include ecotoxicological effects as part of the assessment of relevance. Those aspects have been replaced by a reference to the Guidance document on aquatic ecotoxicology (SANCO/3268/2001, 1/10/2001).
The SCP's assessment, from 1999, of the ecotoxicological risk of the metabolite RPA 203328 was done according to the same principles as outlined by the Guidance document on aquatic ecotoxicology: (a) comparison of toxicity profiles of the metabolite and the parent molecule; (b) comparison of resulting TER values with the respective triggers of Annex VI of directive 91/414/EEC. Hence, as to the first step, in the light of the recent versions of both guidance documents, there is no need for the Committee to change its evaluation of the ecotoxicological properties of RPA 203328.
As to the second step, the Committee can not complete the risk assessment since the exposure estimate (PEC[10] values) has to be revised in the light of the new data (see opinion on question 1, above).

II. 2 Toxicity

In a gene mutation assay with *S. typhimurium* strains there was no evidence for mutagenicity at dose levels up to cytotoxic doses (2,500 µg. plate+/- S9) of RPA 203328. In an in vivo mouse micronucleus assay, there was no indication of a clastogenic and/or aneugenic effect associated with administration of RPA 203328. In a CHO/HGPRT forward mutation assay with duplicate cultures and a confirmatory assay, there was no indication of either mutagenicity or cytotoxicity at the highest dose level of 2,700 µg/ml. Overall, there was no evidence for a genotoxic potential RPA 203328.

In a 28-day oral study, RPA 203328 was administered in the diet to male and female rats. There were no compound-related adverse effects on survival, clinical signs, body weight, food consumption, clinical chemistry, hematology and gross or microscopic pathology up to the highest dose tested of 1,118 mg/kg/day in male and 1,269 mg/kg/day in female rats.

[9] TER: Toxicity Exposure Ratio

[10] PEC surface water

Following the recommendations of the draft Guidance document on relevant metabolites (SANCO/221/2000 rev 7b 3/7/2002) and the opinion of the SCP (SCP/GUID-METAB-bis/002 Final expressed on 17/12/2002), the Committee considered the toxicological data of the parent compound. It was noted that RPA 203328 is also an animal metabolite of isoxaflutole. The critical effects of isoxaflutole are liver (in mice and rats) and thyroid (in rats only) tumours. In its previous opinion (adopted on 18 May 1999), the SCP concluded that liver tumours were likely to be "the result of the inductive action of isoxaflutole on the liver cells" and that thyroid tumors were the results of hormonal imbalance and as such "have no relevance to man". The NOAEL for the non-neoplastic liver effects (periacinar hypertrophy) was 3 mg/kg b.w./day in a 12-week oral toxicity study in rats with isoxaflutole

Since in the 28-day oral toxicity study, the metabolite RPA 203328 did not cause any liver effect at the highest dose tested (which is about 3 orders of magnitude higher the NOAEL of the parent) the metabolite appears not to play a relevant role in the toxic effects on the liver caused by isoxaflutole.
On these basis, and taking also into account that RPA 203328 does not present alerting structures, the SCP is of the opinion that this metabolite is not toxicologically relevant under the considered scenario of exposure (groundwater). Therefore, the Committee does not see the need to change its conclusion expressed in the opinion adopted on 18 May 1999 (SCP/ISOXA/012 Final).

E. REFERENCES

1. OECD (2000) OECD Guideline for the testing of chemicals. Adsorption-desorption using a batch equilibrium method. OECD, Paris, 45 pp.
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