EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

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

Isoxaflutole

Sanco/3136/99-Final

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COMMISSION WORKING DOCUMENT - DOES NOT NECESSARILY REPRESENT THE VIEWS OF THE COMMISSION SERVICES

Review report for the active substance **isoxaflutole**

Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 15 April 2003 in view of the inclusion of isoxaflutole in Annex I of Directive 91/414/EEC.

1. Procedure followed for the evaluation process

This review report has been established as a result of the evaluation of the new active substance isoxaflutole, made in the context of the work provided for in Articles 5 and 6 of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

In accordance with the provisions of Article 6(2) of Directive 91/414/EEC, the Dutch authorities received on 6 March 1996 an application from Rhône-Poulenc Agro (now Bayer CropScience), hereafter referred to as the applicant, for the inclusion of the active substance isoxaflutole in Annex I to the Directive. The Dutch authorities indicated to the Commission on 4 April 1996 the results of a first examination of the completeness of the dossier, with regard to the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive. Subsequently, and in accordance with the requirements of Article 6(2), a dossier on isoxaflutole was distributed to the Member States and the Commission.

The Commission referred the dossier to the Standing Committee on the Food Chain and Animal Health in the meeting of the working group 'legislation' thereof on 22 April 1996, during which the Member States confirmed the receipt of the dossier.

In accordance with the provisions of Article 6(3), which requires the confirmation at Community level that the dossier is to be considered as satisfying, in principle, the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive and in accordance with

the procedure laid down in Article 20 of the Directive, the Commission confirmed in its Decision 96/524/EC[1] of 29 July 1996 that these requirements were satisfied.

Within the framework of that decision and with a view to the further organisation of the works related to the detailed examination of the dossier provided for in Article 6(2) and (4) of Directive 91/414/EEC, it was agreed between the Member States and the Commission that the Netherlands would, as rapporteur Member State, carry out the detailed examination of the dossier and report the conclusions of its examination accompanied by any recommendations on the inclusion or non-inclusion and any conditions relating thereto, to the Commission as soon as possible and at the latest within a period of one year.

The Netherlands submitted to the Commission on 20 February 1997 the report of its detailed scientific examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of isoxaflutole in Annex I to the Directive.

On receipt of the draft assessment report, the Commission forwarded it for consultation to all the Member States as well as to the sole applicant on 26 February 1997.

The Commission organised further an intensive consultation of specialised scientific experts from a representative number of Member States, to review the draft assessment report and the comments received thereon (peer review), in particular on each of the following disciplines :

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions.

The meetings for this consultation were organised on behalf of the Commission by the Pesticide Safety Directorate (PSD) in York, United Kingdom, from April to June 1997.

The report of the peer review (i.e. full report) was circulated, for further consultation, to Member States and the sole applicant on 30 July 1997**.**

The dossier, draft assessment report and the peer review report (i.e. full report) including in particular an outline resumé of the remaining technical questions, were referred to the Standing Committee on the Food Chain and Animal Health, and specialised working groups of this Committee, for final examination, with participation of experts from the 15 Member States. This final examination took place from April 1997 to April 2003, and was finalised in the meeting of the Standing Committee on 15 April 2003.

The present review report contains the conclusions of this final examination; given the importance of the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications submitted after the peer review as basic information for the final

[1] OJ N° L220, 30.08.96, p.27

examination process, these documents are considered respectively as background documents A, B and C to this review report and are part of it.

These documents were also submitted to the Scientific Committee for Plants for a separate independent scientific consultation. In a first consultation the Scientific Committee was asked to comment on potential toxicological and ecotoxicological effects of a degradation product of the active substance (RPA 203328); on statistical analyses of tumour incidence in the 2 year rat study; and on the observation of developmental effects in laboratory animals. In its opinion[2] the Committee noted that the degradation product RPA 203328 under worst case conditions might leach into groundwater with expected concentrations exceeding 0.1 ppb. The Committee identified no toxicological or ecotoxiclogical concern with regard to this degradation product. The Committee also identified no concern for humans related to possible carcinogenic or developmental effects.

In a second consultation the Scientific Committee was asked to comment on the appropriate degradation kinetics to be assumed in model calculations of the leaching behaviour. The Committee found certain parameters used in the modelling were insufficiently justified and the half life time of degradation for the RPA 203328 metabolite may have been under-estimated[3].

The model calculations of the leaching behaviour were subsequently revised along the lines suggested by the Scientific Committee.

This review report contains the conclusions of the present assessment for isoxaflutole. Given the importance of, the draft assessment report (monograph), the peer review report (i.e. full report), and the comments and clarifications (of Member States, applicant and third parties) submitted after the peer review, as basic background information supporting this review, these documents are considered respectively as supporting background documents A, B and C to this review report.

2. Purposes of this review report

This review report, including the background documents and appendices thereto, have been developed and finalised in support of the Directive 2003/68/EC[4] concerning the inclusion of isoxaflutole in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing isoxaflutole they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and

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[2] Opinion of the scientific Committee on Plants regarding the inclusion of isoxaflutole in Annex 1 of Directive 91/414/EEC concerning the placing of plant protection products on the market. SCP/ISOXA/012-Final of 3 June 1999.

[3] 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. SCP/ISOXAFLUTOLE-bis-002 Final of 30 January 2003.

[4] OJ No L 177, 16.07.2003, p.12.

granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In parallel with the provisions of Article 7(6) of Regulation 3600/92 for existing active substances, the Commission and the Member States will keep available or make available this review report for consultation by any interested parties or will make it available to them on their specific request. Moreover the Commission will send a copy of this review report (not including the background documents) to the applicant.

The information in this review report is, at least partly, based on information which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated possession of regulatory access to the information on which this review report is based.

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing isoxaflutole will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each isoxaflutole containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the following uses which were proposed and supported by the sole submitter:

- herbicide in maize with a maximum application rate of 0.1 kg as/ha.

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC.

4. Specific conclusions which are highlighted in this evaluation

4.1 Residues of isoxaflutole in foodstuffs

The review has established that the residues arising from the proposed uses, consequent on application consistent with good plant protection practice, have no harmful effects on human or animal health. The Theoretical Maximum Daily Intake (TMDI) for a 60 kg adult is 0,2 % of the Acceptable Daily Intake (ADI), based on the FAO/WHO European Diet (August 1994). This low intake value reflects the current limited use pattern for this active substance.

4.2 Exposure of operators, workers and bystanders

The review has identified acceptable exposure scenarios for operators, workers and bystanders, which require, however, confirmation for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

4.3 Ecotoxicology

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account as detailed in section 7 of this report.

5. Identity and Physical/chemical properties

The main identity and the physical/chemical properties of isoxaflutole are given in Appendix I.

The active substance shall have a minimum purity of 950 g/kg technical product.

The review has established that for the active substance notified by the applicant, none of the manufacturing impurities considered are, on the basis of information currently available, of toxicological or environmental concern.

6. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in Annex VI of that Directive, the most important endpoints as identified during the evaluation process are listed in Appendix II.

7. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing isoxaflutole

On the basis of the proposed and supported uses, the following particular issues have been identified as requiring particular and short term (within 12 months at the latest) attention from the Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

Member States should pay particular attention to the potential for groundwater contamination, when the active substance is applied in regions with vulnerable soil and/or climate conditions. Risk mitigation measures or monitoring programs should be applied where appropriate.

8. List of studies to be generated/submitted

No further studies were identified which were considered at this stage, and under the current inclusion conditions necessary in relation to the inclusion of isoxaflutole in Annex I.

However, as outlined above, when granting authorisations Member States may require additional information to ensure adequate protection of ground water resources, e.g. field degradation studies or monitoring programs in critical regions.

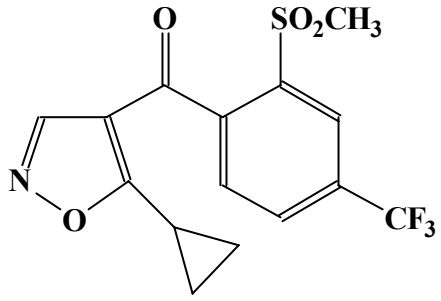
9. Updating of this review report

The technical information in this report may require periodic updating to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Such adaptations will be examined and finalised in the Standing Committee on the Food Chain and Animal Health, in connection with any amendment of the inclusion conditions for isoxaflutole in Annex I of the Directive.

APPENDIX I

Identity, physical and chemical properties

ISOXAFLUTOLE

Common name (ISO)	Isoxaflutole
Development Code (for new actives only)	RPA 201772
Chemical name (IUPAC)	5-cyclopropyl-4-(2-methylsulfonyl-4-trifluoromethylbenzoyl) isoxazole
Chemical name (CA)	5-cyclopropyl-4-isoxazolyl[2-(methylsulfonyl-4-trifluoromethyl) phenyl]-methanone
CIPAC No	575
CAS No	141112-29-0
EEC No	Not yet allocated
FAO SPECIFICATION	Not yet allocated
Minimum purity	950 g/kg
Molecular mass	359.53
Molecular formula	$C_{15}H_{12}F_3NO_4S$
Structural formula	

Melting point	Approx. 140 °C, decomposition above 200 °C
Boiling point	Decomposition < 360 °C
Appearance	White (pure) or yellow (technical) granular powder
Relative density	1590 g/l at 20 °C (99.7%)
Vapour pressure	1 x 10^{-6} Pa at 20 °C (98.7%)
Henry's law constant	1.87 x 10^{-5} Pa·m^3·mol^{-1} at 20 °C (98.7%)
Solubility in water	6.2 mg/l at 20 °C (pH 5.5)
Solubility in organic solvents	At 20 °C (99.7 %): Acetone 293 g/l Dichloromethane 346 g/l Ethylacetate 142 g/l N-hexane 0.10 g/l Toluene 31.2 g/l Methanol 13.8 g/l
Partition co-efficient (log P_{OW})	Log P_{ow} = 2.32 (pH not important)
Hydrolytic stability (DT_{50})	(25 °C): pH 5 11.1 d pH 7 20.1 h pH 9 3.2 h Hydrolysis product: RPA 202248
Dissociation constant	No dissociation anticipated: study not required
Quantum yield of direct photo-transformation in water at ε >290 nm	7.83 x 10^{-4}
Flammability	not highly flammable
Explosive properties	not explosive
UV/VIS absorption (max.)	204 nm and 269 nm in neutral medium Absorption occurs > 290 nm
Photostability in water (DT_{50})	pH 5 at 25 °C: DT_{50} = 40 h, Xenon lamp (λ > 290 nm)

APPENDIX II

END POINTS AND RELATED INFORMATION

ISOXAFLUTOLE

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Oral rat: 60%, mainly within 24 h
Distribution:	Highest levels in liver and kidneys, rat
Potential for accumulation:	Low
Rate and extent of excretion:	> 85 % in urine and faeces, rat; mainly within 24 h
Toxicologically significant compounds:	Parent compound and RPA 202248 (diketonitrile)
Metabolism in animals:	Extensive, saturated at high doses

Acute toxicity

Rat LD_{50} oral:	> 5000 mg/kg bw
Rat LD_{50} dermal:	> 2000 mg/kg bw
Rat LC_{50} inhalation:	> 5.23 mg/l
Skin irritation:	not classified
Eye irritation:	not classified
Skin sensitization (test method used and result):	not classified (Magnusson Kligmann & modified Buehler)

Short term toxicity

Target / critical effect:	Periacinar hypertrophy in liver, ocular lesions, haematological effects
Lowest relevant oral NOAEL / NOEL:	3 mg/kg bw/d, rat
Lowest relevant dermal NOAEL / NOEL:	100 mg/kg bw/d, 21d rat
Lowest relevant inhalation NOAEL / NOEL:	no data available, not required

Genotoxicity

Negative

Long term toxicity and carcinogenicity

Target / critical effect:	Liver and thyroid effects
Lowest relevant NOAEL:	2 mg/kg bw/d; rat

Carcinogenicity:	Liver and thyroid tumours in high dose group.

Reproductive toxicity

Target / critical effect - Reproduction:	Reproductive effects (pup weight gain) at maternally toxic doses.
Lowest relevant reproductive NOAEL / NOEL	2 mg/kg bw/d
Target / critical effect - Developmental toxicity:	Rat oral, minor effects (delayed ossification)
Lowest relevant developmental NOAEL / NOEL	NOAEL maternal = 100 mg/kg bw/d, NOAEL development = 10 mg/kg bw/d, No teratogenic effects

Delayed neurotoxicity

No relevant effects

Other toxicological studies

Toxicology metabolites - no concern for metabolite RPA 203328; Mechanistic studies (eye lesions, tumour formation) performed on the active substance.

Medical data

Currently limited as isoxaflutole is a new active substance

Summary

	Value	Study	Safety factor
ADI:	0.02 mg/kg bw	2 y rat study	AF=100
AOEL systemic	0.02 mg/kg bw/d	90 d oral rat study (60 % absorption)	AF=100
ARfD (acute reference dose):	Not allocated (not necessary)		

Dermal absorption

60 % default value based on physical chemical properties and toxicodynamic observations

2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:	1 %
Non-extractable residues after 100 days:	6 % 9 % after 120 d
Major metabolites above 10 % of applied active substance: name and/or code % of applied rate (range and maximum)	RPA 202248, max. 95 % after 7 d RPA 203328, max. 90 % after 91 - 120 d

Supplemental studies

Anaerobic:	Studies not available, not required
Soil photolysis:	Not sensitive to light
Remarks:	-

Rate of degradation

Laboratory studies

DT_{50}lab (20 °C, aerobic):	Active substance: 0.5, 4 d (mean 2.3 d) RPA 202248: 17, 75 d (mean 46 d) RPA 203328: 205, 853 d (mean 529 d)
DT_{90}lab (20 °C, aerobic):	Not determined
DT_{50}lab (10 °C, aerobic):	Active substance: 5 d RPA 202248: 72 d
DT_{50}lab (20 °C, anaerobic):	Studies not available, not required

Field studies **(Italy, France, Germany, UK)**	
DT_{50f} from soil dissipation studies:	Active substance: 0.5 – 2.4 d (mean 1.3 d, n = 4); normalised to 20 °C and pF2: 0.3 – 1.5 d (mean 0.9 d); RPA 202248: 6.3 – 15.1 d (mean 11.5 d, n = 4); normalised to 20 °C and pF2: 5.8 – 10.4 d (mean 8.7 d); RPA 203328: 14.5 – 76.3 d (mean 43.4 d, n = 4); normalised to 20 °C and pF2: 15.1 – 56.3 d (mean 34.0 d); For FOCUS gw modelling - (normalised to 20 °C and pF2): Active substance: mean 0.9 d RPA 202248: mean 8.7 d RPA 203328: mean 34.0 d (8 scenarios)
DT_{90f} from soil dissipation studies:	Not determined
Soil accumulation studies:	Not performed
Soil residue studies:	Not performed

Remarks	
e.g. effect of soil pH on degradation rate	-

Adsorption/desorption

K_f / K_{oc}:	K_{oc}: Active substance: 93 - 131 L/kg (mean 112 L/kg, n = 4, 1/n = 0.945); RPA 202248: 54 - 159 L/kg (mean 108 L/kg, n = 8, 1/n = 0.941); RPA 203328: 0 L/kg (no reliable results; conservative worst case approach)
K_d:	K_d: not determined
pH dependence:	no
	For FOCUS gw modelling - Active substance: mean: 112 L/kg RPA 202248: mean: 108 L/kg RPA 203328: mean: 0 L/kg

Mobility

Laboratory studies:

Column leaching:	Not performed
Aged residue leaching:	Ageing 3 - 22 h Residues in leachate: Sandy loam: 44-57 % (OM 1.5%) Silty clay: 1-3 % (OM 12.9%) Clay loam: 73-77 % (OM 4.1%) Loam sediment: 2-0 % (OM 14.7%) Sand: 93-93 % (OM 0.2%) RPA 202248 in leachate of 3 soils RPA 203328 in leachate of 1 soil Ageing time insufficient for RPA 203328

Field studies:

Lysimeter/Field leaching studies:	Not performed

Remarks:	-

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:	DT_{50} at 25 °C: pH 4/5 = 11.1 d pH 7 = 20.1 h pH 9 = 3.2 h
Major metabolites:	RPA 202248
Photolytic degradation:	DT_{50} at 25 °C: pH 5 = 40.0 h
Major metabolites:	not determined

Biological degradation

Ready biological degradability:	Not readily biodegradable
Water/sediment study:	
DT_{50} water:	Not available from data supplied
DT_{90} water:	Not available from data supplied
DT_{50} whole system:	Active substance: 0.34 - 0.54 d RPA 202248: 255 - 700 d RPA 205834: 52 - 97 d
DT_{90} whole system:	Not available from data supplied
Distribution in water / sediment systems (active substance)	Not available because of rapid degradation of active substance
Distribution in water / sediment systems (metabolites)	<u>water phase</u> compound max % (at day) % at 100d RPA 202248 52 (2) ; 64 (1) 18 ; 28 RPA 205834 15 (2) ; 20 (7) 2 ; 3 <u>sediment</u> RPA 202248 39 (62); 23 (100) 37 ; 23 RPA 205834 14 (14) ; 8 (30) 10 ; 4 loam system ; clay loam system
Mineralization after 100 days:	< 1%
Non-extractable residues after 100 days:	23%
Accumulation in water and/or sediment:	No

Degradation in the saturated zone

Anaerobic water/sediment study Active substance: DT_{50} < 2 h RPA 202248: DT_{50} > 365 d RPA 205834: DT_{50} > 365 d

Remarks:

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2.3 Fate and behaviour in air

Volatility

Vapour pressure:	1 x 10^{-6} Pa at 25 °C
Henry's law constant:	1.87 x 10^{-5} Pa·m^3·mol^{-1} at 20 °C

Photolytic degradation

Direct photolysis in air:	Not performed
Photochemical oxidative degradation in air DT_{50}:	Photoreaction with OH radicals: Rate constant 5.7 x 10^{-6}/s Corresponds to a DT_{50} of 34 daylight hours
Volatilisation:	Studies not available, not required

Remarks:	-

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:	LD_{50} (rat) > 5000 mg/kg bw
Acute toxicity to birds:	LD_{50} (*Anas platyrhynchos*) > 2150 mg/kg bw
Dietary toxicity to birds:	LC_{50} (*Anas platyrhynchos*) > 4150 ppm
Reproductive toxicity to birds:	Not required (only one application on bare soil and active substance is not persistent)
Short term oral toxicity to mammals:	Not required

Aquatic Organisms

Isoxaflutole

Acute toxicity fish:	LC_{50} (*Oncorhynchus mykiss*) > 1.7 mg a.s./l, 96 h study
Long term toxicity fish:	NOEC (*Oncorhynchus mykiss*) = 0.08 mg a.s./l, 28 d study
Bioaccumulation fish:	BCF: 11 (calculated, based on Kow (=220))
Acute toxicity invertebrate:	EC_{50} (*Daphnia magna*) > 1.5 mg a.s./l, 48 h study
Chronic toxicity invertebrate:	NOEC (*Daphnia magna*) = 0.35 mg a.s./l, 21 d study
Acute toxicity algae:	EC_{50} (*Selenastrum capricornutum*) = 0.12 mg a.s./l, 120 h study
Toxicity aquatic plants:	EC_{50} (*Lemna gibba*) = 16 µg/l (3d EC_{50}), 14 d study
Chronic toxicity sediment dwelling organism:	NOEC *(Chironomus riparius*) = 100 µg/l, 22 d study

Metabolite RPA 202248

Acute toxicity fish:	LC_{50} (*Oncorhynchus mykiss*) > 15 mg a.s./l, 96 h study
Bioaccumulation fish:	BCF: 0.04 (calculated, based on Kow (=0.9))
Acute toxicity invertebrate:	EC_{50} (*Daphnia magna*) > 60 mg a.s./l, 48 h study
Acute toxicity algae:	EC_{50} (*Selenastrum subspicatus*) > 20 mg a.s./l, 72 h study
Toxicity aquatic plants:	EC_{50} (*Lemna gibba*) = 55 µg/l, (14 d study)

Metabolite RPA 203328

Acute toxicity fish:	LC_{50} (*Oncorhynchus mykiss*) = 160 mg a.s./l, 96 h study
Acute toxicity invertebrate:	EC_{50} (*Daphnia magna*) > 150 mg a.s./l, 48 h study
Acute toxicity algae:	EC_{50} (*Selenastrum capricornutum*) > 9.4 mg a.s./l, 120 h study

Metabolite RPA 205834

Acute toxicity fish:	LC_{50} (*Oncorhynchus mykiss*) > 35 mg a.s./l, 96 h study
Bioaccumulation fish:	BCF: 2 (calculated, based on Kow (=41))
Acute toxicity invertebrate:	EC_{50} (*Daphnia magna*) > 100 mg a.s./l, 48 h study
Acute toxicity algae:	EC_{50} (*Selenastrum subspicatus*) > 15 mg a.s./l, 72 h study

Honeybees

Acute oral toxicity:	LC_{50} >168.7 µg a.s./bee
Acute contact toxicity:	LC_{50} >100 µg a.s./bee

Other arthropod species

Laboratory studies — test substance: formulation: EXP31130A (WG 750 g/kg)

Aphidius rhopalosiphi	E (total effect, 150 g a.s./ha) = 61% (adults; parasitisation) E (mortality): 0 % 24 h; 30 % 48 h
Typhlodromus pyri	E (total effect, 150 g a.s./ha) = 15% (protonymphs; mortality, fecundity)
Poecilus cupreus	NOEL = 195 g/ha, 14 d study with adults
Pardosa spp.	E (total effect, 150 g a.s./ha) = 71% (adults; mortality, fecundity) E (mortality): 50 %

Extended laboratory studies — test substance: formulation: EXP31130A (WG 750 g/kg)

Aphidius rhopalosiphi	E (total effect, 150 g a.s./ha) = 77% (adults; mortality, fecundity) E (mortality): 40 % higher tier studies are not required, due to the application on bare soil (no exposure expected)
Pardosa spp.	only significant effect at 100 g/ha on food-intake (40%), effect on mortality < 30%, effects on mortality at 4 g a.s./ha (based on 4% drift at 1 m): 0 %

Earthworms

Isoxaflutole

Acute toxicity:	LC_{50} > 1000 mg a.s./kg soil
Reproductive toxicity:	Not required

Metabolite RPA 203328

Acute toxicity:	LC_{50} > 1000 mg as/kg soil

Soil micro-organisms

Isoxaflutole

Nitrogen mineralization:	No unacceptable effects at 0.2 and 1.0 mg/kg
Carbon mineralization:	No unacceptable effects at 0.2 and 1.0 mg/kg

Metabolite RPA 203328

Nitrogen mineralization:	No unacceptable effects at 0.9 mg/kg
Carbon mineralization:	No unacceptable effects at 0.9 mg/kg

APPENDIX III

ISOXAFLUTOLE

List of studies which were submitted during the evaluation process and were not cited in the draft assessment report:

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA 2.7.3	L. Uceda, F. Yslan	1996	EXP31130, Stability after 2 years storage at ambient temperature Generated by: Rhone-Poulenc Agro. Submitted by: Rhone-Poulenc Agro. Report/file N$^{o:}$ CRLD/AN/9616509 Study 94-121 /2A Date of report: 26 Nov. 1996 GLP, Unpublished
IIA 4.2/01	Bourgade, C., Diot, R, Jendrzejcak, N., Yslan, F.	1998	Isoxaflutole and its metabolite (RPA202248): analytical method for the determination of residues in raw and processed maize products using immuno-affinity purification. Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N$^{o:}$ CRLD/AN/9815782 (Method AR 161-97) Date of report: June 05, 1998 GLP Unpublished
IIA 4.2/02	Luscombe, B.M.	1998	The use of immuno-chemistry in residue analysis. A summary to support a new IFT plant MOA. Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N$^{o:}$ not given Date of report: not specified Not GLP Unpublished
IIA 4.2/03	Diot, R, Yslan, F.	1998	Isoxaflutole and its metabolite (RPA202248): analytical method for the determination of residues in raw and processed maize products. Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N$^{o:}$ CRLD/AN/9816718 (Method AR 169-98) Date of report: October 19, 1998 GLP Unpublished

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 5.4.2/02	Proudlock, R.J., Grant, R.A., Dawe, I.S	1997	RPA 201772 - Rat Liver DNA Repair (UDS) Test Generated by: Huntingdon Life Sciences Ltd., U.K. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: RNP 546/973665 Date of report: October 29, 1997 GLP Unpublished
IIA 5.5.1/02	Lee, P.N.	1997	Study RPA 201772 a.i. 104 Week Rat Dietary Study of Isoxaflutole Statistical Analysis and Interpretation of Microscopic and macroscopic Data for the Thyroids Generated by: P.N. Lee Statistics and Computing Ltd., Surrey, U.K. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: - Date of report: September 15, 1997 Not GLP Unpublished
IIA 5.5.1/03	Anonymous	1997	SUPPLEMENTAL INFORMATION Historical histopathology data, CD rat-selected 2 year studies, thyroid tymours. Data provided for use with RHA 499. Generated by: Huntingdon Life Sciences, Submitted by: Rhone-Poulenc Agro, France. Report/file N°: Date of report: 8 September 1997 Not GLP Unpublished
IIA 5.8.1/01	Anonymous	1997	Critical Review of Published data on Eye Lesions Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: - Date of report: August, 1997 Not GLP Unpublished
IIA 5.8.1/02	Anonymous	1997	The Literature review cited in Isoxaflutole European dossier Annex II tier 2, concerning section 5.8.1 <Eye Lesion Mechanistic Overview>. Generated by: - Submitted by: Rhone-Poulenc Agro, France. Report/file N°: - Date of report: August, 1997 Not GLP Published

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 5.6.2/03	Repetto, M. and Berthe, P.	1997	POSITION PAPER Isoxaflutole : evaluation of the rat teratology study. Generated by: Rhone-Poulenc Agro, France Submitted by: Rhone-Poulenc Agro, France. Report/file N°: Appendix 4, Response Document to the Monograph Date of report: March 14, 1997 Not GLP Unpublished
IIA 5.6.2/04	Berthe, P.	1998	POSITION PAPER Isoxaflutole, response document to the Scientific Committee on Plants (SCP), evaluation of isoxaflutole developmental effects. Generated by: - Rhone-Poulenc Agro, France Submitted by: Rhone-Poulenc Agro, France. Report/file N°: Date of report: August 10, 1998 Not GLP Unpublished
IIA 5.6.1/03	Berthe, P.	1999	POSITION PAPER Two-Generation Reproduction Study with RPA 201772 in Rats, "Large renal pelvis" incidence in female F2 weanlings. Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: - Date of report: March 11, 1999 Not GLP Unpublished

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 6.1	Nandihalli, U.B.	1996	Freezer Storage Stability of RPA 201772 in Field Corn Samples Generated by: Corning Hazleton Inc. Madison, Wisconsin Submitted by: Rhone-Poulenc Agro, France. Report/file N°: CHW 6224-223 Date of report: November 7, 1996 GLP Unpublished

B.8 Environmental fate and behaviour

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA 7.1.1	Hardy, I.	2001	Isoxaflutole: Kinetic modelling analysis of a European terrestrial field soil dissipation study. Aventis Crop Science, Report no. CX01033A. GLP Unpublished
IIA 7.1.1.2.2/01	Gatzweiler, E.W.	1996	RPA 201772: Terrestrial Field Dissipation Study Generated by: Rhone-Poulenc Agriculture Ltd. Ongar, England Submitted by: Rhone-Poulenc Agro France Report/file N^{o} - Date of report: February, 1996 GLP Unpublished
IIA 7.1.2/7.1.3	Burr, C.M.	1996	[^{14}C]-RPA202248: Adsorption / desorption to and from four soils and an aquatic sediment, Rhône-Poulenc Agriculture Ltd. Report No: 201213. GLP Unpublished
IIA 7.1.2/7.1.3	Burr, C.M.	1996	[^{14}C]-RPA203328: Adsorption / desorption to and from four soils and an aquatic sediment, Rhône-Poulenc Agriculture Ltd. Report No: 201220. GLP Unpublished
IIA 7.2	Kubiak, R.	1997	Investigation of the volatilisation of 14C-isoxaflutole formulated corresponding to EXP31130A from plant and soil surfaces under laboratory conditions. Generated by: SLFA, Germany Submitted by: Rhone-Poulenc Agro France Report/file N^{o} RPA23 Date of report: February 26, 1997 GLP Unpublished
IIIA 9.2.1	Hardy, I.A.J.	2001	Isoxaflutole: Leaching Risk Assessment for isoxaflutole and two metabolites using the European FOCUS groundwater scenario's. Aventis report C015656. GLP Unpublished

B.9 Ecotoxicology

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA 8.2.1	Odin-Feurtet, M.	1997	Isoxaflutole - Toxicity to the sediment dwelling chironomid larvae (Chironomus riparius) - 28 days-. Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: SA 97335 Date of report: December 18, 1997 GLP Unpublished
IIA 8.2.8/02	Hoberg, J.R.	1999	Isoxaflutole (IFT) - Toxicity to the Duckweed, *Lemna gibba*. Rhône-Poulenc Agro, Report no. 603849. GLP Unpublished
IIA 8.2.8/03	Hoberg, J.R.	1997	RPA 202248 technical - Toxicity to Duckweed, *Lemna gibba*. Rhône-Poulenc Agro, Report no. 97-9-7066. GLP Unpublished
IIA 8.4.1.1/02	Odin-Feurtet, M.	1997	RPA 203328 Acute Toxicity (14 days) to Earthworms (Eisenia foetida). Artificial soil method. Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: SA 97408 Date of report: October 28, 1997 GLP Unpublished
IIA 8.5/02	McMurray, A.	1997	A Laboratory Assessment of the Effects of RPA 203328 on Soil Micro flora Respiration and Nitrogen Transformations According to EPPO Bulletin 24, 1016 (1994). Generated by: Chemex International plc. UK. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: ENV3016 / GOoD 14070 Date of report:18 December, 1997 GLP Unpublished
IIIA 10.5/ IIA 8.5	McCahon, P.	1997	<u>POSITION PAPER</u> Response to requirement for additional ecotoxicology data. Generated by: Rhone-Poulenc Agro, France. Submitted by: Rhone-Poulenc Agro, France. Report/file N°: Appendix 3, Response Document to the Monograph Date of report: March 14, 1997 Not GLP Unpublished

APPENDIX IV

List of uses supported by available data

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment		
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max
maize	Italy, Spain	EXP 31130 A	F	weeds	WG	750 g/kg	spraying, soil treatment	after sowing, pre-emergence (May)	1		0.05	200	0.100
maize	Germany	EXP 31130 A	F	weeds	WG	750 g/kg	spraying, soil treatment	after sowing, pre-emergence (May)	1		0.025-0.05	200-400	0.100
maize	France	EXP 31130 A	F	weeds	WG	750 g/kg	spraying, soil treatment	after sowing, pre-emergence (May)	1		0.02-0.05	200-500	0.100

maize	Netherlands	Merlin (EXP 31130 A)	F	weeds	WG	750 g/kg	sprayin g, soil treatme nt	after sowing, pre-emerge nce (May)	1		0.025-0.05	200-400	0.100
maize	Greece	EXP 31130 A	F	weeds	WG	750 g/kg	sprayin g, soil treatme nt	after sowing, pre-emerge nce (May)	1		0.025-0.033	300-400	0.100

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting,
(h) drench
Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions