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Document Title

Summary of the fate and behaviour in the environment for Isoxaflutole

Data Requirements

EU Regulation 1107/2009 & EU Regulation 283/2013
Document MCA
Section 7: Fate and behaviour in the environment

According to the guidance document, SANCO 10181/2013, for
preparing dossiers for the approval of a chemical active substance

Date

2013-11-22

Author(s)

Bayer CropScience

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Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number

[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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CA 7 FATE AND BEHAVIOUR IN THE ENVIRONMENT

Information on the updated dossier for the Annex I Renewal

Data on the fate and behaviour of isoxaflutole (RPA 201772) in soil, water and air were submitted within the EU Basic Dossier for Annex I inclusion in the year 1995. This document therefore focuses on those environmental fate studies which were **not** submitted within in the EU Basic Dossier.

For a better overview existing data and their evaluation resulting from the process of Annex I inclusion are summarized shortly amended by new data generated in order to fulfil current requirements. The numbering and the headlines correspond to latest EU requirements.

The studies investigating into the environmental fate of isoxaflutole were performed with the following position of ^{14}C-radiolabel:

(§): [phenyl-UL-^{14}C]isoxaflutole
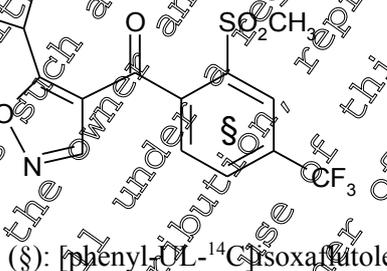
In addition, studies were performed with diketonitrile metabolite RPA 202248 labelled in the cyclopropyl ring:

(*): [cyclopropyl-1-^{14}C]RPA 202248

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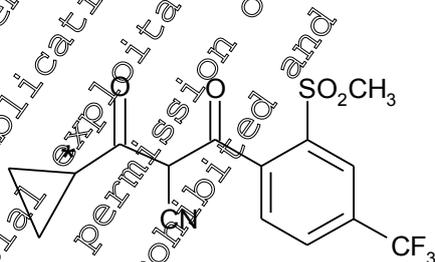
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CA 7.1 Fate and behaviour in soil

CA 7.1.1 Route of degradation in soil

CA 7.1.1.1 Aerobic degradation

Documents given in grey text were submitted within the EU Basic Dossier for Annex I inclusion in 1995.

Report:	██████x; ████; ████; ████;1994;M-158435-01
Title:	RPA201772: Aerobic soil metabolism
Report No:	R000347
Document No:	M-158435-01-1
Guidelines:	**USEPA (=EPA): N, 162-1, (1982);Deviation not specified**
GLP/GEP:	**yes**

Report:	████ ; ████;1995;M-213110-01
Title:	Herbicides: RPA 201772 Route of degradation (aerobic metabolism) in one soil (interim report)
Report No:	C022444
Document No:	M-213110-01-1
Guidelines:	**EU (=EEC): annex I, section 7.1 (1995);Deviation not specified**
GLP/GEP:	**yes**

Report:	████d; ████;1996;M-240821-01
Title:	Herbicides: Isoxaflutole Route of Degradation (Aerobic Metabolism) in one Soil
Report No:	B003826
Document No:	M-240821-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

Report:	████7; ████; ████; ████;1996;M-240822-01
Title:	RPA 201772: Rate of Degradation under Aerobic Conditions in Three Soil Types
Report No:	B003827
Document No:	M-240822-01-1
Guidelines:	**EU (=EEC): 7171/VI/94-EN rev 1; FAO: Draft Rev.3, Part 1,1.1;Deviation not specified**
GLP/GEP:	**yes**

Report:	████; ████;2012;M-427583-01
Title:	[Cyclopropyl-1-14C]RPA 202248:: Aerobic degradation/metabolism in one European soil
Report No:	MEF-11/486
Document No:	M-427583-01-1
Guidelines:	**OECD 307; US EPA OPPTS 835.4100 and OPPTS 835.4200; EU 95/36/EC amending 91/414/EEC;not specified**
GLP/GEP:	**yes**

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The route of degradation in aerobic soil had been investigated under laboratory conditions in three studies:
- two soils at 21°C and moisture at 75% of the field capacity at 0.33 bar following application of phenyl-UL-^{14}C-labeled active substance (KCA 7.1.1.1 /01);
- one soil under standard conditions at 20°C and moisture at 45% maximum water holding capacity (MWHC) after application of phenyl-UL-^{14}C-labeled active substance (KCA 7.1.1.1 /02 and KCA 7.1.1.1 /03);
- three soils under standard conditions at 20°C and moisture at 40 % MWHC following application of phenyl-UL-^{14}C-labeled active substance (KCA 7.1.1.1 /04).

The data requirement was addressed under Point 7.1.1.1.1 of the Dossier submitted and evaluated within the process of evaluation for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently there is no detailed description of this existing data in this update.

The evaluation revealed that the degradation of isoxaflutole predominantly proceeded via ring opening at the isoxazole heterocyclic ring system and rearrangement in the formation of the major (>10% AR) and predominant metabolite diketonitrile RPA 202248. The step can be induced by chemical and biotical processes. The biotic degradation of RPA 202248 resulted in the formation of benzoic acid RPA 203328 as a major metabolite. Finally, metabolite RPA 205834 was observed at trace level in aerobic soil degradation tests. The degradation in aerobic soil was accompanied by formation of non-extractable residues (NER) while the extent of mineralization was low under the conditions of the laboratory.

At the time of review for Annex I inclusion metabolites RPA 202248 and RPA 203328 occurred as major compounds in tests on route of degradation in aerobic soil. The two compounds were thus considered as residues in the environmental risk assessments for soil, ground water and surface water.

For current risk assessments no further metabolites were considered when following the introduction of new data requirements including new trigger values as laid out in Commission Regulation 283/2013 amending Regulation 1107/2009.

The metabolic pathway in aerobic soil under conditions of the laboratory is summarized in Figure 7.1.1.1.

In order to demonstrate the degradability of potential residues originating from the cyclopropane ring in aerobic soil, a study was performed starting from the rapidly formed metabolite diketonitrile RPA 202248 rather than from the correspondingly labeled active substance (KCA 7.1.1.1 /05).

Invalidation of study KCA 7.1.1.1 /01:
During the review in preparation for Annex I Renewal it was found that extraction of soil samples was performed by applying several successive extraction steps in the course of the study. These included ambient extraction and up to two further extraction steps, i.e. extraction with acidified solvent and further extraction methods like Soxhlet extraction. The latter steps of extraction started for both soils either after 14 days of incubation (sandy loam) or straight after application at day zero (clay) till study end. For example, the levels of radioactivity amounted to 8.5% of applied radioactivity for the sandy loam soil by day 14 or 9.1% for the clay soil by day zero to be 16.0% (sandy loam) and 10.5% (clay) after 12 months of incubation.
However, the radioactivity in these additional extracts was not subject to analysis. Therefore their contribution to the overall distribution of components in the extractable portion of radioactivity formed must be unknown. Consequently, there is no adequate description of the total pattern of metabolites possible for this study.

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Study KCA 7.1.1.1 /01 is therefore regarded as invalid with no consideration within the process of Annex I renewal of isoxaflutole.

Figure 7.1.1.1-1 Proposed pathway of metabolism of isoxaflutole (RPA 201772) in aerobic soil

Isoxaflutole, IFT
RPA 201772

RPA 205834
(minor)

Diketonitrile, DKN
RPA 202248

Benzoic acid, BA
RPA 203328

Non-Extractable Residues (NER) and Carbon Dioxide

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Report:	d; ;2012;M-427583-01
Title:	[Cyclopropyl-1-14C]RPA 202248:: Aerobic degradation/metabolism in one European soil
Report No:	MEF-11/486
Document No:	M-427583-01-1
Guidelines:	**OECD 307; US EPA OPPTS 835.4100 and OPPTS 835.4200; EU 95/36/EC amending 91/414/EEC;not specified**
GLP/GEP:	**yes**

Executive Summary

The degradation of [cyclopropyl-1-^{14}C]-RPA 202248 was investigated in one European soil under aerobic conditions by incubation in the dark at 20 °C and a soil moisture of 55% of MWHC for 91 days in maximum. The test was performed at a test concentration of 0.533 mg test substance/kg soil, equivalent to a field application rate of 200 g a.s./ha.

Recovery of radioactivity was 96.6% $\pm$ 3.7%. Total extractable radioactivity decreased from 101.5% on day zero to 5.9% on day 91. The decrease of extractable radioactivity was accompanied by the formation of non-extractable residues (NER) to account for 38.9% AR after 91 days. Mineralisation was significant to account for 47.5 % of AR determined as ^{14}C-carbon dioxide by day 91. Formation of other organic volatile components was insignificant ($\leq$ 0.1% AR).

As a result of rapid biotransformation in soil no other formation of metabolites than ^{14}C-carbon dioxide was observed at a significant level in the course of the study.

The biotic character of degradation of [^{14}C]-RPA 202248 in aerobic soil was clearly underlined by the formation of ^{14}C-carbon dioxide as the major product of conversion along with the formation of non-extractable (bound) residues.

The degradation of [cyclopropyl-1-^{14}C]-RPA 202248 in aerobic soil was fast to result in a half-life of 14 days based on an SFO best fit kinetic model.

I. Material and Methods

A. Materials

1. Test Material: [Cyclopropyl-1-^{14}C]RPA 202248 (AE 0540092, BCS-AB59005)

Specific radioactivity: 4.08 MBq/mg (110.26 µCi/mg)

Radiochemical purity: > 98% (HPLC, radiodetection)

Chemical purity: > 99% (HPLC-UV)

Sample ID: KML 9250

2. Soil: The soil had been freshly collected from the field followed by sieving to 2 mm. The physico-chemical characteristics are summarized in Table 7.1.1.1-1.

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Table 7.1.1.1-1: Characteristics of test soil

Soil	
Geographic Location (City / State / Country)	▮ / ▮, Germany
GPS coordinates	▮
Pesticide use history	No use for previous 5 years
Collection procedures	Sample taken with shovel and transport in plastic bag
Sampling depth	0 – 20 cm
Storage conditions	Ambient
Storage length	2 days prior to use
Soil preparation	Sieved (2 mm)
Soil Series / Taxonomic name (USDA)	Loamy, mixed, mesic Typic Argudalfs
Texture Class (USDA)	silt loam
Sand [50 μm - 2 mm] (%)	19
Silt [2 μm - 50 μm] (%)	64
Clay [< 2 μm] (%)	17
pH, saturated paste	6.8
pH in water	6.7
pH in 1 N aq. KCl	6.1
pH in $CaCl_2$ (0.01 M)	6.5
Organic Matter [A] (%)	2.8
Organic Carbon (%)	1.6
Microbial biomass (mg microbial C/kg dw soil) Day 0 (start) Day 91 (study end) Day 91 (study end, solvent)	668 551 477
CEC (meq/100 g)	12.2
55% of MWHC (g/100 g)	28.6
MWHC (g water /100 g soil)	52
Moisture at 0.33 bar = pF 2.5 (g water /100 g soil)	21
Bulk density (sieved) (g/mL)	1.12

[A]) % organic matter = % organic carbon × 1.724;
CEC: Cation exchange capacity; MWHC: Maximum Water Holding Capacity; n.d.: not determined

B. Study design

1. Experimental conditions: Samples of 100 g dry weight of soil each were filled into glass incubation flasks and pre-equilibrated prior to treatment at approximate study conditions (darkness, 20 °C, moisture content of 55% MWHC) for 4 days. At start, each sample received 0.533 mg test substance/kg soil, a dose representing a field rate of 200 g a.s./ha. Following application the samples were attached to 'static' systems with traps to collect ^{14}C-carbon dioxide and other volatile components. Samples were incubated at 20 ± 1 °C and a moisture content of 55% MWHC in the dark for 91 days in maximum. In addition, untreated soil samples were incubated under the same conditions for determination of soil microbial activity.

2. Sampling: Duplicate samples were removed for work-up after 0, 1, 3, 7, 14, 30, 58 and 91 days of incubation. Samples for determination of soil microbial biomass were investigated after 0 and 91 days of incubation. The complete samples were immediately processed by extraction and HPLC analysis was usually performed the same day. Therefore no additional investigations of storage stability were necessary.

3. Analytical procedures: The entire soil sample in each test vessel was processed by a stepwise extraction procedure. The initial step was performed with 80 mL aqueous acetonitrile solution (4:1, v/v) three times successively by shaking the soil/solvent mixture at ambient temperature for 30 min. After separation by centrifugation the soil was extracted again with the same volume of the same solvent mixture twice successively by heating in a microwave extractor at 70°C for 10 min with stirring, followed by centrifugation. Microwave and ambient extracts were combined and an aliquot (10 mL) concentrated to a small volume (2 mL) prior to analysis.

The ^{14}C-material balance was established for each sample by extraction, analysis of volatiles and combustion of non-extractable residues. Following quantitation of radioactivity in extracts by LSC, analysis was performed by reversed phase HPLC and ^{14}C-flow-through detection techniques. The determination of non-extractable residues (NER) was performed by combustion/LSC of aliquots of the air-dried extracted soil.

The LOQ of the HPLC analytical method was estimated to be 0.9% AR on the basis of the LOD of the radio-detector and based on the smallest peaks observed in various chromatograms in the course of the study.

C. Determination of degradation kinetics: Degradation data were kinetically evaluated by use of the software KinGui, version 1.1. Following calculations of fits with kinetic models SFO, FOMC and DFOP, the best fit was evaluated to be a minimum in the significance test and the error of chi-square (χ^2), followed by visual assessment.

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II. Results and Discussion

A. Data: The results of aerobic biotransformation of [cyclopropyl-1-^{14}C]RPA 202248 after incubation in one European soil are summarized in Table 7.1.1.1-2.

Table 7.1.1.1-2: Degradation of [cyclopropyl-1-^{14}C]RPA 202248 in silt loam soil ▇▇▇▇ under aerobic conditions (mean ± SD)

Component		Sampling interval (days)							
		0	**1**	**3**	**7**	**14**	**30**	**58**	**91**
RPA 202248	Mean*	100.9	95.0	91.7	76.8	57.3	17.8	3.3	2.1
	SD	±1.2	±0.6	±1.2	±0.5	±0.0	±0.5	±0.0	±0.2
Total other unidentified**	Mean*	0.5	0.0	0.0	0.0	0.0	3.4	4.2	3.8
	SD	±0.0	±0.0	±0.0	±0.0	±0.0	±0.1	±0.4	±0.1
Total extractable radioactivity	Mean*	101.5	95.0	91.7	76.8	57.3	21.2	7.7	5.9
	SD	±0.7	±0.6	±1.2	±0.5	±0.0	±0.6	±0.2	±0.0
Non-extractable radioactivity	Mean*	0.7	3.3	8.3	17.8	27.0	42.4	40.9	38.9
	SD	±0.0	±0.1	±0.1	±0.3	±0.1	±0.4	±0.3	±0.3
$^{14}CO_2$	Mean*	0.0	0.2	0.9	2.7	11.6	30.2	43.2	47.5
	SD	±0.0	±0.0	±0.0	±0.0	±0.4	±0.3	±0.4	±0.0
Other volatiles	Mean*	0.0	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	SD	±0.0	±0.0	±0.0	±0.0	±0.0	±0.0	±0.0	±0.0
Total radioactivity (%)	Mean*	102.1	98.5	100.9	97.3	95.9	93.8	91.8	92.3
	SD	±0.7	±0.7	±1.3	±0.1	±0.4	±0.5	±0.5	±0.3

Values given as percentages of initially applied radioactivity
SD = standard deviation; * Mean values of two replicates; ** Distributed into six components in maximum with none of the individual components observed at more than 1.0% AR in the course of the study

B. Mass balance: The total material balances of radioactivity showed a complete recovery to range from 91.8 – 102.1% AR. The results are summarised in more detail in Table 7.1.1.1-3. Conclusively there were no signs for losses of radioactivity from sample work-up and processing.

Table 7.1.1.1-3: Total material balances of radioactivity of ^{14}C-202248 in one EU soil

Soil	▇▇▇▇▇
Total Recovery (% AR)	91.8 – 102.1
Mean (% AR)	96.6
Rel. standard deviation	3.7

Values given as percentages of initially applied radioactivity

C. Bound and extractable residues: Values of extractable radioactivity decreased rapidly with time accompanied by formation of non-extractable residues to finally undergo ultimate degradation as summarized in Table 7.1.1.1-4. Starting from a complete extractability given by day zero (101.5%) values decreased to 5.9% after the maximum incubation period of 91 days.

In turn, values for non-extractable radioactivity (NER) were low by day zero starting from 0.7% to increase to 42.4% by day 30 and to decrease to 38.9% at the last sampling interval (day 91).

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Table 7.1.1.1-4: Extractable and non-extractable residues of ^{14}C-RPA 202248 in one EU soil (mean ± SD)

Soil	Extractable residues (%)		Non-extractable residues (%)	
	Day 0	Day 91	Day 0	Day 91
▉▉▉▉▉	101.5 ±0.7	5.9 ±0.0	0.7 ±0.0	37.9 ±0.3

Values given as percentages of initially applied radioactivity.

D. Volatile radioactivity: ^{14}C-RPA 202248 was extensively mineralised to ^{14}C-carbon dioxide to account for 47.5% AR at study end (day 91). Formation of other volatile radioactivity was insignificant at any sampling interval (≤0.1% AR).

E. Transformation of test substance: ^{14}C-carbon dioxide was formed as the major and predominant transformation product observed in the course of the study. No single component was observed at a significant level while other unidentified components occurred at trace level in the course of the study. The biotic character of RPA 202248 degradation in aerobic soil is underlined by the formation of non-extractable (bound) residues that showed a decline but could not be converted fully to carbon dioxide during the runtime of the study.

F. Degradation kinetics: The degradation kinetics was evaluated by fitting of data to the three kinetic models SFO, FOMC (Gustafson-Holden) and DFOP[1] for the test substance only with the quality of fits assessed according to FOCUS kinetic guidance. The initial concentration at time zero was included in the parameter optimisation. All data points were weighted equally. For optimal goodness of fit, the initial value was also allowed to be estimated by the model. The best-fit kinetic model was selected by applying the criteria for chi-square (χ^2) scaled-error to be a minimum and on the basis of visual assessment. The results of the kinetic evaluation are provided in Table 7.1.1.1-5.

The fits describing degradation of RPA 202248 in the soil resulted in low chi-square (χ^2) errors for all models applied with overall ranges of χ^2-errors being marginal with the SFO kinetic model to result also in a visually acceptable fit.

The degradation half-life of RPA 202248 was 14 days associated with a DT$_{90}$-value of 47 days.

Table 7.1.1.1-5: Kinetics of aerobic degradation of RPA 202248 in one soil at 20°C

Soil	Kinetic model	DT$_{50}$ (days)	DT$_{90}$ (days)	Chi^2 Err (%)	Visual assessment
▉▉▉▉▉	**SFO**	**14**	**47**	**5.1**	**+**
	FOMC	14	48	5.6	+
	DFOP	14	47	5.9	+

Best fits according to the criteria set are marked bold.
Visual assessment: + good, o medium; - bad

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[1] SFO = Single first order; FOMC = First order multi compartment; DFOP = Double first order in parallel

III. Conclusion

Following application of cyclopropyl-1-^{14}C-RPA 202248 to one aerobic soil the formation of other metabolites than ^{14}C-carbon dioxide was insignificant when considering its contribution to investigations into the route of degradation of isoxaflutole residues in aerobic soil.

The degradation of cyclopropyl-1-^{14}C-RPA 202248 in one aerobic soil was fast to result in a half-life of 14 days following SFO as the best fit kinetic model.

Results of kinetic evaluation of this study were also used in report KCA 7.1.2.2.1 /06 in order to derive modeling input parameters.

CA 7.1.1.2   Anaerobic degradation

Report:	▓▓▓▓k; ▓▓▓; ▓▓▓▓▓▓:1995;M-192288-01
Title:	RPA201772 Anaerobic Aquatic Metabolism
Report No:	R016760
Document No:	M-192288-01-1
Guidelines:	**USEPA (=EPA): N-162-3 (1982); Deviation not specified**
GLP/GEP:	**yes**

The route of degradation of isoxaflutole in anaerobic soil had been investigated in one study under laboratory conditions in:

- one water-logged soil under standard conditions (20°C) following application of UL-^{14}C-phenyl-labeled active substance (KCA 7.1.1.2 /01).

The data requirement was addressed under Point 7.1.1.2.1 of the Dossier submitted and evaluated within the process of evaluation for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently there is no detailed description of this existing data in this update.

The evaluation revealed that isoxaflutole degraded slowly under anaerobic conditions of the test to form the same pattern of metabolites as observed under aerobic conditions. The degradation of the active substance isoxaflutole therefore included the formation of the diketonitrile RPA 202248 as a major metabolite. Metabolite RPA 203834 was observed as a major component in addition, while this compound had been observed as a minor compound in aerobic soil. Its transient character was demonstrated by a decrease in the course of the test. Finally, the benzoic acid RPA 203328 was observed as a minor component.
No other metabolites were observed at levels requiring further assessment as laid out in the actual data requirements according to Commission Regulation 283/2013 amending Regulation 1107/2009.

Based on the results it has been concluded that the route of anaerobic soil degradation is identical to that observed in aerobic soil.

CA 7.1.1.3   Soil photolysis

Report:	§; ;1994;M-158351-01
Title:	RPA201772 - Soil photolysis
Report No:	R000311
Document No:	M-158351-01-1
Guidelines:	**USEPA: 161-3 (1982); not specified**
GLP/GEP:	**yes**

The route of degradation on irradiated soil surfaces had been investigated in one study under laboratory conditions in:

- one US soil under standard conditions ($25°C$, 75 % of field capacity at 0.33 bar) following application of UL-^{14}C-phenyl-labeled active substance and irradiation with artificial sunlight (xenon burner, cutoff of wave lengths <290 nm) for 31 days in maximum (KCA 7.1.1.3 /01).

The data requirement was addressed under Point 7.1.1.2.2 of the Dossier submitted and evaluated within the process of evaluation for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments with no detailed description here.

The evaluation revealed that isoxaflutole was rapidly degraded in irradiated samples and in dark controls under the conditions of the test. However the qualitative pattern (i.e. route) of metabolites formed as well as their quantitative occurrence (i.e. rate) was practically the same for irradiated samples and for dark control samples incubated in parallel. Metabolites RPA 202248 and RPA 203328 were observed as the only major (>10% AR) components.
Conclusively, the degradation observed in irradiated samples was mainly due to the contribution of biotic degradation. Degradation rates were similar for irradiated samples and dark controls to result in values for the half-life of 22.8 hours (0.95 days) for irradiated samples and 19.7 hours (0.82 days) for dark controls under the conditions of the test.

Consequently, photolytic processes do not contribute significantly to the overall elimination of isoxaflutole residues from the soil environment.

No other metabolites were observed at levels requiring further assessment as laid out in the actual data requirements according to Commission Regulation 283/2013 amending Regulation 1107/2009.

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CA 7.1.2   Rate of degradation in soil

CA 7.1.2.1   Laboratory studies

CA 7.1.2.1.1   Aerobic degradation of the active substance

Report:	████████████n; ████████; ████████;1994;M-158435-01
Title:	RPA201772: Aerobic soil metabolism
Report No:	R000347
Document No:	M-158435-01-1
Guidelines:	**USEPA (=EPA): N, 162-1, (1982);Deviation not specified**
GLP/GEP:	**yes**

Report:	████████████5; ████████;1995;M-213110-01
Title:	Herbicides: RPA 201772 Route of degradation (aerobic metabolism) in one soil (interim report)
Report No:	C022444
Document No:	M-213110-01-1 (Interim report)
Guidelines:	**EU (=EEC): annex I, section 7.1 (1995); Deviation not specified**
GLP/GEP:	**yes**

Report:	████████████6; ████████;1996;M-240821-01
Title:	Herbicides: Isoxaflutole Route of Degradation (Aerobic Metabolism) in one Soil
Report No:	B003826
Document No:	M-240821-01-1 (Final report)
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

Report:	████████5; ████████; ████████;1996;M-240822-01
Title:	RPA 201772: Rate of Degradation under Aerobic Conditions in Three Soil Types
Report No:	B003827
Document No:	M-240822-01-1
Guidelines:	**EU (=EEC): 7171/VI/94-EN rev 1; FAO: Draft Rev.3, Part 1,1.1; Deviation not specified**
GLP/GEP:	**yes**

Report:	████████████n ████████;1996;M-213113-01
Title:	RPA 201772: Rate of degradation under aerobic conditions in one soil at 10 degrees C
Report No:	C022446
Document No:	M-213113-01-1
Guidelines:	**EU (=EEC): 7171/VI/94-EN rev.1, section 7.1.1.1 (1994); FAO: Annex to Environmental ...., revision I;Deviation not specified**
GLP/GEP:	**yes**

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Report:	g; ;2013;M-464601-01
Title:	Isoxaflutole: Kinetic modelling evaluation of aerobic soil degradation study data to derive trigger endpoints
Report No:	VC/13/007C
Document No:	M-464601-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009; not applicable**
GLP/GEP:	**no**

Report:	n; ;2013;M-464596-01
Title:	Isoxaflutole: Kinetic modelling evaluation of aerobic soil degradation study data to derive modelling endpoints
Report No:	VC/13/007B
Document No:	M-464596-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009; not applicable**
GLP/GEP:	**no**

For the active substance isoxaflutole laboratory data on the rate of degradation in aerobic soil can be derived from studies performed under the following conditions:

- two soils at 21°C and moisture at 75% of the field capacity at 0.33 bar after application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.1 /01);
- one soil under standard conditions at 20°C and moisture at 45 % maximum water holding capacity, (MWHC) after application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.1 /02 and KCA 7.1.2.1.1 /03);
- three soils under standard conditions at 20°C and moisture at 40% MWHC following application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.1 /04);
- one soil at 10°C and 40 % MWHC and application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.1 /05).

This data requirement had been addressed under Point 7.1.1.2 of the Dossier submitted and evaluated within the process of evaluation for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

Following latest guidance on kinetic evaluation, the data from existing studies have been re-evaluated therefore superseding the existing kinetic evaluations.

The evaluations were performed separately in order to derive values for the half-lives and the DT$_{90}$ for comparison with trigger endpoints and half-lives for modeling endpoints for input into environmental risk assessments.

As explained under KCA 7.1.1.1 in more detail, study KCA 7.1.2.1.1 /01 had been invalidated and thus not included into the current evaluations.

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Isoxaflutole

Report:	h; ;2013;M-464601-01
Title:	Isoxaflutole: Kinetic modelling evaluation of aerobic soil degradation study data to derive trigger endpoints
Report No:	VC/13/007C
Document No:	M-464601-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009; not applicable**
GLP/GEP:	**no**

Executive Summary

For the active substance isoxaflutole degradation data as referenced under KCA 7.1.2.1.1 /02 to KCA 7.1.2.1.1 /05 were kinetically evaluated according to FOCUS Guidance to derive values for the half-life and the DT_{90} in aerobic soil for comparison with trigger endpoints[2].

For metabolites RPA 202248 and RPA 203328 the kinetic analysis was performed in combination with parent compound data, amended by aerobic soil degradation data from separate tests with RPA 202248. The results are summarized under Point 7.1.2.1.2.

For the evaluation degradation data of the active substance isoxaflutole in soil under aerobic conditions of the laboratory were considered from three studies following application of UL-^{14}C-phenyl-labelled active substance to five different soils.

Non-normalised values of the DT_{50} and the DT_{90} were derived from SFO best fits in three soils and DFOP best fits in two soils with results summarized in Table 7.1.2.1.1-1.

From tests at 20°C, non-normalised half-lives of isoxaflutole ranged from 0.3 days for clay loam soil 95/05 to 3.9 days for loam soil 95/02 while values for the DT_{90} ranged from 1.0 day for soil 95/05 to 18.6 days for soil 95/02.

At 10°C, the DT_{50} was 6.1 days and the DT_{90} was 35.6 days in soil 95/02.

Table 7.1.2.1.2-1: Summary of results of kinetic evaluation of degradation for isoxaflutole in aerobic soil in the laboratory for comparison against EU triggers

Compound	Isoxaflutole
20°C, Non-normalised DT_{50}, range (days)	0.3 – 3.9
Worst case DT_{50} (days)	3.9
20°C, Non-normalised DT_{90}, range (days)	1.0 – 18.6
Worst case DT_{90} (days)	18.6
10°C, Non-normalised DT_{50} (days)	6.1
10°C, Non-normalised DT_{90} (days)	35.6

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[2] Please note that KCA 7.1.2.1.1 /01 has been invalidated and thus excluded. For details, see CA 7.1.1.1 /01.

I. Material and Methods

For the parent compound isoxaflutole details on study conduct and its results have been summarized under Point CA 7.1.1.1. The degradation data were kinetically evaluated following FOCUS guidance with the software KinGUI, version 2.

The measured values were taken into account as reported and thus treated as individual replicates. All sets with their data points were weighted equally. The concentration at time zero was included in the parameter optimisation with the initial value being allowed to be estimated by the model.

In cases where the radioactive residues in soil were below the limit of detection (LOD) the respective values were set to 0.5 LOD for the evaluation for time points before or after which a value above LOD was determined. For some studies no LOD was given in the original report. In these cases no values were added.

In some cases degradation products of the applied substance were already detected at time zero. In such cases the respective percentages were added to the parent values and the values for the metabolite were set to zero.

All radioactive residues in soil were used for the kinetic evaluation. For some of the studies performed for very long periods of up to one year the evaluations for deriving modelling endpoints used only data measured up to day 120 days which is the maximum recommended duration for laboratory studies according to OECD Guideline 307 (2002).

For fits of compounds under evaluation, SFO kinetics was tested first due to its simplicity and its nearly exclusive use in environmental exposure models.

In general, also the use of other kinetic model approaches is possible as proposed by FOCUS. The evaluation thus considered also the model approaches first order multiple-compartment (FOMC), dual first order in parallel (DFOP) and Hockey Stick (HS), in principle, following the scheme for identification of the appropriate kinetic model as proposed by FOCUS.

To check the parameters for their significance a single-sided t-test was used. The probability of t should be low or equal to zero as this probability can be assumed to be higher the more uncertain a parameter is. In general, a value of 0.05 for the probability of t is considered as appropriate with degradation parameters being regarded as significant at this level.

II. Results and Discussion

Following application of the parent substance isoxaflutole to aerobic soil the nearly exclusive and successive formation of metabolites RPA 202248 and RPA 203328 was observed thus supporting a 'linear' pathway under aerobic conditions. Formation fractions for metabolites were thus set to one regarded as being suitable for this assessment.

Calculation of non-normalised DT_{50}-values based on best fits:

For isoxaflutole the kinetic evaluation of soil degradation tests using the SFO approach did not result in acceptable fits to the experimental data. For two data sets the evaluation according to FOMC resulted in a better fit than SFO to describe the degradation data. Finally the DFOP model was chosen as optimal fit for the two data sets that had shown better fits already by use of the FOMC model. The

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Isoxaflutole

resulting non-normalised values for the DT_{50} and the DT_{90} derived are summarized in Table 7.1.2.1.1-2.

Table 7.1.2.1.1-2: Non-normalised DT_{50}-values for isoxaflutole in aerobic soils under laboratory conditions for trigger evaluation

Soil (Origin)	Label position	DT_{50} (days)	DT_{90} (days)	Model
95/02, loam, 20°C (Study 1)	phenyl	3.9	18.6	DFOP
95/04, sandy loam, 20°C (Study 2)	phenyl	2.4	8.1	SFO
95/05, clay loam, 20°C (Study 2)	phenyl	0.3	1.0	SFO
95/06, loamy sand, 20°C (Study 2)	phenyl	0.6	1.8	SFO
95/02, loam, 10°C (Study 3)	phenyl	6.1	35.6	DFOP

Study 1: KCA 7.1.2.1.1 /02 and KCA 7.1.2.1.1 /03; Study 2: KCA 7.1.2.1.1 /04; Study 3: KCA 7.1.2.1.1 /05

III. Conclusion

The evaluation according to FOCUS kinetic guidance resulted in values for half-lives and the DT_{90} of the parent compound isoxaflutole for comparison with EU trigger endpoints.
The approach for fitting with experimental data resulted in the use of the single-phase SFO and the bi-phasic kinetic model DFOP for calculation.
Values of non-normalised half-lives and DT_{90} from best fits to measured data ranged from 0.3 to 3.9 days. The corresponding DT_{90} ranged from 1.0 day to 18.6 days.
At 10°C, the corresponding values for the DT_{50} and DT_{90} were 6.1 days and 35.6 days.

Report:	███████████ **2013:M-464596-01**
Title:	Isoxaflutole: Kinetic modelling evaluation of aerobic soil degradation study data to derive modelling endpoints
Report No:	VC/13/007B
Document No:	M-464596-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Executive Summary

For isoxaflutole degradation data as referenced under KCA 7.1.2.1.1 /02 to KCA 7.1.2.1.1 /05 were kinetically evaluated according to FOCUS Guidance to derive modelling endpoints for use as input parameters in environmental risk assessments[3]
For metabolites RPA 202248 and RPA 203928 the kinetic analysis was performed in combination with parent compound data amended by aerobic soil degradation data from separate tests with RPA 202248 and summarized under Point CA 7.1.2.1.2.
For the evaluation degradation data of isoxaflutole in soil under aerobic conditions of the laboratory were considered from three studies following application of UL-^{14}C-phenyl-labelled active substance to five different soils.

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[3] Please note that KCA 7.1.2.1.1 /01 has been invalidated and thus excluded. For details, see KCA 7.1.1.1 /01.

A stepwise approach was made for the calculation of normalised half-lives in soil. The initial step consisted of best fits to the measured data following the SFO kinetic model. In case of unacceptable fits according to the criteria set bi-phasic models, i.e. FOMC or DFOP were applied.

The SFO model adequately described the measured data for all data sets. In a next step, values were normalised by comparison of study incubation conditions to reference conditions (20°C, pF2 moisture) with results summarized in Table 7.1.2.1.1 -3.

For use as modelling endpoint, the overall mean normalised half-life of isoxaflutole was 0.9 days.
The formation fractions were one for RPA 202248 and 0.96 for RPA 203328.

Table 7.1.2.1.2-3: Normalised laboratory DT$_{50}$-values for isoxaflutole in aerobic soil in the laboratory for use as modelling input parameters in environmental exposure assessments

Compound	Isoxaflutole
Normalised (20°C, pF2) DT$_{50}$, range (days)	0.3 – 3.9
Mean (geometric)	**0.9**

1. Material and Methods

For the parent substance isoxaflutole details on study conduct and its results have been summarized under Point CA 7.1.1.1. The degradation data were kinetically evaluated following FOCUS guidance with the software KinGUI, version 2.

The measured values were taken into account as reported and thus treated as individual replicates. All sets with their data points were weighted equally. The concentration at time zero was included in the parameter optimisation with the initial value being allowed to be estimated by the model.

In cases where the radioactive residues in soil were below the limit of detection (LOD) the respective values were set to 0.5 LOD for the evaluation for time points before or after which a value above LOD was determined. For some studies no LOD was given in the original report. In these cases no values were added.

In some cases degradation products of the applied substance were already detected at time zero. In such cases the respective percentages were added to the parent values and the values for the metabolite were set to zero.

All radioactive residues in soil were used for the kinetic evaluation. For some of the studies performed for very long periods of up to one year the evaluations for deriving modelling endpoints used only data measured up to day 120 days which is the maximum recommended duration for laboratory studies according to OECD Guideline 307 (2002).

For fits of compounds under evaluation, SFO kinetics was tested first due to its simplicity and its nearly exclusive use in environmental exposure models.

In general, also the use of other kinetic model approaches is possible as proposed by FOCUS. The evaluation thus considered also the model approaches first order multiple-compartment (FOMC), dual first order in parallel (DFOP) and Hockey Stick (HS), in principle, following the scheme for identification of the appropriate kinetic model as proposed by FOCUS.

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To check the parameters for their significance a single-sided t-test was used. The probability of t should be low or equal to zero as this probability can be assumed to be higher the more uncertain a parameter is. In general, a value of 0.05 for the probability of t is considered as appropriate with degradation parameters being regarded as significant at this level.

The DT_{50}-values derived were normalised to standard reference temperature 20 °C and soil moisture 100 % field capacity in order to obtain standardised input parameters for predictions of environmental concentrations. This normalisation was conducted according to the standard approach by FOCUS.

The degradation of isoxaflutole in aerobic soil resulted in the predominant and successive formation of metabolites RPA 202248 and RPA 203328. From observation in the course of the tests, it is reasonable to assume a 'linear' pathway for their formation, i.e. the components were formed successively.

II. Results and Discussion

Following application of the parent substance isoxaflutole to aerobic soil the nearly exclusive and successive formation of metabolites RPA 202248 and RPA 203328 was observed thus supporting a 'linear' pathway under aerobic conditions. Formation fractions for metabolites were thus set to one regarded as being suitable for this assessment. The resulting formation fractions are summarized in Table 7.1.2.1.1-4.

Calculation of non-normalised DT_{50}-values based on SFO best fit for isoxaflutole

For the parent substance the kinetic evaluation of soil degradation tests using the SFO approach resulted in acceptable fits to the experimental data for all data sets. The results are summarized in Table 7.1.2.1.1-5.

Normalised DT_{50} values for isoxaflutole

For the use in environmental modeling the degradation half-lives were normalised to reference conditions of 100 % field capacity regarding soil moisture and 20°C for the temperature. The parameters used in the laboratory tests and the respective correction factors calculated are summarized in Table 7.1.2.1.1-6. The half-lives resulting from normalisation are summarized in Table 7.1.2.1.1-7.

Table 7.1.2.1.1-4: Formation fractions of metabolites RPA 202248 and RPA 203328 from application of parent substance isoxaflutole to aerobic soil under laboratory conditions

Soil (Origin)	Label position	Formation fraction for process	
		Isoxaflutole to RPA 202248	RPA 202248 to RPA 203328
95/02, loam, 20°C (Study 1)	1	1.00	1.00
95/04, sandy loam, 20°C (Study 2)	1	1.00	0.868
95/05, clay loam, 20°C (Study 2)	1	1.00	1.00
95/06, loamy sand, 20°C (Study 2)	1	1.00	0.966
95/02, loam 10°C (Study 3)	1	1.00	1.00
Mean (arithmetic)		**1.00 ***	**0.96**

Label position: 1 = phenyl

Study 1: KCA 7.1.2.1.1 /02 and KCA 7.1.2.1.1 /03; Study 2: KCA 7.1.2.1.1 /04; Study 3: KCA 7.1.2.1.1 /05

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Table 7.1.2.1.1-5: Non-normalised DT$_{50}$-values for parent substance isoxaflutole in aerobic soils under laboratory conditions

Soil (Origin)	Label position	DT$_{50}$ (days)	Model
95/02, loam, 20°C (Study 1)	1	4.2	SFO
95/04, sandy loam, 20°C (Study 2)	1	2.4	SFO
95/05, clay loam, 20°C (Study 2)	1	0.3	SFO
95/06, loamy sand, 20°C (Study 2)	1	0.6	SFO
95/02, loam, 10°C (Study 3)	1	6.7	SFO

Label position: 1 = phenyl

Study 1: KCA 7.1.2.1.1 /02 and KCA 7.1.2.1.1 /03; Study 2: KCA 7.1.2.1.1 /04; Study 3: KCA 7.1.2.1.1 /05

Table 7.1.2.1.1-6: Correction factors for soil temperature and moisture content

Soil (Origin)	Incubation temperature (°C)	Incubation moisture * (% w/w)	pF 2 moisture ** (% w/w)	Correction factor
95/02, loam, 20°C (Study 1)	20	26.96	25.52	1.000
95/04, sandy loam, 20°C (Study 2)	20	27.13	23.19	1.000
95/05, clay loam, 20°C (Study 2)	20	35.01	62.48	0.667
95/06, loamy sand, 20°C (Study 2)	20	17.47	28.28	0.714
95/02, loam, 10°C (Study 3)	10	26.96	25.52	0.387

* Values given in study report

** Calculated values according to FOCUS, 2000

Study 1: KCA 7.1.2.1.1 /02 and KCA 7.1.2.1.1 /03; Study 2: KCA 7.1.2.1.1 /04; Study 3: KCA 7.1.2.1.1 /05

Table 7.1.2.1.1-7: Normalised laboratory DT$_{50}$-values in aerobic soil for parent compound isoxaflutole for use as modelling input parameters in environmental exposure assessments

Soil (Origin)	DT$_{50}$ (days)	DT$_{90}$ (days)	Chi^2- error (%)	t-test	VA
95/02, loam, 20°C (Study 1)	4.2	13.9	9.3	<2e-16	Good
95/04, sandy loam, 20°C (Study 2)	2.4	8.1	3.8	<2e-16	Very good
95/05, clay loam, 20°C (Study 2)	0.2	0.7	3.4	<2e-16	Very good
95/06, loamy sand, 20°C (Study 2)	0.4	1.3	4.9	<2e-16	Very good
95/02, loam, 10°C (Study 3)	2.6	8.6	10.4	<2e-16	Good
Mean (geometric)	**0.9**				

Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05

III Conclusion

The evaluation according to FOCUS kinetic guidance resulted in values for half-lives of the parent compound isoxaflutole in aerobic soil for use as modeling input parameters in environmental risk assessments.

As a result of fitting to the measured data the use of SFO was regarded as the appropriate kinetic model to derive non-normalised values for the DT$_{50}$ in a first step. The values were then normalised for moisture (pF 2) and temperature (20°C).

The values derived from laboratory tests in five EU soils are regarded as suitable and reliable for use in environmental exposure assessments.

For the active substance isoxaflutole, a normalised half-life of 0.9 days was calculated as modelling endpoint.

For the formation fraction of active substance to metabolite RPA 202248 a mean value of 1.00 was calculated while for the formation of RPA 203328 from RPA 202248 a mean value of 0.96 was derived.

CA 7.1.2.1.2 Aerobic degradation of metabolites, breakdown and reaction products

Report:	;1994;M-158435-01
Title:	RPA201772: Aerobic soil metabolism
Report No:	R000347
Document No:	M-158435-01-1
Guidelines:	**USEPA (=EPA): N, 162-1, (1982); Deviation not specified**
GLP/GEP:	**yes**

Report:	;1995;M-213110-01
Title:	Herbicides: RPA201772 Route of degradation (aerobic metabolism) in one soil (interim report)
Report No:	C022444
Document No:	M-213110-01-1
Guidelines:	**EU (=EEC): annex I, section 7.1 (1995);Deviation not specified**
GLP/GEP:	**yes**

Report:	;1996;M-240821-01
Title:	Herbicides: Isoxaflutole Route of Degradation (Aerobic Metabolism) in one Soil
Report No:	B003826
Document No:	M-240821-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

Report:	;1996;M-240822-01
Title:	RPA 201772: Rate of Degradation under Aerobic Conditions in Three Soil Types
Report No:	B003827
Document No:	M-240822-01-1
Guidelines:	**EU (=EEC): 7171/VI/94-EN rev 1; FAO: Draft Rev.3, Part 1,1.1;Deviation not specified**
GLP/GEP:	**yes**

Report:	3; ;1996;M-213113-01
Title:	RPA 201772: Rate of degradation under aerobic conditions in one soil at 10 degrees C
Report No:	C022445
Document No:	M-213113-01-1
Guidelines:	**EU (=EEC): 7171/VI/94-EN rev.1, section 7.1.1.1 (1994); FAO: Annex to Environmental ... revision I;Deviation not specified**
GLP/GEP:	**yes**

Report:	t; ;2012;M-427583-01
Title:	[Cyclopropyl-1-14C]RPA 202248:: Aerobic degradation/metabolism in one European soil
Report No:	MEF-11/486
Document No:	M-427583-01-1
Guidelines:	**OECD 307; US EPA OPPTS 835.4100 and OPPTS 835.4200; EU 95/36/EC amending 91/414/EEC;not specified**
GLP/GEP:	**yes**

Report:	8; ;2012;M-464601-01
Title:	Isoxaflutole: Kinetic modelling evaluation of aerobic soil degradation study data to derive trigger endpoints
Report No:	VC/13/007C
Document No:	M-464601-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Report:	9; ;2013;M-464596-01
Title:	Isoxaflutole: Kinetic modelling evaluation of aerobic soil degradation study data to derive modelling endpoints
Report No:	VC/13/007B
Document No:	M-464596-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

For isoxaflutole metabolites laboratory data on the rate of degradation in aerobic soil had been derived from studies performed under the following conditions:

- two soils at 21°C and a moisture of 75% of the field capacity at 0.33 bar following application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.2 /01);
- one soil under standard conditions at 20°C and moisture at 45 % maximum water holding capacity (MWHC) after application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03);
- three soils under standard conditions at 20°C and moisture at 40% MWHC following application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.2 /04);
- one soil at 10°C and 40 % MWHC and application of phenyl-UL-^{14}C-labelled active substance (KCA 7.1.2.1.2 /05).

This data requirement had been addressed under Point 7.1.1.2 of the Dossier submitted and evaluated within the process of evaluation for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

Following latest guidance on kinetic evaluation the data from existing studies have been re-evaluated. The new kinetic evaluations considered new rate data from a separate test performed with cyclopropyl-1-^{14}C-labelled RPA 202248 (KCA 7.1.2.1.2 /06) in addition. The test was performed to investigate the degradation behavior of the cyclopropyl-ring system and to support the determination of a robust data set for this metabolite.

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The kinetic evaluations were performed separately in order to derive values for the comparison with trigger endpoints (KCA 7.1.2.1.2 /07) and modeling endpoints (KCA 7.1.2.1.2 /08) for input into environmental risk assessments.

The re-evaluation following new guidance in the kinetic analysis of degradation data in aerobic soil supersede the existing evaluations.

As explained under KCA 7.1.1.1 in more detail, study KCA 7.1.2.1.1 /01 had been invalidated and thus not included into the current evaluations.

Report:	9; 2012;M-427583-01
Title:	[Cyclopropyl-1-14C]RPA 202248:: Aerobic degradation/metabolism in one European soil
Report No:	MEF-11/486
Document No:	M-427583-01-1
Guidelines:	**OECD 307; US EPA OPPTS 835.4100 and OPPTS 835.4200; EU 95/36/EC amending 91/414/EEC;not specified**
GLP/GEP:	**yes**

The study has been summarised in more detail under KCA 7.1.1.1 /05 of this document.

The kinetic evaluation of the degradation of [cyclopropyl-2-^{14}C]-RPA 202248 in aerobic soil resulted in a non-normalised DT_{50} of 14 days and a DT_{90} of 47 days based on an SFO best fit kinetic model. The values may be used for comparison with trigger endpoints and as modelling input in environmental risk assessments.

Report:	; 2013;M-464601-01
Title:	Isoxaflutole: Kinetic modelling evaluation of aerobic soil degradation study data to derive trigger endpoints
Report No:	VC/13/007C
Document No:	M-464601-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Executive Summary

For the active substance isoxaflutole degradation data were kinetically evaluated under KCA 7.1.2.1.1 /06 according to FOCUS Guidance to derive endpoints for comparison with trigger endpoints.

For metabolites RPA 202248 and RPA 203328 the kinetic analysis was performed in combination with parent compound data as referenced under KCA 7.1.2.1.2 /02 to KCA 7.1.2.1.2 /05[4].

The degradation data for RPA 202248 and RPA 203328 was derived from tests with active substance isoxaflutole in aerobic soil under conditions of the laboratory in four studies after application of UL-^{14}C-phenyl-labelled active substance to four different soils[5]. Additional information on the rate of degradation of RPA 202248 was available for one soil (see KCA 7.1.2.1.2 /06).

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[4] Please note that KCA 7.1.2.1.1 /01 has been invalidated and thus excluded. For details, see KCA 7.1.1.1 /01.
[5] Please note that KCA 7.1.2.1.1 /01 has been invalidated and thus excluded. For details, see KCA 7.1.1.1 /01.

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Non-normalised values of the DT_{50} and the DT_{90} were derived from SFO best fits for three data sets and DFOP best fits for two data sets with results summarized in Table 7.1.2.1.2 -1.

Non-normalised half-lives for metabolite RPA 202248 ranged from 10.4 days for sandy loam soil 95/04 to 43.4 days for loam soil 95/02 while values for the DT_{90} ranged from 34.4 days for sandy loam soil 95/04 to 144 days for loam soil 95/02.

At 10°C, the corresponding values for the DT_{50} and DT_{90} were 44.8 days and 149 days in the loam soil 95/02.

Non-normalised half-lives from tests performed at 20°C for metabolite RPA 203328 ranged from 3.5 days to more than 1000 days. Values for the DT_{90} ranged from 11.6 days to more than 1000 days. For tests performed at 10°C, the corresponding values for the DT_{50} and DT_{90} were 112 days and 379 days.

Table 7.1.2.1.2-1: Non-normalised DT_{50}-values for metabolites RPA 202248 and RPA 203328 in aerobic soil under laboratory conditions for trigger evaluation

Compound	RPA 202248	RPA 203328
20°C, Non-normalised DT_{50} , range (days)	10.4 - 43.4	3.5 - >1000
Worst case DT_{50} (days)	43.4	>1000
20°C, Non-normalised DT_{90} , range (days)	34.4 - 144	11.6 - >1000
Worst case DT_{90} (days)	144	>1000
10°C, Non-normalised DT_{50} (days)	44.8	112
10°C, Non-normalised DT_{90} (days)	149	379

I. Material and Methods

Data sets were derived from studies with the parent compound and a separate study with RPA 202248. The details on study conduct and their results have been summarized under Point CA 7.1.1.1. The degradation data were kinetically evaluated following FOCUS guidance with the software KinGUI, version 2.

The measured values were taken into account as reported and thus treated as individual replicates. All sets with their data points were weighted equally. The concentration at time zero was included in the parameter optimisation with the initial value being allowed to be estimated by the model.

In cases where the radioactive residues in soil were below the limit of detection (LOD) the respective values were set to 0.5 LOD for the evaluation for time points before or after which a value above LOD was determined. For some studies no LOD was given in the original report. For these cases no values were added.

In some cases degradation products of the applied substance were already detected at time zero. In such cases the respective percentages were added to the parent values and the values for the metabolite were set to zero.

All radioactive residues in soil were used for the kinetic evaluation. For some of the studies performed for very long periods of up to one year the evaluations for deriving modelling endpoints used only data measured up to day 120 days which is the maximum recommended duration for laboratory studies according to OECD Guideline 307 (2002).

For fits of compounds under evaluation, SFO kinetics was tested first due to its simplicity and its nearly exclusive use in environmental exposure models.

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In general, also the use of other kinetic model approaches is possible as proposed by FOCUS. The evaluation thus considered also the model approaches first order multiple-compartment (FOMC), double first order in parallel (DFOP) and Hockey Stick (HS), in principle, following the scheme for identification of the appropriate kinetic model as proposed by FOCUS.

To check the parameters for their significance a single-sided t-test was used. The probability of t should be low or equal to zero as this probability can be assumed to be higher the more uncertain a parameter is. In general, a value of 0.05 for the probability of t is considered as appropriate with degradation parameters being regarded as significant at this level.

II. Results and Discussion

Following application of the parent substance isoxaflutole to aerobic soil the nearly exclusive and successive formation of metabolites RPA 202248 and RPA 203328 was observed thus supporting a 'linear' pathway under aerobic conditions. Formation fractions for metabolites were thus set to one.

Calculation of non-normalised DT_{50}-values based on best fits:

For the parent compound isoxaflutole the kinetic evaluation of soil degradation tests using the SFO approach did not result in acceptable fits to the experimental data. For two data sets the evaluation according to FOMC resulted in a better fit than SFO to describe the degradation data. Finally the DFOP model was chosen as optimal fit for the two data sets that had shown better fits already by use of the FOMC model. From combination of best fits obtained for the active substance with SFO fits for the metabolites the resulting non-normalised values for the DT_{50} and the DT_{90} are summarized in Table 7.1.2.1.1-3 for metabolite RPA 202248 and Table 7.1.2.1.1-4 for metabolite RPA 203328.

Table 7.1.2.1.2-2: Non-normalised DT_{50}-values for metabolite RPA 202248 (AE 0540092) in aerobic soils under laboratory conditions for trigger evaluation

Soil (Origin)	DT_{50} (days)	DT_{90} (days)	ffm*	Chi²-error (%)	t-test	VA
95/02, loam, 20°C (Study 1)	43.4	144	1.00	11.3	<2e-16	Good
95/04, sandy loam, 20°C (Study 2)	10.4	34.4	1.00	14.7	<2e-16	Good
95/05, clay loam, 20°C (Study 2)	41.7	139	1.00	5.6	<2e-16	Very good
95/06, loamy sand, 20°C (Study 2)	29.4	97.6	1.00	13.5	8.2e-15	Good
95/02, loam, 10°C (Study 3)	44.8	149	1.00	14.7	<2e-16	Acceptable

Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05
VA = Visual Assessment; ffm = formation fraction: where ffm was optimised to 1 during evaluations, the data was refitted with ffm = 1

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Table 7.1.2.1.2-3: Non-normalised DT$_{50}$-values for metabolite RPA 203328 (AE B197555) in aerobic soils under laboratory conditions for trigger evaluation

Soil (Origin)	DT$_{50}$ (days)	DT$_{90}$ (days)	ffm	Chi^2-error (%)	t-test	VA
95/02, loam, 20°C (Study 1)	204	678	1.00*	3.2	5.49e-11	Excellent
95/04, sandy loam, 20°C (Study 2)	>1000	>1000	0.868	4.8	0.180	Good
95/05, clay loam, 20°C (Study 2)	3.5	11.6	1.00*	16.0	<2e-16	Acceptable
95/06, loamy sand, 20°C (Study 2)	>1000	>1000	0.966	19.4	0.5	Acceptable
95/02, loam, 10°C (Study 3)	112	379	1.00*	6.2	<2e-16	Excellent

Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05
VA = Visual Assessment; ffm = formation fraction: where ffm was optimised to 1 during evaluations, the data was refitted with ffm = 1

III. Conclusion

The evaluation according to FOCUS kinetic guidance resulted in values for half-lives and the DT$_{90}$ for metabolites RPA 202248 and RPA 203328 for comparison with EU trigger endpoints.
The fitting with experimental data resulted in a combined use of the bi-phasic kinetic model DFOP and the SFO model for the parent compound isoxaflutole with SFO kinetics for the metabolites.

For metabolite RPA 202248 non-normalised half-lives from best fits to measured data ranged from 10.4 days to 43.4 days. The corresponding values for the DT$_{90}$ ranged from 34.4 days to 144 days. At 10°C, the corresponding values for the DT$_{50}$ and DT$_{90}$ were 44.8 days and 149 days.

For metabolite RPA 203328 calculable values of non-normalised half-lives and DT$_{90}$ from best fits to measured data ranged from 3.5 days to 204 days while values for the DT$_{90}$ ranged from 11.6 days to 678 days. For tests performed at 10°C, the corresponding values for the DT$_{50}$ and DT$_{90}$ were 112 days and 379 days.

Report:	████ ████;2013;M-464596-01
Title:	Isoxaflutole Kinetic modelling evaluation of aerobic soil degradation study data to derive modelling endpoints
Report No:	XC/13/007B
Document No:	M-464596-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Executive Summary
For metabolites RPA 202248 and RPA 203328 degradation data were kinetically evaluated according to FOCUS Guidance to derive modelling endpoints as input parameters for environmental risk assessments.
The kinetic analysis was performed in combination with parent compound data as referenced under KCA 7.1.2.1.2 /02 to KCA 7.1.2.1.2 /05[6]. The evaluation considered degradation data of the active substance isoxaflutole in soil under aerobic conditions of the laboratory from four studies following

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[6] Please note that KCA 7.1.2.1.1 /01 has been invalidated and thus excluded. For details, see KCA 7.1.1.1 /01.

application of UL-^{14}C-phenyl-labelled active substance to four different soils. For RPA 202248 these were amended by aerobic soil degradation data from a separate test (KCA 7.1.2.1.2 /06).

A stepwise approach was made for the calculation of normalised half-lives in soil. The initial step consisted of best fits to the measured data following the SFO kinetic model. In case of unacceptable fits according to the criteria set bi-phasic models, i.e. FOMC or DFOP were applied.

The evaluation resulted in the SFO model to adequately describe the fit to measured data for all data sets. In a next step, values were normalised by comparison of study incubation conditions to reference conditions (20°C, pF2 moisture) with results summarized in Table 7.1.2.1.1 -4.

For use as modelling endpoints, overall mean normalised half-lives were 18.9 days for RPA 202248 when including data from the separate study with RPA 202248 (see KCA 7.1.2.1.2 /06) and 121 days for RPA 203328.

Mean values for formation fractions were one for metabolite RPA 202248 and 0.96 for RPA 203328.

Table 7.1.2.1.2-4: Normalised laboratory DT$_{50}$-values for RPA 202248 and RPA 203328 in aerobic soil in the laboratory for use as modelling input parameters in environmental exposure assessments

Compound	RPA 202248	RPA 203328
Normalised (20°C, pF2) DT$_{50}$, range (days)	10.4 – 44.9	2.3 - 1000
Mean (geometric)	**18.9***	**121**

* Including a DT$_{50}$-value of 14.2 days from KCA 7.1.2.1.2 /06

I. Material and Methods

Studies with the parent substance isoxaflutole are summarized under Point CA 7.1.1.1. The degradation data were kinetically evaluated following FOCUS guidance with the software KinGUI, version 2. The measured values were taken into account as reported and thus treated as individual replicates. All sets with their data points were weighted equally. The concentration at time zero was included in the parameter optimisation with the initial value was estimated by the model.

In cases where the radioactive residues in soil were below the limit of detection (LOD) the respective values were set to 0.5 LOD for the evaluation for time points before or after which a value above LOD was determined. For some studies no LOD was given in the original report. In these cases no values were added.

In some cases degradation products of the applied substance were already detected at time zero. In such cases the respective percentages were added to the parent values and the values for the metabolite were set to zero.

All radioactive residues in soil were used for the kinetic evaluation. For some of the studies performed for very long periods of up to one year only data up to 120 days were used which is the maximum recommended duration for laboratory studies according to OECD Guideline 307 (2002).

SFO kinetics was tested first due to its simplicity and its nearly exclusive use in environmental exposure models.

In general, also the use of other kinetic model approaches is possible as proposed by FOCUS. The evaluation thus considered also the model approaches first order multiple-compartment (FOMC),

double first order in parallel (DFOP) and Hockey Stick (HS), in principle, following the scheme for identification of the appropriate kinetic model as proposed by FOCUS.

To check the parameters for their significance a single-sided t-test was used. The probability of t should be low or equal to zero as this probability can be assumed to be higher the more uncertain a parameter is. In general, a value of 0.05 for the probability of t is considered as appropriate with degradation parameters being regarded as significant at this level.

According to FOCUS, the DT_{50}-values were normalised to standard reference temperature 20 °C and soil moisture 100 % field capacity in order to obtain standardised input parameters for predictions of environmental concentrations.

The degradation of isoxaflutole in aerobic soil resulted in the predominant and successive formation of metabolites RPA 202248 and RPA 203328. From observation in the course of the tests, it is reasonable to assume a 'linear' pathway for their formation, i.e. the components were formed successively.

II. Results and Discussion

Following application of the parent substance isoxaflutole to aerobic soil the nearly exclusive and successive formation of metabolites RPA 202248 and RPA 203328 was observed thus supporting a 'linear' pathway under aerobic conditions. Formation fractions for metabolites were thus set to one regarded as being suitable for this assessment

Calculation of non-normalised DT_{50}-values based on SFO best fit:

For metabolites RPA 202248 and RPA 203328 the kinetic evaluation of soil degradation tests using the SFO approach resulted in acceptable fits to the experimental data for all data sets. The results are summarised in Table 7.1.2.1.2-5 and Table 7.1.2.1.2-6.

Normalised DT_{50}-values for RPA 202248 and RPA 203328

For the use in environmental modeling the degradation half-lives were normalised to reference conditions of 100 % field capacity regarding soil moisture and 20°C for the temperature as summarized under Table, Table 7.1.2.1.2-7. The values of half-lives resulting from normalisation are summarized in Table 7.1.2.1.2-8 and Table 7.1.2.1.2-9.

Table 7.1.2.1.2-5: Non-normalised DT_{50}-values for metabolite RPA 202248 in aerobic soil under laboratory conditions

Soil (Origin)	Label position	DT_{50} (days)	Model
95/02, loam, 20°C (Study 1)	1	44.9	SFO
95/04, sandy loam, 20°C (Study 2)	1	10.4	SFO
95/05, clay loam, 20°C (Study 2)	1	41.7	SFO
95/06, loamy sand, 20°C (Study 2)	1	29.4	SFO
95/02, loam, 20°C (Study 3)	1	44.6	SFO

Label position: 1 = phenyl

Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05

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Table 7.1.2.1.2-6: Non-normalised DT$_{50}$-values for metabolite RPA 203328 in aerobic soil under laboratory conditions

Soil (Origin)	Label position	DT$_{50}$ (days)	Model
95/02, loam, 20°C (Study 1)	1	210	SFO
95/04, sandy loam, 20°C (Study 2)	1	>1000	SFO
95/05, clay loam, 20°C (Study 2)	1	3.5	SFO
95/06, loamy sand, 20°C (Study 2)	1	>1000	SFO
95/02, loam, 10°C (Study 3)	1	104	SFO

Label position: 1 = phenyl

Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05

Table 7.1.2.1.2-7: Correction factors for soil temperature and moisture content

Soil (Origin)	Incubation temperature (°C)	Incubation moisture * (% w/w)	pF 2 moisture ** (% w/w)	Correction factor
95/02, loam, 20°C (Study 1)	20	26.96	25.52	1.000
95/04, sandy loam, 20°C (Study 2)	20	27.13	23.19	1.000
95/05, clay loam, 20°C (Study 2)	20	35.01	62.45	0.667
95/06, loamy sand, 20°C (Study 2)	20	17.47	28.28	0.714
95/02, loam, 10°C (Study 3)	10	26.96	25.52	0.387

* Values given in study report
** Calculated values according to FOCUS, 2000
Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05

Table 7.1.2.1.2-8: Normalised laboratory DT$_{50}$-values in aerobic soil for metabolite RPA 202248 for use as modelling input parameters in environmental exposure assessments

Soil (Origin)	DT$_{50}$ (days)	DT$_{90}$ (days)	ffm *	Chi²- error (%)	t-test	VA
95/02, loam, 20°C (Study 1)	44.9	149	1.00	11.3	<2e-16	Good
95/04, sandy loam, 20°C (Study 2)	10.4	34.4	1.00	14.7	<2e-16	Good
95/05, clay loam, 20°C (Study 2)	27.8	92.5	1.00	5.6	<2e-16	Very good
95/06, loamy sand, 20°C (Study 2)	21.0	69.7	1.00	13.5	8.20e-15	Good
95/02, loam, 10°C (Study 3)	17.3	57.4	1.00	17.0	<2e-16	Acceptable
▮▮▮▮▮	14.2	47.3	-	5.1	1.4e-11	Good
Mean (geometric)**	18.9					
Average			1.00			

* Geometric mean of 27.8 days calculated first for soil 95/02.

Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05

* ffm = formation fraction. When ffm had been optimized to 1 during evaluations, the data was refitted with ffm = 1; VA = Visual assessment for acceptance of fit
** Includes result for soil ▮▮▮▮▮, see KCA 7.1.2.1.2 /06.

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Table 7.1.2.1.2-9: Normalised laboratory DT$_{50}$-values in aerobic soil for metabolite RPA 203328 for use as modelling input parameters in environmental exposure assessments

Soil (Origin)	DT$_{50}$ (days)	DT$_{90}$ (days)	ffm *	Chi^2- error (%)	t-test	VA
95/02, loam, 20°C (Study 1)	210	698	1.00	3.8	<2e-16	Excellent
95/04, sandy loam, 20°C (Study 2)	1000	1000	0.868	4.8	0.180	Good
95/05, clay loam, 20°C (Study 2)	2.3	7.7	1.00	16.9	<2e-16	Acceptable
95/06, loamy sand, 20°C (Study 2)	1000	1000	0.966	19.4	0.5	Acceptable
95/02, loam, 10°C (Study 3)	40.3	134	1.00	4.8	<2e-16	Excellent
Mean (geometric)	121					
Average			0.96			

* ffm = formation fraction. When ffm had been optimized to 1 during evaluations, the data was refitted with ffm = 1; VA = Visual assessment for acceptance of fit
Study 1: KCA 7.1.2.1.2 /02 and KCA 7.1.2.1.2 /03; Study 2: KCA 7.1.2.1.2 /04; Study 3: KCA 7.1.2.1.2 /05

III. Conclusion

The evaluation according to FOCUS kinetic guidance resulted in values for half-lives of the metabolites RPA 202248 and RPA 203328 in aerobic soil for use as modeling input parameters in environmental risk assessments.

SFO was the appropriate kinetic model to derive non-normalised values for the DT$_{50}$. The non-normalised half-lives were then referenced for moisture (pF 2) and temperature (20°C).

The values derived from laboratory tests in five EU soils are regarded as suitable and reliable for use as modelling endpoints in environmental exposure assessments.

The geometric mean of normalised half-lives was 20.3 days for metabolite RPA 202248 and 121 days for metabolite RPA 203328.

CA 7.1.2.1.3   Anaerobic degradation of the active substance

Report:	5; ;1995;M-192288-01
Title:	RPA201772 Anaerobic Aquatic Metabolism
Report No:	R016760
Document No:	M-192288-01-1
Guidelines:	USEPA (=EPA): N. 162-3 (1982) Deviation not specified
GLP/GEP:	yes

The rate of degradation was calculated within the respective study on route of degradation in anaerobic soil (KCA 7.1.2.1.3/ 01).

The data requirement had been addressed under Point 7.1.1.2.1.4 of the Dossier submitted and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently, there is no detailed description of this existing data in this update.

Within the evaluation it was concluded that isoxaflutole degraded rapidly in anaerobic soil in the laboratory. The half-life was less than 2 hours (< 0.08 days).

CA 7.1.2.1.4 Anaerobic degradation of metabolites, breakdown and reaction products

Report:	n; ;1995;M-192288-01
Title:	RPA201772 Anaerobic Aquatic Metabolism
Report No:	R016760
Document No:	M-192288-01-1
Guidelines:	**USEPA (=EPA): N, 162-3 (1982);Deviation not specified**
GLP/GEP:	**yes**

The data requirement had been addressed under Point 7.1.1.2.1.5 of the Dossier submitted and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that the pathway for degradation of isoxaflutole under aerobic and anaerobic conditions is the same to form RPA 202248 and RPA 205834 as major metabolites along with traces of the benzoic acid RPA 203328. For RPA 202248 and RPA 205834, half-lives of 316 days and 131 days were calculated in the study report.

It should be noted that RPA 205834 was observed at trace level, i.e. significantly below 5% AR, in aerobic soil degradation. RPA 205834 showed maximum values of occurrence at very early time points in the test (i.e. 28% after 0.25 days) thus indicating that this compound was formed from ring-opening of the active substance directly.

Keeping in mind the fast degradation of the active substance under aerobic conditions and that there is time between application and a potential flooding of the field, a formation and occurrence of RPA 205834 under conditions of the field is highly unlikely. Moreover, the establishment of anaerobic conditions requires time available then for aerobic degradation of the active substance during this transition period.

In addition, isoxaflutole is intended for use in corn where anaerobic conditions in soil do not occur for long periods and usually not on a full field plot scale. Metabolites formed under anaerobic conditions will be degraded when the soil turns back to aerobic conditions after a period of low oxygen content. This will prevent accumulation of metabolites in the soil. For these reasons aerobic degradation studies on specific anaerobic metabolites, degradation and reaction products in soil are not required.

Moreover it is a common observation that only structural elements are converted being susceptible to reduction (i.e. nitro groups). It is thus predicable that a conversion or transformation of other structural elements like those in isoxaflutole and its residues is simply slowed-down, resulting in the observed 'stability' of the components observed under the conditions of anaerobic soil testing.

This more generally applicable conclusion can be derived from information available when screening Bayer-internal tests submitted as well as regulatory data published meanwhile in EFSA Conclusion Reports.

CA 7.1.2.2   Field studies

CA 7.1.2.2.1 Soil dissipation studies

Report:	b; ;1996;M-234225-01
Title:	RPA 201772: terrestrial field soil dissipation study
Report No:	C034014
Document No(s):	Report includes Trial Nos.:
	AR53-94
	M-234225-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

Report:	p; ;2001;M-200916-01
Title:	Isoxaflutole: Kinetic modelling analysis of a European terrestrial field soil dissipation study
Report No:	C015653
Document No:	M-200916-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Report:	g ;2012;M-428564-01
Title:	Determination of the residues of AE 0540092 in/on soil after spraying of AE 0540092 WP 20 in the field in Germany, United Kindom, France (North), Italy and Spain
Report No:	10-2702
Document No(s):	Report includes Trial Nos.
	10-2702-01
	10-2702-02
	10-2702-03
	10-2702-04
	10-2702-05
	10-2702-06
	M-428564-01-1
Guidelines:	**Commission Directive 95/36/EC amending Council Directive 91/414/EEC (Annexes I and II, Fate and Behavior in the Environment), July 14, 1995;not specified**
GLP/GEP:	**yes**

Report:	b; ;1997;M-234239-01
Title:	Storage stability in soils from the European terrestrial field soil dissipation isoxaflutole and metabolites study P94/009
Report No:	C034021
Document No(s):	Report includes Trial Nos.:
	95-85
	M-234239-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

Report:	g; ;2013;M-464592-01
Title:	Kinetic modelling analysis of AE 0540092 and AE B197555 from a field soil residue study conducted in Europe (Normalisation to 20degree and pF2)
Report No:	VC/13/007A
Document No:	M-464592-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7.1.1 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Report:	u; ;2013;M-464899-01
Title:	Isoxaflutole: Kinetic modelling endpoint summary
Report No:	VC/13/007J
Document No:	M-464899-01-1
Guidelines:	**Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

The data requirement had been addressed under Point 7.1.2.2 of the Dossier submitted and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently there is no detailed description of this existing data in this update.

Although all of the laboratory DT_{50}-values of the active substance were less than the specified triggers the study was performed due to variable half-lives for metabolites RPA 202248 and RPA 203328 from tests with the active substance depending on the kinetic model and method of calculation used.
A study had been therefore performed at four locations in the EU investigating the dissipation of isoxaflutole, RPA 202248 and RPA 203328 under practical conditions of the field (KCA 7.1.2.2.1 /01) followed by kinetic analysis of the data (KCA 7.1.2.2.1 /02).

The evaluation during the Annex I inclusion process revealed half-lives referenced to standard conditions (20°C, pF 2 moisture) for isoxaflutole, RPA 202248 and RPA 203328 in soil under field conditions at four sites in the EU. Half-lives were found to range from 0.28 to 1.53 days for isoxaflutole (average: 0.87 days), 5.83 to 10.41 days for RPA 202248 (average: 8.71 days) and from 15.1 to 56.25 days for RPA 203328 (average: 34.04 days).

KCA 7.1.2.2.1 /01 and its kinetic evaluation under KCA 7.1.2.2.1 /02 were submitted earlier within the process of Annex I inclusion. Following a review of these existing data against latest guidance in kinetic evaluation of field data (EFSA, 2010), it was decided to perform a new study in order to generate robust data for environmental risk assessments. The re-evaluation revealed, for example, that there was a lack of sampling intervals to allow for a robust kinetic evaluation.
The new field data generated under KCA 7.1.2.2.1 /03 and evaluated under KCA 7.1.2.2.1 /04 and KCA 7.1.2.2.1 /05 thus superseded the existing field data and their evaluations. Finally, in order to fulfill latest guidance according to EFSA (EFSA, 2013) laboratory and field data were evaluated to derive modeling endpoints as input parameters for environmental risk assessments (KCA 7.1.2.2.1 /06).

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Report:	y; ;2012;M-428564-01
Title:	Determination of the residues of AE 0540092 in/on soil after spraying of AE 0540092 WP 20 in the field in Germany, United Kindom, France (North), Italy and Spain
Report No:	10-2702
Document No(s):	Report includes Trial Nos.: 10-2702-01 10-2702-02 10-2702-03 10-2702-04 10-2702-05 10-2702-06 M-428564-01-1
Guidelines:	**Commission Directive 95/36/EC amending Council Directive 91/414/EEC (Annexes I and II, Fate and Behavior in the Environment), July 14, 1995;not specified**
GLP/GEP:	**yes**

Executive Summary

The dissipation of RPA 202248 (AE 0540092) in soil was investigated under European field conditions after application of the formulated test substance at a nominal rate of 100 g/ha onto bare soil at the six sites, i.e. ▮▮▮▮ (Germany), ▮▮▮▮ (United Kingdom), ▮▮▮▮ (Northern France), ▮▮▮▮ (Germany), ▮▮▮▮ (Italy) and ▮▮▮▮ (Spain). The sites were representative for northern and southern ecoregions of Europe.

After spraying of 0.5 kg/ha of the product AE 0540092 WP 20 onto bare soil residues were incorporated into the soil directly after treatment. At day zero soil samples were taken directly after spraying and after soil incorporation. Sampling was continued up to 413 days post-application to a maximum depth of 100 cm.

After processing of samples by homogenisation, milling and extraction these were analyzed for residues of RPA 202248 and RPA 203328 using HPLC/MS/MS detection in the presence of stable-labeled internal reference standard.

Quantifiable residues of RPA 202248 and RPA 203328 were detected in the top 30 cm of soil at all test sites thus indicating a low mobility in the course of the study.

At the last sampling interval residues of RPA 202248 in soil were less than the LOD of 1.5 µg/kg soil. Metabolite RPA 203328 was detected at maximum concentrations starting from 9.11 g/ha to 32.5 g/ha within the first 70 days after treatment. The residues of RPA 203328 showed a decline below the LOD of 1.5 µg/kg soil at all sites by DAT-89 to DAT-188. The results thus indicate the degradability and transient character of this metabolite under the conditions of the field.

In terms of best fits to measured data the dissipation of RPA 202248 in the field can be described by mono- as well as bi-phasic kinetics with the bi-phasic model DFOP to be the best fit for three test sites (▮▮▮▮ D, ▮▮▮▮, UK, and ▮▮▮▮, SP) while it was the SFO model for the other three sites (▮▮▮▮, F; ▮▮▮▮, D, and ▮▮▮▮, I).

On the basis of best statistical and visual fits values of dissipation half-lives for comparison with trigger endpoints were found to range from 8 to 40 days. The associated values for the DT_{90} ranged from 37 to 177 days.

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Based on the results a rapid degradation of RPA 202248 was demonstrated for a field situation at sites representative for the northern and southern EU.

<div align="center">

I. Material and Methods

</div>

A.   Materials
1. Test Material: AE 0540092

Chemical Code	AE 0540092 (RPA 202248)
Type of Formulation	WP 20 (Wettable Powder)
Specification No.	102000024302
Content of test item in formulation	200 g/kg
Batch Number	2010-000873

2. Trial Locations
The sites were neither subjected to erosion, nor to flooding or run-off. The test plots had no significant slope and were nearly free of stones. Properties of the trial sites along with their soil characteristics are presented in more detail in Table 7.1.2.2.1-1.

The soil cultivation and other agronomic activities for maintenance of the trial plots were conducted according to local agricultural practice. These are not considered to have an influence on the results and the outcome of the study. Prior to application the soil was prepared to have a fine crumb structure.

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Table 7.1.2.2.1-1: **Properties of the test sites and their soils**

Trial No.	10-2702-01		10-2702-02	
Site:				
Designation/site	, Germany,		, United Kingdom, Field	
Latitude				
Longitude				
Country	Germany		United Kingdom	
Ecoregion	Northern EU		Northern EU	
Plot Size (m²)	225		444	
Site History	2008 Grass 2009 Grass No plant protection products used.		2009 Grass No plant protection products used.	
Distance from weather station used for climatic measurements	20 km		At trial location. Sunshine hours 13 km Long-term averages 43 km	
Meteorological conditions compared to long-term average within normal levels (Yes/No)	Overall Yes		Overall Yes	
Other details, if any				
Soil depth (cm)	0 – 30	30 – 50	0 – 30	30 – 50
Surface soil texture (USDA)	Loam	Loam	Clay	Clay loam
Sand (%)	35	35	29	37
Silt (%)	48	40	26	24
Clay (%)	17	25	45	39
pH (water)	6.1	5.0	7.3	7.4
pH (CaCl₂)	5.7	4.6	7.2	7.2
CEC (meq/100g)	11.7	9.6	32.3	26.4
Chalk (% CaCO₃)	0.3	<0.1	0.6	0.3
Organic carbon (%)	3.0	0.8	1.9	0.8
Bulk density (g/cm³)	n.d.	n.d.	n.d.	n.d.
WHC max pF 0.05 (g/100 g)	64.6	51.5	59.6	57.7
WHC pF 2 (vol%)	37.3	30.2	29.8	24.8
WHC pF 2.5 (vol%)	33.0	28.1	28.8	25.5
Initial soil moisture (g/100g)	n.d.	n.d.	n.d.	n.d.

n.d. = not determined

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Table 7.1.2.2.1-1: Properties of the test sites and their soils (continued)

Trial No.	10-2702-03		10-2702-04	
Site:	▮		▮	
Designation	▮, France, Plot ▮		▮ Germany, Plot ▮	
Latitude	▮		▮	
Longitude				
Country	France		Germany	
Ecoregion	Northern EU		Northern EU	
Plot Size (qm²)	369		225	
Site History	2007 No crop 2008 No crop 2009 No crop Use of Roundup flash in 2007, 2008 and 2009		2008 Grass 2009 Grass No plant protection products used	
Distance from weather station used for climatic measurements	5 to 6 km		At trial location	
Meteorological conditions compared to long-term average within normal levels (Yes/No)	Overall Yes Very dry spring 2011		Overall Yes	
Other details, if any	-		-	
Soil depth (cm)	0 – 30	30 – 50	0 – 30	30 – 50
Surface soil texture (USDA)	Silt loam	Silt loam	Silt loam	Loam
Sand (%)	19	15	21	37
Silt (%)	62	68	58	44
Clay (%)	19	17	21	19
pH (water)	7.2	7.4	6.7	6.5
pH (CaCl$_2$)	7.0	7.2	6.4	6.2
CEC (meg/100g)	13.2	11.5	12.4	12.3
Chalk (% CaCO$_3$)	0.2	0.4	0.2	0.1
Organic carbon (%)	1.4	0.7	1.3	0.4
Bulk density (g/cm³)	n.d.	n.d.	n.d.	n.d.
WHC max (g/100 g)	54.9	50.9	54.2	46.5
WHC pF 2 (vol%)	34.8	32.7	31.9	26.3
WHC pF 2.5 (vol%)	27.2	27.4	23.4	20.2
Initial soil moisture (g/100 g)	n.d.	n.d.	n.d.	n.d.

n.d. = not determined

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Table 7.1.2.2.1-1: Properties of the test sites and their soils (continued)

Trial No.	10-2702-05		10-2702-06	
Site:	▮▮▮		▮▮▮	
Designation	▮▮, Italy, Az. ▮▮▮		▮▮▮, Spain, ▮▮▮ Plot ▮, Parcel ▮	
Latitude	45° 21' 12.92''N		41° 53' 15.09''N	
Longitude	11° 11' 30.32''E		2° 44' 23.65''E	
Country	Italy		Spain	
Ecoregion	Southern EU		Southern EU	
Plot Size (qm²)	720		200	
Site History	2007 Wheat 2008 Wheat 2009 Wheat No plant protection products used.		2006 No crop 2009 Grass Use of experimental fungicide (BYF 14182 SC 100) in 2006 and Lontrel Super in 2006	
Distance from weather station used for climatic measurements	10 km		At trial location Sunshine hours 10 km	
Meteorological conditions compared to long-term average within normal levels (Yes/No)	Overall Yes Spring to winter 2010 were very wet		Overall Yes	
Other details, if any				
Soil depth (cm)	0 – 30	30 – 50	0 – 30	30 – 50
Surface soil texture (USDA)	Silty clay loam	Loam	Sandy loam	Sandy loam
Sand (%)	18	25	54	59
Silt (%)	53	50	33	24
Clay (%)	29	25	13	17
pH (water)	7.9	8.0	6.1	6.0
pH (CaCl₂)	7.7	7.8	5.8	5.6
CEC (meq/100g)	14.6	13.8	8.2	9.9
Chalk (% carbon)	22.5	20.4	0.1	0.2
Organic carbon (%)	1.2	0.7	0.7	0.3
Bulk density (g/cm³)	n.d.	n.d.	n.d.	n.d.
WHC max (g/100 g)	56.2	56.2	37.2	39.0
WHC pF 2 (vol%)	33.6	28.9	18.8	15.3
WHC pF 2.5 (vol%)	26.7	25.5	15.7	13.5
Initial soil moisture (g/100g)	n.d.	n.d.	n.d.	n.d.

n.d. = not determined

B. Study design

1. Application. AE 0540092 was applied once as the formulated product WP 20 at a rate of 0.5 kg product/ha in 500 L/ha spraying solution in spring (April to June) 2010. The rate was equivalent to a nominal field application rate of 100 g test item/ha. The product was applied onto bare plots followed by mechanical incorporation into the soil directly after treatment. As part of agricultural maintenance of the field plots the emerging vegetation was either mulched by mechanical measurements or treated with a total herbicide (glyphosate) to keep the plots free of plants. Details on application are summarized in Table 7.1.2.2.1-2.

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Table 7.1.2.2.1-2: **Data on the application equipment**

Trial No.	Device	Nozzle Type	Working Width (m)	No. of Nozzles	Pressure (bar)
▮▮▮▮▮, Germany 10-2702-01	Knapsack-sprayer / spraying boom	Agrotop 03 110° VG 020292	1.5	3	2
▮▮▮▮▮, UK 10-2702-02	Knapsack sprayer / spraying boom	Teejet Flat Fan 110° ENG SPR11	3	6	2
▮▮, France 10-2702-03	Knapsack-sprayer / spraying boom	Teejet TJXR 8001 VS FR11-30, FR11-137	2.25	9	3
▮▮▮▮, Germany 10-2702-04	Knapsack-sprayer / spraying boom	Agrotop 03 110° VG 020292	1.5	3	2
▮▮▮, Italy 10-2702-05	Knapsack-sprayer / spraying boom	Albuz AVI ISO 110 015 110°	4	8	5
▮▮▮▮▮▮, Spain 10-2702-06	Knapsack sprayer / spraying boom	Teejet AIXR 11002 SPA1-110	2	4	2.6

2. Sampling and sample processing: Samples were taken for analysis following zero (pre incorporation), 0.1 (post incorporation), 3-4, 7, 9-11, 13-15, 20-22, 26-31, 49-66, 89-94, 119-126, 170-188 days after treatment (DAT). An additional sampling interval was taken for all sites except ▮▮▮▮ ▮▮▮▮ (UK) by 353-363 DAT.

The sampling spots were distributed randomly across the plots for generating representative total samples. Sampling was performed up to a depth of 10 cm with a soil piercer (Ø 50 mm) for samples taken by day zero. At the later sampling intervals a "Wacker Hammer" (Ø 48-49.5 mm) was used to collect soil cores up to a maximum depth of 30 cm (3-4 DAT), 50 cm (13-15 DAT), 75 cm (20-22 DAT) or 100 cm (after 26-31 DAT till study end).

By day zero and the following a total of 17 to 20 soil cores were taken per treated plot while 10 to 20 cores were sampled from untreated controls by DAT zero and 353.

The samples were deep-frozen within 24 hours after collection and stored frozen until further processing for analysis as described under point 4.

3. Irrigation and weather data: Weather data of air temperature, precipitation including irrigation, and hours of sunshine were recorded by weather stations located at each of the test sites during the tests. The data were briefly included in Table 7.1.2.2.1-1. Apart from temporary deviations for all sites and some significant variances for site ▮▮▮▮ (Italy) during spring to winter 2010 the records demonstrate typical conditions of weather on site when being compared to their long-term averages.

4. Work-up of samples and analytical procedure: After sampling the soil cores were stored frozen for processing and analysis. The frozen cores were cut into 10 cm segments with each segment being combined with those from other cores for homogenization by milling.

Sub-samples of 20 g of homogenised soil each were extracted by addition of 40 mL of an acidified (formic acid, 0.22 mL/L solvent) mixture of water/acetonitrile (1/4, v/v) and the agitation of the

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resulting slurry in a microwave extractor. Fine particles of soil were removed by centrifugation of an aliquot of 1.5 mL of the extract.

Identification and quantitation of analytical targets, i.e. the test item RPA 202248 (AE 0540092) and the benzoic acid RPA 203328 (AE B197555) was performed by use of HPLC-MS/MS coupling techniques and by their detection in MS via the Multiple Reaction Monitoring (MRM) mode. Potential matrix effects were eliminated by addition of an internal standard solution containing a stable-isotope labeled reference material of each analytical target after extraction.

The method reported as BCS Method No. 01198[7] had been validated by investigations in two contrary soil matrices, a silt loam (⬛⬛⬛) and a sandy loam (⬛⬛⬛). The mass spectrometric detection used two MRM transitions for each analyte investigated, i.e. a ratio m/z 358 → 79 for quantification and m/z 358 → 64 for confirmation of analyte RPA 202248. A transition m/z 267 → 159 (quantification) and m/z 267 → 223 (confirmation) was used for the benzoic acid analyte RPA 203328.

The method was shown to be linear in a range from 0.8 to 100 µg/L with associated correlation coefficients ranging from 0.9991 to 0.9998. Overall mean recoveries were within the range of 70 to 110%. The LOQ of the method was 5 µg/kg soil and the LOD was 1.5 µg/kg for each single analytical target investigated.

Studies investigating the storage stability of RPA 202248 and RPA 203328 in frozen soil had been performed earlier with details summarized under KCA 7.1.2.2.1 /04 in the following. The results indicated stability of RPA 202248 and RPA 203328 residues in frozen soil for at least 18 months. RPA 202248 and RPA 203328 were not detected in untreated controls (< LOD).

The results obtained in terms of a concentration (*i.e.* µg analyte/kg of wet soil) were converted into the corresponding rates expressed as g/ha by considering the actual weight of the wet soil core and its volume for determination of the actual bulk density of the wet soil sample. The actual bulk density was multiplied with the concentration of the given compound in wet soil and referred to one hectare area for the calculation of the corresponding rates per hectare as given in Table 7.1.2.2.1-3 and Table 7.1.2.2.1-4 for RPA 202248 and in Table 7.1.2.2.1-5 to Table 7.1.2.2.1-6 for RPA 203328.

5. Calculation of dissipation rates: Following FOCUS Guidance the dissipation of residues of RPA 202248 and RPA 203328 under field conditions was kinetically evaluated by use of the software KinGUI (Vers.1.1) for a fit of experimental data with a standard set of kinetic models available. The quality of fits was assessed by visual inspection and criteria based on the error of chi^2 (χ^2) and a t-test for testing of significance. The initial concentration of RPA 202248 was included in the parameter optimisation procedure.

II. Results and Discussion

A. Application verification and recovery: The use of non-radiolabelled test substance implies no possibility for the determination of a complete material balance of all components including those forming NER and volatile products from mineralisation. However, it is not within the objectives of the study to establish a full route of degradation under field conditions. The focus must be therefore on

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[7] The method is detailed in report M-430249-01-1 (KCA 4.2.1 /01, Freitag & Oel, 2012).

determination of the kinetics and thus rate of dissipation of residues as defined from route studies with radiolabelled active substance in the laboratory.

As some general point, it should be considered that, within the range of deviations observed, the overall rate of dissipation is hardly influenced by the actually measured concentrations. As a rule of thumb and from observations made in laboratory testing such influence may be given for deviations starting with a factor of five or more for the initial concentration under aerobic conditions.

Taking into account these aspects the measured initial mean concentrations of RPA 202248 were well to excellently in line with the nominal application rate of 100 g/ha. The values were detailed in Table 7.1.2.2.1-3 and Table 7.1.2.2.1-4. Recoveries ranged from 70.0 g test item/ha at site ▮▮▮▮ ▮▮ to 87.8 g/ha at site ▮▮▮▮▮▮▮▮ representing 70.0 to 87.8% of the intended application rate. The range of recoveries is regarded as acceptable within the objectives of the study when considering that concentrations of residues in soil are variable in a field situation by their nature due to a number of parameters of influence and their associated errors:

- Applications are not completely homogeneous
- Potential influence from spray drift
- Following incorporation into soil homogenization is rather challenging under conditions of the field.

The dissipation of more than 50% of the actually applied amount of RPA 202248 occurred at about 15 days (▮▮▮▮▮▮▮▮), 66 days (▮▮▮▮▮▮▮▮), 21 days (▮▮▮▮), 26 days (▮▮▮▮▮▮), 28 days (▮▮▮▮) and 14 days (▮▮▮▮▮▮▮▮) after treatment (Table 7.1.2.2.1-3 and Table 7.1.2.2.1-4). Quantifiable residues of RPA 202248 were detected in the top 10 to 20 cm of soil for most sites thus indicating a fast degradation associated with low mobility in the course of the study. The only exception was the Italian site ▮▮▮▮ with some detects in the 20 to 30 cm soil layer starting from DAT 3 to DAT 28. Again, there we no detects at or below the top 20 to 30 cm soil layer at later sampling intervals underlining fast degradation in a field situation.

Residues of RPA 203328 showed maximum values of 22.7 g metabolite/ha for site ▮▮▮▮▮▮▮ at DAT-62, 9.11 g/ha for site ▮▮▮▮▮▮▮▮ at DAT-66, 23.8 g/ha for site ▮▮▮▮ at DAT-21, 9.81 g/ha for site ▮▮▮▮▮▮ at DAT-20, 10.4 g/ha for site ▮▮▮▮ at DAT-22 and 32.5 g/ha for site ▮▮▮▮ ▮▮ at DAT-29 (Table 7.1.2.2.1-5 and Table 7.1.2.2.1-6). For all sites a decline of residues below the LOD of 1.5 µg/kg soil was observed for RPA 203328 starting from DAT-89 at site ▮▮▮▮▮ to DAT-188 at site ▮▮▮▮. As for RPA 202248 quantifiable residues of RPA 203328 were detected in the top 10 to 20 cm of soil thus indicating a fast degradation associated with low mobility in the course of the study.

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Table 7.1.2.2.1-3: Residue data (g/ha) for the dissipation of RPA 202248 (AE 0540092) in soil under field conditions for sites ███████████, ███████████ and ██████

██████████ (Germany) 10-2702-01			███████████ (UK) 10-2702-02			████████ (France) 10-2702-03		
DAT (days)	(g/ha)	(%)*	DAT (days)	(g/ha)	(%)*	DAT (days)	(g/ha)	(%)*
0**	73.1	73.1	0**	87.8	87.8	0**	81	81
0.1	62.3	62.3	0.1	80.7	80.7	0.1	71.3	71.3
3	45.9	45.9	4	52.1	52.1	3	49.0	49.0
7	52.4	52.4	7	71.7	71.7	7	72.5	72.5
10	40.2	40.2	10	48.4	48.4	9	68.9	68.9
15	27.1	27.1	14	75.9	75.9	14	45.6	45.6
21	25.1	25.1	21	57.4	57.4	21	41.8	41.8
29	30.1	30.1	31	55.9	55.9	28	22.8	22.8
62	12.6	12.6	66	35.9	35.9	49	11.9	11.9
93	6.94	6.9	94	25.2	25.2	92	3.87	3.9
120	4.85	4.9	126	6.90	6.9	119	1.3	1.1
170	1.13	1.1	180	1.13	1.1	188	<LOD	-
353	<LOD	-	-	-	-	358	<LOD	-

DAT: days after treatment
* Values refer to a nominal rate of 100 g test item /ha
** Initial concentration for samples before soil incorporation

Table 7.1.2.2.1-4: Residue data (g/ha) for the dissipation of RPA 202248 (AE 0540092) in soil under field conditions for sites ███████████, ██████ and ███████████

██████████ (Germany) 10-2702-04			██████ (Italy) 10-2702-05			███████████ (Spain) 10-2702-06		
DAT (days)	(g/ha)	(%)*	DAT (days)	(g/ha)	(%)*	DAT (days)	(g/ha)	(%)*
0**	70.8	70.8	0**	76.5	76.5	0**	70.0	70.0
0.1	53.6	53.6	0.1	84.3	84.3	0.1	54.4	54.4
3	51.7	51.7	3	64.7	64.7	3	45.4	45.4
7	55.6	55.6	7	83.9	83.9	7	40.8	40.8
11	50.4	50.4	10	60.6	60.6	10	27.7	27.7
14	63.2	63.2	13	64.8	64.8	14	30.6	30.6
20	45.8	45.8	22	55.3	55.3	21	15.6	15.6
26	37.3	37.3	28	39.3	39.3	29	9.45	9.5
60	1.13	1.1	63	7.26	7.3	59	1.13	1.1
89	<LOD	-	90	1.13	1.1	93	<LOD	-
120	<LOD	-	120	<LOD	-	128	<LOD	-
175	<LOD	-	182	<LOD	-	178	<LOD	-
363	<LOD	-	360	<LOD	-	351	<LOD	-

DAT: days after treatment
* Values refer to a nominal rate of 100 g test item/ha
** Initial concentration for samples before soil incorporation

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Table 7.1.2.2.1-5: Residue data (g/ha) for the dissipation of RPA 203328 (AE B197555) in soil under field conditions for sites ▇▇▇▇, ▇▇▇▇ and ▇▇

▇▇▇ (Germany) 10-2702-01		▇▇▇ (UK) 10-2702-02		▇▇▇ (France) 10-2702-03	
DAT (days)	(g/ha)	**DAT** (days)	(g/ha)	**DAT**(days)	(g/ha)
0	<LOD	0	<LOD	0	<LOD
0.1	<LOD	0.1	<LOD	0.1	<LOD
3	1.13	4	<LOD	3	4.24
7	5.74	7	<LOD	7	7.33
10	6.63	10	1.13	9	7.70
15	6.69	14	4.51	14	14.5
21	11.6	21	5.92	21	22.8
29	19.5	31	8.34	28	24.2
62	22.7	66	9.11	49	13.7
93	13.1	94	6.81	92	6.87
120	9.08	126	1.13	119	1.13
170	1.13	180	<LOD	183	<LOD
353	<LOD		-	358	<LOD

DAT: days after treatment

Table 7.1.2.2.1-6: Residue data (g/ha) for the dissipation of RPA 203328 (AE B197555) in soil under field conditions for sites ▇▇▇▇, ▇▇ and ▇▇▇

▇▇▇ (Germany) 10-2702-04		▇▇▇ (Italy) 10-2702-05		▇▇▇ (Spain) 10-2702-06	
DAT (days)	(g/ha)	**DAT** (days)	(g/ha)	**DAT**(days)	(g/ha)
0	<LOD	0	<LOD	0	<LOD
0.1	<LOD	0.1	<LOD	0.1	<LOD
3	<LOD	3	3.78	3	8.89
7	1.13	7	7.41	7	15.5
11	4.20	10	7.14	10	15.0
14	7.66	13	8.68	14	24.1
20	9.81	22	10.4	21	21.8
26	9.14	28	8.13	29	32.5
60	1.13	63	2.3	59	24.3
89	<LOD	90	1.13	93	4.69
120	<LOD	120	<LOD	128	1.13
178	<LOD	180	<LOD	178	<LOD
363	<LOD	360	<LOD	351	<LOD

DAT: days after treatment

C. Kinetics of dissipation of RPA 202248 (AE 0540092) in soil: The kinetic evaluation of the dissipation of RPA 202248 in soil under field conditions resulted in best fits represented by the bi-phasic model DFOP for three sites. For the other three sites SFO was determined to be the best fit to the measured data as it is summarized in Table 7.1.2.2.1-7.

Apart from visual assessment the chi²-scaled error 'quantifies' the quality of fit. For best fits its values ranged from 7 to 15% to result dissipation half-lives ranging from 8.2 to 40 days. The associated values for the DT_{90} were 37 to 177 days. These values may be compared with trigger endpoints in environmental exposure assessments.

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Table 7.1.2.2.1-7: Non-normalised half-lives from kinetic analysis of dissipation data of RPA 202248 (AE 0540092) in the field for comparison with trigger endpoints

Location and Trial No.	Kinetic Model	DT$_{50}$ (days)	DT$_{90}$ (days)	Visual Assessment *	Error for Chi^2
, Germany 10-2702-01	SFO	17	58	O	15
	DFOP	**14**	**81**	+	**11**
	FOMC	14	115	+	13
, UK 10-2702-02	SFO	50	165	O	15
	DFOP	**40**	**177**	**O**	**15**
	FOMC	48	175	O	16
, France 10-2702-03	**SFO**	**21**	**69**	**O**	**15**
	DFOP	21	69	O	17
	FOMC	21	71	O	16
, Germany 10-2702-04	**SFO**	**29**	**97**	**O**	**15**
	DFOP	29	97	O	17
	FOMC	29	99	O	16
, Italy 10-2702-05	**SFO**	**28**	**92**	**O**	**12**
	DFOP	28	92	O	13
	FOMC	31	94	O	12
, Spain 10-2702-06	SFO	10	34	O	11
	DFOP	**8.2**	**37**	+	**7**
	FOMC	10	40	O	11

Best fits from overall evaluation are marked bold
* Evaluation of fits as good (+), medium (o) or bad (-)

III. Conclusion

There was no indication for a significant movement of residues of RPA 202248 and its metabolite RPA 203328 into layers below the top 30 cm of soil. The incorporation into soil directly after treatment assured the exclusion of losses by non-biotic degradation factors at the soil surface. The biotic character of degradation of RPA 202248 and RPA 203328 in soil was indicated by the results of laboratory investigations. Plant uptake was minimal due to application to bare soil and by keeping plots free of vegetation in the course of the study.

Residues of RPA 202248 in soil were below the LOD of 1.5 μg/kg soil at all sites by DAT-353 ( ), DAT-180 ( ), DAT-188 ( ), DAT-89 ( ), DAT-90 ( ) and DAT93 ( ).

As for RPA 202248, quantifiable residues of RPA 203328 were detected in the top 10 to 20 cm of soil. Maximum values of RPA 203328 were detected within the first 70 days after treatment starting from 9.11 g/ha to 32.5 g/ha. The residues showed a decline below the LOD of 1.5 μg/kg soil at all sites by DAT-89 to DAT-188. The results indicated the degradability and thus transient character of this metabolite under conditions of the field.

In terms of best fit to measured data the dissipation of RPA 202248 in the field can be described by mono- (SFO) as well as bi-phasic kinetics with the bi-phasic model DFOP to be the best fit for three sites (, D, , UK, and , SP) while it was the SFO model for the other three sites (, F, , D, and , I).

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On the basis of best statistical and visual fit values of dissipation half-lives for comparison with trigger endpoints were found to range from 8 to 40 days. The associated values for the DT_{90} ranged from 37 to 177 days.

Based on the results a rapid degradation of RPA 202248 was demonstrated for a field situation at sites representative for the northern and southern EU.

The kinetic evaluation of field dissipation data was performed separately for the determination of endpoints for use as modelling input parameters (KCA 7.1.2.2.1 /05).

Storage stability of isoxaflutole residues in soil

Report:	x; ;1997;M-234239-01
Title:	Storage stability in soils from the European terrestrial field soil dissipation isoxaflutole and metabolites study P94/009
Report No:	C034021
Document No(s):	Report includes Trial Nos.: 95-85 M-234239-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

The storage stability of the active substance isoxaflutole and its metabolites RPA 202248, RPA 203328 and RPA 205834 in soil under freezer storage conditions as used for samples from field trials was assessed.

Untreated soil from four European test sites,   (I),   (F), Germany (D) and   (UK) of a field dissipation study was used for this storage stability study. Soil samples were fortified each with 50 µg/kg of active substance isoxaflutole, RPA 202248, RPA 203328 and RPA 205834.

Soil samples were analysed by day 0 and after 3, 6, 9, 12, and 18 months of storage in the freezer at <-18 °C.

Soil samples were analyzed for the four analytical targets according to method AR 106-94[8]. Identification and quantitation of the analytical targets was performed by reversed phase high performance liquid chromatography (HPLC) using UV detection at 270 nm or 300 nm with a limit of quantitation (LOQ) of 5 µg/kg soil.

The mean recovery during analyses of the samples was 101 to 104% for the active substance isoxaflutole (n = 7 for each soil), 92 to 97% for RPA 202248 (n = 6), 99 to 83 to 103% for RPA 203328 (n = 6) and 93 to 100% for RPA 205834 (n = 6). Consequently, an average of clearly more than 70% of the initially fortified amount was recovered from the stored samples for all sampling intervals and for all potential analytical targets.

The recovered amounts in four soils after 18 months (approx. 540 days) of storage in a freezer ranged from 93 to 105% for the active substance isoxaflutole, 89 to 100% for RPA 202248, 71 to 106% for

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[8] The analytical method has been submitted in the existing dossier and evaluated during the process of Annex I inclusion (see KCA 4.1.2, doc. M-201587-01-1).

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RPA 203328 and 85 to 103% for RPA 205834. The results are summarized in Table 7.1.2.2.1-8 to Table 7.1.2.2.1-11.

Table 7.1.2.2.1-8: Recoveries of active substance isoxaflutole in soil after frozen storage

Soil	Month	Recovery [%]	Overall mean recovery [%]
▇▇▇ (I)	0	101*	
	3	108	
	6	98	
	9	104	104
	12	105	
	18	105	
▇▇▇ (F)	0	110*	
	3	101	
	6	99	
	9	95	101
	12	105*	
	18	95	
Germany (D)	0	104*	
	3	107	
	6	90	
	9	104	101
	12	105	
	18	98	
▇▇▇ (UK)	0	109*	
	3	112	
	6	97	
	9	99	103
	12	110	
	18	93	

* Mean values of two replicates

Table 7.1.2.2.1-9: Recoveries of RPA 202248 in soil after frozen storage

Soil	Month	Recovery [%]	Overall mean recovery [%]
▇▇▇ (I)	0	98*	
	6	96	
	9	107	97
	12	94	
	18	89	
▇▇▇ (F)	0	99*	
	6	97	
	9	98	99
	12	101	
	18	100	
Germany (D)	0	99*	
	6	85	
	9	87	92
	12	96	
	18	91	
▇▇▇ (UK)	0	102*	
	6	106	93
	9	91*	

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| | 12 | 74 | |
| | 18 | 94 | |

* Mean values of two replicates

Table 7.1.2.2.1-10: Recoveries of RPA 203328 in soil after frozen storage

Soil	Month	Recovery [%]	Overall mean recovery [%]
▮ (I)	0	105*	
	6	88	
	9	70	83
	12	82	
	18	71	
▮ (F)	0	105*	
	6	93	
	9	105	103
	12	106	
	18	106	
Germany (D)	0	103*	
	6	85	
	9	115	101
	12	97	
	18	106*	
▮ (UK)	0	108	
	6	86	
	9	95*	97
	12	89	
	18	106	

* Mean values of two replicates

Table 7.1.2.2.1-11: Recoveries of RPA 205834 in soil after frozen storage

Soil	Month	Recovery [%]	Overall mean recovery [%]
▮ (I)	0	105*	
	6	99	
	9	104	100
	12	94	
	18	98	
▮ (F)	0	105*	
	6	98	
	9	100	100
	12	96	
	18	103	
Germany (D)	0	103*	
	6	85	
	9	80*	93
	12	100	
	18	95	
▮ (UK)	0	103*	
	6	105	
	9	90*	96
	12	96	
	18	85	

* Mean values of two replicates

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Conclusion

The storage stability of the analytical targets isoxaflutole active substance and its potential residues in soil, RPA 202248, RPA 203328 and RPA 205834, under frozen conditions has been demonstrated for a maximum storage time of 18 months.

Kinetic evaluation of field soil dissipation study KCA 7.1.2.2.1 /03

Report:	q; ;2013;M-464592-01
Title:	Kinetic modelling analysis of AE 0540092 and AE B197555 from a field soil residue study conducted in Europe (Normalisation to 20degree and pF2)
Report No:	VC/13/007A
Document No:	M-464592-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7.1.1 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Executive Summary

A kinetic evaluation was conducted for residue data of metabolites RPA 202248 (AE 0540092) and RPA 203328 originating from a field dissipation study conducted at six European sites (KCA 7.1.2.2.1 /03) to derive modeling endpoints for use in environmental exposure assessments. The evaluations were performed according to FOCUS kinetic guidance with the software tool KinGui, version 2.

Residue data of RPA 202248 and RPA 203328 were time-step referenced for temperature and moisture (20°C, pF2 moisture) to result in normalised values for the DT_{50}. The calculations included daily soil temperatures and moisture contents as supported by the model FOCUS PEARL, version 4.4.4. The normalisation of daily weather data followed the use of the Arrhenius approach for temperature correction (Q_{10} of 2.58) and the Walker equation for moisture correction (B-factor of 0.7).

The evaluation resulted in simple first-order (SFO) model fits each applied to the time-step normalised data sets of RPA 202248 and RPA 203328 for five test sites with the only exception for site ▮▮▮▮. Following the use of an inverse Hockey Stick (HS) approach to RPA 202248 data, this model was found to describe the situation best for site ▮▮▮▮. The fits were evaluated on the basis of detailed statistical analysis including visual assessment, chi²-error statistics, significance t-test and correlation analysis. Optimisation of fits to measured data was performed by use of bi-phasic kinetic models. The results are summarized in Table 7.1.2.2.1-12.

The overall geometric mean normalised (20°C, pF2 moisture) half-life in the field was 15.5 days for RPA 202248 and 11.4 days for RPA 203328.

Table 7.1.2.1.2-12: Normalised (20°C, pF2 moisture) field DT_{50}-values for RPA 202248 and RPA 203328 in soil for use as modelling input parameters in environmental exposure assessments

Parameter	RPA 202248	RPA 203328
DT_{50}, range (days)	10.2 – 29.8	2.0 – 43.3
Mean (geometric) DT_{50} (days)	15.5	11.4
Formation fraction from RPA 202248 (average)	-	0.92

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I. Material and Methods

Residue data were pre-processed by setting values between LOD (1.5 µg/kg per single analyte) and LOQ (LOQ = 5.0 µg/kg) to the measured values. Values < LOD were set to 0.5 LOD, in cases where one sampling date earlier or later the residue at the same depth had been >LOD, or if at the same sampling date the residue in the soil layer above had been >LOD. The curve was cut off after the first non-detect (< LOD), if no later value > LOQ followed. At day zero, values being <LOD in the deeper soil layers were set to zero.

Actual values for residues of RPA 203328 were converted to parent compound equivalents prior to further data processing.

Daily values of soil temperature and moisture were derived from daily weather data on precipitation, irrigation, maximum and minimum air temperature, humidity or vapour pressure, wind speed and global solar radiation by simulation with the software FOCUS PEARL. The use of the model assured that the mass balance is correct and that meaningful soil hydraulic values are obtained. With rainfall and potential evapotranspiration being the main driving forces for soil pore water flow these can be measured or calculated with adequate precision respectively.

The time step normalisation approach considered actual conditions in the field from study weather data in combination with the model used for evaluation to result in a correction for the degradation kinetics in ever changing outdoor conditions. The approach resulted in degradation rates and half-lives at reference conditions to be readily transferred to other climatic conditions (FOCUS, 2000). Normalisation was performed by use of a Q10 of 2.58 (average activation energy of 65,400 J/Mol) for temperature and a B-factor of 0.7 in the Walker equation for moisture correction.

Following time-step normalisation of residue data in principle, four kinetic models could be applied for fitting, *i.e.* simple first-order (SFO), first-order multiple-compartment (FOMC, Gustafson-Holden), hockey-stick (HS) and double-first order in parallel (DFOP).

The identification of the appropriate kinetic model to describe the field residue data was based on the three major criteria visual inspection, the scaled chi²-error ε and the significance t-test.

Following the approach by FOCUS, the use of SFO is preferred as the first step of evaluation. In case of its visual acceptability, a chi²-error ε not significantly exceeding 15% and low values for the t-test, no bi-phasic models were to be tested.

II. Results and Discussion

The application of the simple first-order (SFO) model resulted in acceptable fits to measured data for RPA 202248 for all sites with the exception for site ███████. The use of the SFO model resulted in acceptable fits for metabolite RPA 203328 in all cases.

With the combined 'all-SFO' approach for RPA 202248 and RPA 203328 failing acceptance criteria for site ███████, the fitting to measured data was optimized by applying a simulated lag-phase within an inverse Hockey-Stick (HS) kinetic model for RPA 202248 and the SFO model for RPA 203328 data.

Optimized fits were thus obtained for the combined modeling from use of an 'all-SFO' approach for five sites and the combination of a bi-phasic approach (HS model) for RPA 202248 with the SFO

model for site ███████. The results are summarized in Table 7.1.2.2.1-13 for RPA 20248 and Table 7.1.2.2.1-14 for RPA 203328.

Table 7.1.2.2.1-13: Kinetic modeling parameters derived for RPA 202248 from field data after time-step normalisation to reference conditions (20°C, pF2 moisture)

Site	Kinetic model	$DT_{50\ field}$ (days)	$DT_{90\ field}$ (days)	Chi^2- error (%)	t-test	VA
███████, D	SFO	15.6	51.9	21.6	<0.001	Good
███████, UK	SFO	29.8	99.1	17.0	<0.001	Good
███, F	SFO	15.2	50.5	17.0	<0.001	Good
███████, D	HS	10.2	26.1	18.5	<0.001	Acceptable
███, I	SFO	17.5	58.1	10.3	<0.001	Excellent
███████, E	SFO	11.2	37.2	12.1	<0.001	Excellent
Mean (geometric)		15.5				

VA = Visual assessment for acceptance of fit

Table 7.1.2.2.1-14: Kinetic modeling parameters derived for RPA 203328 from field data after time-step normalisation to reference conditions (20°C, pF2 moisture)

Site	Kinetic model	$DT_{50\ field}$ (days)	$DT_{90\ field}$ (days)	ffm *	Chi^2- error (%)	t-test	VA
███████, D	SFO	29.6	98.4	1.000	17.0	<0.001	Very good
███████, UK	SFO	13.7	45.6	0.645	21.5	<0.001	Acceptable
███, F	SFO	14.3	47.6	0.853	23.9	0.007	Good
███████, D	SFO	2.0	6.6	1.000	1.8	<0.001	Excellent
███, I	SFO	4.4	14.7	1.000	9.4	<0.001	Very good
███████, E	SFO	43.3	144.0	1.000	18.0	<0.001	Acceptable
Mean (geometric)		11.4					
Average				0.92			

* ffm = formation fraction. When ffm had been optimized to 1 during evaluations, the data was refitted with ffm = 1
VA = Visual assessment for acceptance of fit

III. Conclusion

Following FOCUS kinetic guidance the geometric mean referenced (20°C, pF2 moisture) half-lives ($DT_{50,\ field}$) for the degradation of RPA 202248 and RPA 203328 under field conditions were calculated to 15.5 days and 11.4 days, respectively. For the formation of RPA 203328 from its predecessor metabolite RPA 202248, an average value for the formation fraction of 0.92 was calculated.

The values are regarded as suitable endpoints for use in modelling of residues of RPA 202248 and RPA 203328 in environmental exposure assessments.

Overall summary of rate of degradation in aerobic soil for use as modelling input parameter in environemental risk asssessments

Report:	▮▮▮▮▮▮ u; ▮▮▮▮▮▮ :2013;M-464899-01
Title:	Isoxaflutole: Kinetic modelling endpoint summary
Report No:	VC/13/007J
Document No:	M-464899-01-1
Guidelines:	**Commission Regulation (EC) No.1107/2009 of 21 October 2009, not applicable**
GLP/GEP:	**no**

The report summarized the kinetic evaluations of aerobic soil degradation data from studies performed under laboratory and field conditions in terms of normalised (20°C, pF2) half-lives and their $DegT_{90}$ under KCA 7.1.2.1.1 /07, KCA 7.1.2.1.2 /08 and KCA 7.1.2.2.1 /05. The evaluation was performed according to EFSA Guidance for the active substance isoxaflutole and metabolites RPA 202248 (AE 0540092) and RPA 203328 (AE B197555) to result in appropriate $DegT_{50}$ values for use as modelling endpoint in environmental risk assessments.

For the active substance isoxaflutole, a geometric mean normalised $DegT_{50}$ of 0.9 days was calculated on the basis of laboratory data and in the absence of field data. The value was regarded as acceptable for use in modelling evaluations.
For metabolite RPA 202248, a geometric mean normalised $DegT_{50}$ of 15.5 days was calculated on the basis of field data available. For comparison with laboratory data an alpha factor of 0.25 was used. The evaluation showed that the 'Test confirmed that field studies showed a shorter DegT50 than laboratory studies'.
For metabolite RPA 203328, a geometric mean normalised $DegT_{50}$ of 11.4 days was calculated on the basis of field data available. For comparison with laboratory data an alpha factor of 0.25 was used. Again, the evaluation showed that the 'Test confirmed that field studies showed a shorter DegT50 than laboratory studies'.
The overall results are summarized in Table 7.1.2.2.1-15.

Table 7.1.2.2.1-15: Summary of mean normalized (20°C, pF2 moisture) $DegT_{50}$-values for isoxaflutole, RPA 202248 and RPA 203328 for use as modeling endpoints

Compound	Mean $DegT_{50}$ (days)	Formation fraction (ffm) (-)
Isoxaflutole	0.9	-
RPA 202248	15.5	1.00 from isoxaflutole
RPA 203328	11.4	1.00 from RPA 202248

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CA 7.1.2.2.2 Soil accumulation studies

The data requirement was addressed under Point 7.1.1.2.3 of the Dossier submitted and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that the values for the DT_{90} of isoxaflutole from laboratory and field tests performed were all significantly less than one year, thus with no indication for accumulation of the active substance in the soil environment.

CA 7.1.3   Adsorption and desorption in soil

CA 7.1.3.1   Adsorption and desorption

CA 7.1.3.1.1 Adsorption and desorption of the active substance

Report:	▮▮▮▮▮▮q;▮▮▮▮▮▮▮▮▮▮▮;▮▮▮▮▮▮▮;▮▮▮▮▮▮▮;▮▮▮▮▮▮▮; ;1993;M-065963-03; Amended; 2004-04-08
Title:	[14C]-RPA 201772: Adsorption/desorption to and from four soils and an aquatic sediment – Addendum report
Report No:	M-065963-03-1
Document No:	M-065963-03-1
Guidelines:	**EPA, Subdivision N, 163-1; Deviation not specified**
GLP/GEP:	**yes**

The adsorption of the active substance isoxaflutole to soil was investigated under conditions of the laboratory in:

- four soils and a sediment under standard conditions of batch equilibrium tests following application of phenyl-UL-^{14}C-labeled active substance (KCA 7.1.3.1.1 /01).

The data requirement had been addressed under Point 7.1.2.1 of the Dossier submitted and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently there is no detailed description of this existing data in this update.

The evaluation within the Annex I inclusion process revealed that the active substance isoxaflutole was moderately adsorbed to soil. Values for the adsorption $K_{F,OC}$ ranged ranged from 93 to 136 mL/g while values for Freundlich coefficients 1/n were from 0.90 to 1.00 when excluding the sediment. Following the DAR the corresponding $K_{F,OM}$ ranged ranged from 54 to 79 mL/g.

Re-calculation of adsorption to soil data for the active substance:

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However, it was found later that values of K_F, $K_{F,OC}$ and 1/n had not been calculated correctly due to non-consideration of interstitial water remaining in the soil after centrifugation at each adsorption and desorption step performed in the study. The data were thus re-evaluated with details of re-evaluation reported in the amended original report under KCA 7.1.3.1.1 /01:

The adsorption/desorption characteristics of [phenyl-UL-^{14}C]isoxaflutole (RPA 201772) were determined for four soils and a sediment under standard conditions of batch equilibrium tests at a concentration range of two orders of magnitude (1.5, 0.75, 0.15 and 0.015 mg/L) at 20°C in the dark.

In the definitive test the overall mean recoveries ranged from 97.2 to 102.8% AR% for the sand soil 93/24, 100.4 to 105.6% for sandy loam soil 93/7, 97.3 to 103.8% for clay loam soil 93/30, 96.3 to 100.2% for silty clay soil 93/32 and 95.8 to 100.9% for the loam sediment 93/31 for all test concentrations and thus found to be in the acceptable range.

The revised Freundlich adsorption coefficients (K_F) ranged from 0.24 to 13.0 mL/g with corresponding values referenced to organic carbon ($K_{F,OC}$) to range from 48 to 149 mL/g (Table 7.1.3.1.1-1). Values for the Freundlich coefficient of adsorption 1/n ranged from 0.87 to 1.03.

Table 7.1.3.1.1-1: Sorption behaviour of isoxaflutole (RPA 201772) in four soils and a sediment

Soil	%OC	% Clay	pH (CaCl2)	CEC	Ads K_F (mL/g)	Ads K_{OC} (mL/g)	Ads 1/n
Sand, US (93/24)	0.5	1.4	7.2	5.4	0.24	48	1.03
Sandy loam, UK (93/7)	0.9	6.3	5.9	4.9	0.84	93	0.87
Clay loam, UK (93/30)	2.4	22.4	6.9	12.2	1.68	70	0.91
Silty clay, UK (93/32)	7.5	43.3	4.8	15.7	8.15	109	0.94
Sediment, UK (93/31)	8.7	15.0	5.8	13.0	13.0	149	0.91

CEC = Cation Exchange Capacity
* Values for sediment not considered

CA 7.1.3.1.2 Adsorption and desorption of metabolites, breakdown and reaction products

Report:	;1995;M-066355-03; Amended 2004-04-08
Title:	[14C]-RPA 202248 Adsorption/desorption to and from four soils - Addendum report
Report No.:	CX/03/070A
Document No:	M-066355-03-1
Guidelines:	**91/414/EEC; 95/36/EC;Deviation not specified**
GLP/GEP:	**yes**

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Report:	$; ; ; ;1996;M-066483-01
Title:	[14C]-RPA 202248: Adsorption/desorption to and from four soils and an aquatic sediment
Report No:	11486
Document No:	M-066483-01-1
Guidelines:	**EPA, Subdivision N, 163-1; Deviation not specified**
GLP/GEP:	**yes**

Report:	ü; ; ;1996;M-209743-02
Title:	RPA 203328: Adsorption/desorption to and from four soils
Report No:	C025651
Document No:	M-209743-02-1
Guidelines:	**EU (=EEC): 95/36/EC Annex 1, Section 7.1.2; OECD: 106; USEPA (=EPA): Subdivision N (1982);Deviation not specified**
GLP/GEP:	**yes**

Report:	1 ;1996;M-158651-01
Title:	[14C]-RPA203328: Adsorption / desorption to and from four soils and a sediment
Report No:	R000447
Document No(s):	Report includes Trial Nos.: 11487 M-158651-01-1
Guidelines:	**USEPA (=EPA): N, 163-1, (1982);Deviation not specified**
GLP/GEP:	**yes**

Report:	2; ; ;2012;M-429399-01
Title:	[cyclopropyl-1-14C] AE 0540092: Adsorption/desorption in five different soils
Report No:	A8200
Document No:	M-429399-01-1
Guidelines:	**EC, Commission Directive 95/36/EC Amending Council Directive 91/414/EEC (Annexes II + III, Fate and Behavior in the Environment); July 14, 1995** **OECD Guideline for Testing of Chemicals, No 106 "Adsorption/Desorption", Jan. 21, 2000** **US EPA, Fate, Transport and Transformation Test Guidelines OPPTS 835.1220 Sediment** **and Soil Adsorption/Desorption Isotherm;not specified**
GLP/GEP:	**yes**

Report:	2; ; ;2004;M-229091-01
Title:	(14C)-RPA 203328: Adsorption / desorption in five soils
Report No:	C040534
Document No:	M-229091-01-1
Guidelines:	**EU (=EEC): 95/36/EC; OECD: 106; USEPA (=EPA): 163-1** **US EPA OPPTS 835.1230;see page 3**
GLP/GEP:	**yes**

The <u>adsorption of metabolite RPA 202248 to soil</u> had been investigated in the laboratory in two studies using:

- four soils under standard conditions of batch equilibrium tests following application of phenyl-UL-^{14}C-labeled test substance (KCA 7.1.3.1.2 /01).

- four soils and a sediment from the US under standard conditions of batch equilibrium tests following application of phenyl-UL-^{14}C- labeled test substance (KCA 7.1.3.1.2 /02).

The point was addressed under Point 7.1.2.2 of the Dossier submitted and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently there is no detailed description of this existing data in this update.

The evaluation during the Annex I inclusion process revealed that metabolite RPA 202248 was moderately adsorbed to soil. For the first study, $K_{F, ads, OC}$ ranged from 54 to 134 mL/g while values for Freundlich coefficients 1/n were from 0.922 to 0.974. Following the DAR $K_{F, om}$ ranged from 32 to 79 mL/g.
For the second study and following the amendment to DAR the corresponding values for the adsorption $K_{F, ads, OC}$ ranged from 94 to 159 mL/g when excluding the sediment. Values for Freundlich coefficients 1/n were from 0.922 to 0.955.

<u>Re-calculation of metabolite RPA 202248 adsorption to soil data</u>
Because the residual water remaining in soil after centrifugation[9] had not been considered adequately within the calculation of values of K_F, $K_{F, ads, OC}$ and 1/n in both studies, the results were re-evaluated being subject to an amendment each to the original reports KCA 7.1.3.1.2 /01 and KCA 7.1.3.1.2 /02.

<u>New adsorption to soil data for metabolite RPA 202248:</u>
The existing adsorption data to soil were amended by new data in order to generate a robust data package describing the adsorption behavior of RPA 202248 in soil (KCA 7.1.3.1.2 /05).

The <u>adsorption of metabolite RPA 203328 to soil</u> had been investigated under conditions of the laboratory in two studies using:

- four soils under standard conditions of batch equilibrium tests following application of phenyl-UL-^{14}C-labeled test substance (KCA 7.1.3.1.2 /03).

- four soils and a sediment from the US under standard conditions of batch equilibrium tests following application of phenyl-UL-^{14}C-labeled test substance (KCA 7.1.3.1.2 /04).

The point was addressed under Point 7.1.2.2 of the Dossier submitted and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
The evaluation finally resulted in invalidation of the existing adsorption data of metabolite RPA 203328.
Consequently there is no detailed description of this existing data in this update.

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[9] Term also used is 'interstitial water'.

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A new study investigating the adsorption behaviour of RPA 203328 in five soils was therefore performed (KCA 7.1.3.1.2 /06).

Re-calculation of adsorption to soil data for metabolite RPA 202248:
It was found later that values of K_F, $K_{F,OC}$ and 1/n had not been calculated correctly due to non-consideration of interstitial water remaining in the soil after centrifugation at each adsorption and desorption step performed in the study. The data were thus re-evaluated with details of re-evaluation reported in the amended original reports under KCA 7.1.3.1.2 /01 and KCA 7.1.3.1.2 /02:

Report:	▬▬▬▬ ; ▬▬▬ ; ▬▬▬▬ ;1995; M-066355-03; Amended: 2004-04-08
Title:	[14C]-RPA 202248: Adsorption/desorption to and from four soils - Addendum report
Report No:	CX/03/070A
Document No:	M-066355-03-1
Guidelines:	**91/414/EEC; 95/36/EC;Deviation not specified**
GLP/GEP:	**yes**

The adsorption/desorption characteristics of [phenyl-UL-^{14}C]RPA 202248 to soil were determined for four soils under standard conditions of batch equilibrium tests at a concentration range of two orders of magnitude (5, 1, 0.2 and 0.04 mg/L) at 20°C in the dark.

In the definitive test the overall mean recoveries ranged from 100.0 to 101.0% AR% for the sandy loam soil 93/22, 98.6 to 99.6% for loam soil 95/02, 97.9 to 101.1% for sandy loam soil 95/04 and 98.9 to 101.7% for the loamy sand soil 95/06 for all test concentrations and thus found to be in the acceptable range.

The revised Freundlich adsorption coefficients (K_F) ranged from 0.12 to 1.87 mL/g with corresponding values referenced to organic carbon ($K_{F, OC}$) to range from 11 to 99 mL/g (Table 7.1.3.1.2-2). Values for the Freundlich coefficient of adsorption 1/n ranged from 0.863 to 0.908.

Table 7.1.3.1.2-1: Sorption behaviour of RPA 202248 in four soils

Soil	% OC	% Clay	pH (CaCl₂)	CEC	Ads K_F (mL/g)	Ads K_{OC} (mL/g)	Ads 1/n
Sandy loam, US (93/22)	1.3	5.2	5.5	5.7	0.35	27	0.863
Loam, UK (95/02)	1.9	20.0	4.3	6.3	1.87	99	0.907
Sandy loam, UK (95/04)	2.2	8.8	4.7	5.7	1.65	75	0.908
Loamy sand, UK (95/06)	1.1	7.4	6.7	6.9	0.12	11	0.863

CEC = Cation Exchange Capacity

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Report:	u; ; ; ; ;1996;M-066483-01
Title:	[14C]-RPA 202248: Adsorption/desorption to and from four soils and an aquatic sediment
Report No:	11486
Document No:	M-066483-01-1
Guidelines:	**EPA, Subdivision N, 163-1;Deviation not specified**
GLP/GEP:	**yes**

The adsorption/desorption characteristics of [phenyl-UL-^{14}C]RPA 202248 to soil were determined for four soils and a sediment under standard conditions of batch equilibrium tests in a concentration range of two orders of magnitude (5, 1, 0.2 and 0.04 mg/L) at 20°C in the dark.

In the definitive test the overall mean recoveries ranged from 93.5 to 101.1% AR% for the clay soil 96/12, 99.1 to 100.2% for the sand soil 96/13, 98.2 to 99.8% (exclusion of one outlier) for loamy sand soil 96/14, 94.6 to 99.4% for silt loam soil 96/15 and 96.5 to 98.9% for the loam sediment 96/16 for all test concentrations and thus found to be in the acceptable range.

The revised Freundlich adsorption coefficients (K_F) ranged from 0.13 to 0.27 mL/g with corresponding values referenced to organic carbon ($K_{F, OC}$) to range from 22 to 62 mL/g when excluding values for the sediment (Table 7.1.3.1.2-2). Values for the Freundlich coefficient of adsorption 1/n ranged from 0.749 to 0.908, again after exclusion of values for the sediment.

Table 7.1.3.1.2-2: Sorption behaviour of RPA 202248 in four US soils and sediment

Soil	%OC	% Clay	pH (water)	CEC	Ads K_F (mL/g)	Ads K_{OC} (mL/g)	Ads 1/n
Clay, US (96/12)	1.2	56.8	6.2	32.8	0.27	22	0.749
Sand, US (96/13)	0.4	2.8	6.8	1.6	0.13	35	0.873
Loamy sand, US (96/14)	0.3	6.8	6.4	1.8	0.21	62	0.908
Silt loam, US (96/15)	0.5	12.8	6.5	10.1	0.19	41	0.862
Loam sediment, US (96/16)	5.0	12.8	5.6	12.6	5.92	119	0.874

CEC = Cation Exchange Capacity

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Report:	████████████ b; ████████; ███████;2012;M-429399-01
Title:	[cyclopropyl-1-14C] AE 0540092: Adsorption/desorption in five different soils
Report No:	AS200
Document No:	M-429399-01-1
Guidelines:	**EC, Commission Directive 95/36/EC Amending Council Directive 91/414/EEC (Annexes II + III, Fate and Behavior in the Environment); July 14, 1995** **OECD Guideline for Testing of Chemicals, No 106 "Adsorption/Desorption", Jan. 21, 2000** **US EPA, Fate, Transport and Transformation Test Guidelines OPPTS 835.1220 Sediment;not specified**
GLP/GEP:	**yes**

Executive Summary

The adsorption/desorption characteristics of [cyclopropyl-1-^{14}C]RPA 202248 (AE 0540092) were determined for five soils (three EU, two US) in a concentration range of two orders of magnitude.

In the definitive test the overall mean recoveries were 94.5% AR ± 1.5% for soil ████████████, 94.8% AR ± 0.6% for soil ████████, 94.6% AR ± 0.8% for soil ████████, 99.0% AR ± 0.7% for soil ████████ and 96.3% AR ± 0.6% for soil ████████ and for all test concentrations and thus found to be in the acceptable range.

The Freundlich adsorption coefficients (K_F) ranged from 0.1016 to 0.6162 mL/g with corresponding values referenced to organic carbon ($K_{F,OC}$) to range from 14.6 to 20.8 mL/g. Values for the Freundlich coefficient of adsorption 1/n ranged from 0.9995 to 0.9999.

I. Material and Methods

A. Materials

1. **Test Material:** [cyclopropyl-1-^{14}C]RPA 202248 (AE 0540092)
   Specific radioactivity: 4.08 MBq/mg (110.26 µCi/mg)
   Radiochemical purity: > 98% (HPLC)
   Chemical purity: >99% (HPLC)
   Sample ID: KML 9239

2. **Soil:** Sorption tests were performed with five soils covering a range of pH, organic carbon content and texture. The characteristics of soils originating from Germany and the US are summarised in Table 7.1.3.1.2-3.

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Table 7.1.3.1.2-3: Characteristics of test soils

Soil	(WuW)	(HaH)			
Geographic Location (City/State/Country)	Germany	Germany	Germany	California, US	Nebraska, US
GPS coordinates					
Pesticide use history	None within the last four years prior to sampling			None within the last two years prior to sampling	None within the last four years prior to sampling
Collection procedures	Field sampled with shovel/spade into aerated plasic bags (buckets)				
Sampling depth	0–20 cm			0–18 cm	0–20 cm
Storage conditions	0 – 10 °C [C]				
Storage duration	102 days [C]	102 days [C]	102 days [C]	806 days [C]	806 days [C]
Soil preparation	Air-dried and sieved to 2 mm				
Soil Taxonomic Classification (USDA) [D]	N/A	N/A	N/A	N/A	N/A
Soil Series [D]	N/A	N/A	N/A	N/A	N/A
Textural Class (USDA)	sandy loam	silt loam	loam	sandy loam	silt loam
Sand (%) [A]	57	27	37	56.0	12.7
Silt (%) [A]	30	60	40	32.6	60.8
Clay (%) [A]	13	13	23	11.4	26.5
pH (0.01 M CaCl$_2$)	5.1	6.3	7.3	6.7	6.6
pH (Water)	5.4	6.5	7.5	6.8	7.2
Org. Matter [B] (%)	3.44	4.99	7.57	1.1	2.9
Org. Carbon (%)	2.0	2.9	4.4	0.7	1.7
CEC (meq/100 g)	10.3	12.9	19.2	16.1	16.1

[A]) According to USDA classification; [B]) % Organic matter =% organic carbon x 1.72; [C]) After receipt at the testing facility.
CEC: Cation exchange capacity; N/A = Not available

B. Study design

1. Experimental conditions: For the definitive test samples of 20 g (10 g)[10] dry weight of soil (2 mm) were weighed each into centrifuge tubes to which *ca.* 18 mL of 0.01 M aqueous calcium chloride was added. The resulting slurry was pre-equilibrated for at least 16 hours followed by the addition of 2 mL of the corresponding application solution to result in a final volume of 20 mL and a soil/solution ratio of 1:1 (1:2). Within pre-tests controls containing no soil were prepared for determination of stability of the test item in calcium chloride solution and adsorption tests to the walls of the test vessels.
Initial nominal concentrations of the ^{14}C-test substance in the aqueous phase were 1, 0.3, 0.1, 0.03 and 0.01 mg/L thus covering two orders of magnitude.

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[10] 20 g of soil ▮, ▮ or ▮; 10 g of soil ▮ or ▮ II.

No organic co-solvent was present in samples during the tests. An initial pH of 6.7 was determined for the aqueous 0.01 M calcium chloride solution in the absence of soil. Each determination was performed in duplicate by shaking with an overhead shaker in the dark at 20±1°C.

Preliminary tests included the determination of the adequate soil-to-solution ratio (24 hours) and the corresponding adequate equilibration times needed for adsorption (total shaking time of 120 hours) for all soils.

For the definitive test an adsorption step of 24 hours was followed by a single desorption step of 24 hours at all test concentrations. The desorption step was carried out by replacing the aqueous supernatant after adsorption by fresh aqueous 0.01 M calcium chloride solution for each sample.

For work-up the aqueous supernatant was separated from soil by decantation and centrifugation (10 min, 5000 rpm). Radioactivity in water and soil extracts was determined by liquid scintillation counting (LSC). Non-extractable radioactivity in soil was determined by combustion followed by LSC to establish a full material balance.

Finally the adsorption parameters were calculated using the Freundlich adsorption isotherm.

2. Analytical procedures: Radioactivity was determined by liquid scintillation counting (LSC). The purity and stability of the test item was investigated by reversed phase radio HPLC analysis using ^{14}C-flow-through detection techniques.

II. Results and Discussion

A. Mass balance and results of preliminary tests

Solubility and stability tests in aqueous 0.01 M calcium chloride solution confirmed stability under the conditions of the test. Pre-tests on adsorption to the walls of test vessels by shaking an aqueous solution of the test substance in the absence of soil showed no adsorption.

Pre-tests on adsorption equilibrium to soil resulted in mass balances ranging from 96.7 to 97.9% of AR for all soils after 120 hours (Table 7.1.3.1.2-4). In parallel, the stability of the test substance was confirmed by parental mass balances of more than 90% of AR.

For the definitive tests the overall mass balance for individual samples for all concentrations and all soils investigated ranged from 91.9 to 100.3% of AR. The resulting mean recoveries (Table 7.1.3.1.2-5) were found to range from 94.5% (soil ▉▉▉▉▉▉) to 99.0% (soil ▉▉▉▉▉▉) with standard deviations ranging from ± 0.6% AR (soils ▉▉▉▉▉ and ▉▉▉▉▉▉) to ± 1.5% AR (soil ▉▉▉▉▉▉).

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Table 7.1.3.1.2-4: **Preliminary test: Recovery of [cyclopropyl-1-^{14}C]RPA 202248 in samples from determination of adsorption equilibrium after 120 hours.**

Soil			II		
Supernatant*	48.9	35.4	48.1	52.9	44.2
Soil extract*	41.6	55.6	42.5	43.4	46.4
Non-extractable residues in soil, if measured	5.5	6.3	5.7	1.5	6.8
Total recovery of test item	90.5	91.0	90.6	96.3	90.6
Total recovered radioactivity	97.9	97.9	96.7	97.8	97.4

* Test item was shown to be stable by HPLC analysis.

Table 7.1.3.1.2-5: **Definitive test: Total recovery of [cyclopropyl-1-^{14}C]RPA 202248 in samples following adsorption and desorption phase of 48 hours in total.**

Soil Test concentration (mg/L)			II		
1.01	96.5	95.8	94.8	98.2	95.7
0.30	95.0	95.1	95.2	98.9	95.6
0.10	94.1	94.5	93.2	98.8	96.3
0.03	91.9	94.0	95.6	98.9	96.6
0.01	95.0	94.5	93.9	100.3	97.3
Mean recovery	94.5	94.8	94.6	99.0	96.3
SD	± 1.5	± 0.6	± 0.8	± 0.7	± 0.6

Values derived from mean values of duplicate samples in terms of percentages of AR. SD = standard deviation

B. Transformation of parent compound: The stability of the test substance was confirmed by HPLC analysis to result in parental mass balances of more than 90% of AR.

C. Findings: The definitive tests were performed at a ratio of 1:2 for soils ▮▮▮ and ▮▮▮ II and a ratio of 1:1 for soils ▮▮▮ , ▮▮▮ and ▮▮▮ . Pre-tests showed that the adsorption equilibrium was reached after 24 hours. The definitive tests were therefore performed for an adsorption time of 24 hours followed by a desorption step of 24 hours.

The adsorption behaviour of [cyclopropyl-1-^{14}C]RPA 202248 could be accurately described within a nominal concentration range of 0.01 mg/L to 1.0 mg/L by the Freundlich equation for all soils (Table 7.1.3.1.2-6). The adsorption constants $K_{F(ads)}$ of the Freundlich isotherms ranged from 0.1016 to 0.6162 mL/g with associated Freundlich exponents 1/n to be below 1 for all soils (0.8586 to 0.9185). To some extent the desorption behaviour to soil was thus affected by the concentration of the test item. The corresponding correlation coefficients of adsorption isotherms ranged from 0.9995 to 0.9999 therefore indicating a good linear fit to the measured data. When being normalized for organic carbon content of soil values of adsorption K_{OC} varied from 11.6 mL/g (soil ▮▮▮) to 30.8 mL/g in maximum (soil ▮▮▮).

Desorption constants $K_{F, des}$ according to Freundlich ranged from 0.1149 mL/g (soil ▮▮▮) to 0.9194 mL/g (soil ▮▮▮). The corresponding values for $K_{OC, des}$ ranged from 14.5 mL/g (soil ▮▮▮ II) to 46.0 mL/g (soil ▮▮▮).

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Once adsorbed to soil particles values of RPA 202248 for desorption K_{OC} were slightly higher than the corresponding values of adsorption K_{OC} thus indicating some strengthening of binding.

Table 7.1.3.1.2-6: Adsorption and desorption constants of RPA 202248 (AE 0540092) in soil

| Soil | Soil type | Adsorption | | | | | Desorption | | | |
		pH*	K_F (mL/g)	1/n	R^2	K_{OC}** (mL/g)	K_F (mL/g)	1/n	R^2	K_{OC}*** (mL/g)
	sandy loam	5.1	0.6162	0.8999	0.9998	30.8	0.9194	0.8826	0.9986	46.0
	silt loam	6.3	0.3709	0.8643	0.9997	12.8	0.4266	0.8418	0.9993	14.7
II	loam	7.3	0.5331	0.8586	0.9995	12.1	0.6375*	0.8239	0.9989*	14.5*
CA	sandy loam	6.7	0.1016	0.9185	0.9999	14.5	0.1149	0.9100	0.9988	16.4
NE	silt loam	6.6	0.1971	0.9157	0.9998	11.6	0.2535	0.8920	0.9997	14.9

pH: Value given as determined with 0.01 M calcium chloride solution
K_F: Freundlich coefficients of adsorption (**) and desorption (***) respectively
1/n : Slope of the Freundlich adsorption/desorption isotherms
K_{oc}: Adsorption coefficient per organic carbon (K_s x 100/% organic carbon)
R^2: Regression coefficient of Freundlich equation
* Values calculated with only replicate b for highest test concentration

III. Conclusion

Values in terms of Freundlich $K_{OC, ads}$ were moderate for metabolite RPA 202248 to range from 11.6 to 30.8 mL/g for the five soils tested.
The desorption constants according to Freundlich ($K_{OC, des}$) were slightly higher than the respective adsorption constants, indicating some enhanced sorption of the compound once adsorbed to soil.

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Overall summary on adsorption of RPA 202248 in soil:

Investigations into the adsorption of RPA 202248 in soil were performed in three studies in total covering a whole range of soils as detailed in studies KCA 7.1.3.1.2 /01, KCA 7.1.3.1.2 /02 and KCA 7.1.3.1.2 /05. The adsorption data from 13 soils as compiled in Table 7.1.3.1.2-7 resulted in an arithmetic mean $K_{F,OC}$ value of 34.9 mL/g and a mean value of 0.876 for 1/n for use in environmental risk assessments.

Table 7.1.3.1.2-7: Adsorption behaviour of RPA 202248 in soil

Soil	%OC	% Clay	pH (CaCl2)	CEC	Ads K_F (mL/g)	Ads K_{OC} (mL/g)	Ads 1/n
Sandy loam, US (93/22)	1.3	5.2	5.5	5.7	0.35	27	0.863
Loam, UK (95/02)	1.9	20.0	4.3	6.3	1.87	99	0.907
Sandy loam, UK (95/04)	2.2	8.8	4.7	5.7	1.65	75	0.908
Loamy sand, UK (95/06)	1.1	7.4	6.7	6.9	0.12	11	0.863
Clay, US (96/12)	1.22	56.8	6.2	22.8	0.27	22	0.749
Sand, US (96/13)	0.38	2.8	6.8	1.58	0.13	35	0.873
Loamy sand, US (96/14)	0.34	6.8	6.4	4.84	0.21	62	0.908
Silt loam, US (96/15)	0.47	12.8	6.5	10.12	0.19	41	0.862
Sandy loam ▇▇▇	2.0	13	5.1	10.3	0.6162	30.8	0.8999
Silt loam ▇▇▇	2.9	13	6.6	12.9	0.3709	12.8	0.8643
Loam ▇▇▇ II	4.4	27	7.3	19.2	0.5331	12.1	0.8586
Sandy loam ▇▇▇ CA	0.7	11.4	6.7	16.1	0.1016	14.5	0.9185
Silt loam ▇▇▇ ME	1.7	26.5	6.6	16.1	0.1971	11.6	0.9157
Mean (average)						34.9	0.876

CEC = Cation Exchange Capacity (mval/100 g soil)
pH: Value according to 0.01 M calcium chloride method
K_F: Freundlich coefficients of adsorption (**)
1/n : Slope of the Freundlich adsorption isotherms
K_{oc}: Adsorption coefficient per organic carbon (K_F x 100/% organic carbon)

Report:	⊐; ; ;2004;M-229091-01
Title:	(14C)-RPA 203328: Adsorption / desorption in five soils
Report No:	C040534
Document No:	M-229091-01-1
Guidelines:	**EU (=EEC): 95/36/EC; OECD: 106; USEPA (=EPA): 163.1** **US EPA OPPTS 835.1230;see page 3**
GLP/GEP:	**yes**

Executive Summary

The adsorption/desorption characteristics of [phenyl-UL-^{14}C]RPA 203328 (AE B197555) were determined for five soils in a concentration range of two orders of magnitude. In the definitive test the overall mean values of recoveries for all concentrations were 102.3% of AR ± 0.9% for soil ████ ████ 105.4% ± 2.3% for soil ████████, 101.3% ± 0.5% for soil ████████, 100.6% ± 0.8% for soil ████████ and 97.0% ± 0.7% for soil ████ thus indicating quantitative recoveries.

Values for the coefficients of adsorption according to Freundlich (K$_{C\,ads}$) ranged from 0.00881 to 0.0283 mL/g for the three soils ████████, ████████ and ████ evaluable. The corresponding values related to organic carbon (K$_{oc\times ads}$) ranged from 0.88 to 1.49 mL/g. Values for the Freundlich coefficient of adsorption 1/n for the three soils ranged from 0.978 to 0.9998.

Adsorption of RPA 203328 to soil was therefore very low.

I. Material and Methods

A. Materials

1. **Test Material:** [phenyl-UL-^{14}C]RPA 203328 (AE B197555)
   Specific radioactivity: 2.86 MBq/mg (769.3 MBq/mmol)
   Radiochemical purity: 99.8% (HPLC)
   Chemical purity: not reported
   Sample ID: SEL 0289

2. **Soil:** Sorption tests were performed with five soils covering a range of pH, organic carbon content and texture. The characteristics of soils originating from the UK and Germany are summarised in Table 7.1.3.1.2-8.

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Table 7.1.3.1.2-8: Characteristics of test soils

Soil	(03/18)	(03/20)	(03/23)	(03/29)	(03/35)
Geographic Location (City/State/Country)	Field Station , , UK	Farm, , UK	Grounds Farm, , UK	, , UK	, , Germany
Grid reference					
Soil preparation	(Partly) Air-dried and sieved to 2 mm				
Textural Class (USDA)	sandy loam	clay loam	sandy clay	sandy loam	silt loam
Sand (%) [A]	72.4	43.2	49.9	68.3	28.5
Silt (%)[A]	11.0	23.5	14.1	25.3	61.1
Clay (%)[A]	16.6	33.3	36.0	6.5	10.3
pH (0.01 M CaCl2)	7.6	7.3	5.9	6.3	5.6
pH (Water)	7.7	7.6	6.6	7.1	6.5
pH (1 M KCl)	7.2	7.1	6.3	6.3	5.6
Org. Matter [B] (%)	2.6	3.3	5.7	1.7	2.8
Org. Carbon (%)	1.5	1.9	3.3	1.0	1.6
CEC (meq/100 g)	39.4	17.4	17.8	8.3	9.6
Moisture content (%)	14.70	8.54	19.49	2.12	19.91
Max. WHC @ 0.05 bar (%)[C]	43.9	44.7	66.9	27.5	60.8
Max. WHC @ 0.33 bar (%)[C]	20.7	30.6	44.0	17.6	28.5
CaCO3-equivalents (g/kg)	72.5	3.8	<0.05	1.0	1.0
Phosphorous, total (mg/kg)	740.7	729.0	608.5	855.5	664.8
Nitrogen, total (g/kg)	1567.8	1722.0	2632.2	826.0	1148.1

[A] According to USDA classification; [B] % Organic matter =% organic carbon x 1.72; [C] Max. WHC = maximum water holding capacity; CEC = Cation exchange capacity

B. Study design

1. Experimental conditions: For the definitive test samples of 40 g dry weight of soil (2 mm) were weighed each into centrifuge tubes, to which ca. 40 mL of 0.01 M aqueous calcium chloride was added. The resulting slurry was pre-equilibrated for at least 12 hours followed by the addition of 1 mL of the corresponding application solution to result in a final aqueous volume of 40 mL and a soil/solution ratio of 1:1. Being part of pre-tests control samples containing no soil were prepared the same way for determination of stability of the test item in calcium chloride solution and for testing of adsorption to the walls of the test vessels. The initial nominal concentrations of the ^{14}C-test substance in the aqueous phase were 1, 0.3, 0.1, 0.03 and 0.01 mg/L thus covering two orders of magnitude.

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No organic co-solvent was present in samples during the tests. An initial pH of 6.3 to 7.2 was determined for the aqueous 0.01 M calcium chloride solution in the absence of soil. Each determination was performed in duplicate by shaking with an overhead shaker in the dark at 20±1°C. Preliminary tests for all soils included the determination of the adequate soil-to-solution ratio (24 hours) and the corresponding adequate equilibration times needed for adsorption (total shaking time of 168 hours).

For the definitive test the adsorption time of 24 hours for ▮▮▮▮▮ soil and 168 hours for the other soils was followed by a three desorption steps of 24 hours each at all test concentrations. The desorption step was carried out by replacing the aqueous supernatant (10 mL for ▮▮▮▮▮ soil) after adsorption by fresh aqueous 0.01 M calcium chloride solution for each sample.

For work-up the aqueous supernatant was separated from soil by decantation and centrifugation (10 min, 5000 rpm). Radioactivity in water and soil extracts was determined by liquid scintillation counting (LSC). Non-extractable radioactivity in soil was determined by combustion followed by LSC to establish a full material balance.

Finally the adsorption parameters were calculated using the Freundlich adsorption isotherm.

2. Analytical procedures: Radioactivity was determined by liquid scintillation counting (LSC). The purity and stability of the test item was investigated by reversed phase radio-HPLC analysis using ^{14}C-flow-through detection techniques.

II. Results and Discussion

B. Mass balance and results of preliminary tests

Solubility and stability tests in aqueous 0.01 M calcium chloride solution confirmed stability under the conditions of the test. Pre-tests on adsorption to the walls of test vessels by shaking an aqueous solution of the test substance in the absence of soil showed no adsorption. Pre-tests showed also the stability of the test substance under the conditions of the test.

For the definitive tests the overall mass balance for individual samples at all concentrations and for all soils investigated ranged from 95.9 to 108.0% of AR. These values resulted from exclusion of two values of single replicates of the 0.01 and 0.03 mg/L test concentrations each in the ▮▮▮▮▮ soil. The resulting mean recoveries (Table 7.1.3.1.2-9) were found to range from 97.0% for soil ▮▮▮ to 105.4% for soil ▮▮▮▮▮▮ associated with standard deviations ranging from ± 0.5% AR for soil ▮▮▮▮▮▮ to ± 2.3% AR for soil ▮▮▮▮▮.

Table 7.1.3.1.2-9: Definitive test: Total recovery of [phenyl-UL-^{14}C]RPA 203328 in samples following an adsorption phase of 168 hours* and three desorption steps of 24 hours each in total

Soil Test concentration (mg/L)					
1.00	100.8	101.6	101.3	100.7	98.2
0.30	101.9	104.4	101.5	100.9	97.2
0.10	102.8	105.8	100.3	99.1	96.7
0.03	102.6	107.3**	101.5	100.5	97.1
0.01	103.4	108.0**	101.7	101.6	95.9
Mean recovery	102.3	105.4	101.3	100.6	97.0

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Soil **Test concentration** (mg/L)	■■■	■■■	■■■	■■■	■■
SD	± 0.9	± 2.3	± 0.5	± 0.8	± 0.7

Mean values of duplicate samples in terms of percentages of AR

* Adsorption phase was 24 hours for ■■■■■ soil

** Values for single replicates due to mass balances out of acceptable range for other replicate

B. Transformation of parent compound: The stability of the test substance was confirmed by HPLC analysis in pre-tests and in the definitive test.

C. Findings: The definitive tests were performed at a ratio of 1:1 for all soils. Pre-tests showed that the adsorption equilibrium was reached after 24 hours for ■■■■■■ soil while it had not been reached for the other soils. The definitive tests were therefore performed for an adsorption time of 24 hours for soil ■■■■■ and for 168 hours for the other. Each adsorption phase was followed by three successive desorption steps each for 24 hours.

Desorption values were influenced by the low overall adsorption and thus high values of radioactivity remaining in the interstitial water after the adsorption step. The values presented in the study report were therefore not summarized in more detail in this document since the values calculated are regarded to have no scientific validity.

As a consequence of the poor adsorption the adsorption behaviour of ^{14}C-RPA 203328 could not be accurately described by the Freundlich equation for soils ■■■■■■■ and ■■■■■■ (Table 7.1.3.1.2-10). For the remaining soils ■■■■■■, ■■■■■■ and ■■■ the adsorption constants $K_{F(ads)}$ from Freundlich isotherms ranged from 0.00881 to 0.0283 mL/g (mean of 0.0185 mL/g) with associated Freundlich exponents 1/n significantly below 1 (0.569 to 0.853) and a mean of 0.649. The desorption behaviour to soil was thus affected by the concentration of the test item.

The corresponding correlation coefficients of adsorption isotherms ranged from 0.9978 to 0.9998 thus indicating a good linear fit to the measured data. Normalisation for organic carbon content of soil resulted in values of adsorption K_{OC} ranging from 0.88 (soil ■■■■■■) to 1.49 mL/g in maximum (soil ■■) with an arithmetic mean of 1.17 mL/g.

No desorption constants $K_{F, des}$ are presented in this document since the overall low adsorption prevented the determination of reliable data.

Table 7.1.3.1.2-10: Adsorption and desorption constants of RPA 203328 (AE B197555) in soil

Soil	Soil type	Adsorption					1st Desorption			
		pH	K_F (mL/g)	1/n	R^2	K_{OC} (mL/g)	K_F (mL/g)	1/n	R^2	K_{OC}*** (mL/g)
■■■	sandy loam	7.6	*	*	0.130	*	0.0159	0.692	0.995	1.06
■■■	clay loam	7.2	0.0283	0.569	0.9998	1.49	0.0840	0.613	1.000	4.42
■■■	sandy clay	5.9	*	*	0.585	*	0.0759	0.747	0.976	2.30
■■■	sandy loam	6.3	0.00881	0.853	0.978	0.88	0.0523	0.944	0.998	5.23

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■	silt loam	5.6	0.0183	0.649	0.994	1.14	0.0460	0.594	0.997	2.87

pH: Value given as determined with 0.01 M calcium chloride solution
K_F: Freundlich coefficients of adsorption (**) and desorption (***), respectively
1/n : Slope of the Freundlich adsorption/desorption isotherms
K_{oc}: Adsorption coefficient per organic carbon (K x 100/% organic carbon)
R^2: Regression coefficient of Freundlich equation
* No use of results due to too low correlation
** Mean of valid soils

III. Conclusion

Values of adsorption in terms of $K_{F, OC}$ were therefore low for metabolite RPA 203328 to range from 0.88 to 1.44 mL/g.
With virtually no to very low adsorption observed no scientifically meaningful value could be determined for the corresponding desorption constants $K_{F, OC}$.

CA 7.1.3.2   Aged sorption

Ageing of isoxaflutole residues in soil and the use of desorption parameters were not considered in current risk assessments.

CA 7.1.4   Mobility in soil

CA 7.1.4.1   Column leaching studies

CA 7.1.4.1.1 Column leaching of the active substance

Column leaching studies with the active substance isoxaflutole were not performed.
This data requirement had been addressed under Point 7.1.3.1.1 of the existing Dossier and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that instead of performing a column leaching study, the mobility in soil is assessed by data on their persistence (e.g. half-lives) under aerobic conditions in the laboratory and, by the adsorption to soil. These data allow for an adequate description of the behaviour of the parent compound in soil in environmental risk assessments.
A column leaching study with parent compound is therefore regarded as not necessary.

CA 7.1.4.1.2 Column leaching of metabolites, breakdown and reaction products

Column leaching studies with soil metabolites of isoxaflutole were not performed.
This data requirement had been addressed under Point 7.1.3.1.2 of the existing Dossier and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that instead of performing a column leaching study, the mobility of metabolites RPA 202248 and RPA 203328 in soil can be adequately assessed by data on their persistence (e.g. half-lives) under aerobic conditions and the adsorption to soil. These data allow for a description of the mobility of soil-born residues in environmental risk assessments.

Column leaching studies with metabolites are therefore regarded as not necessary.

CA 7.1.4.2   Lysimeter studies

Lysimeter studies with the active substance isoxaflutole were not performed.

This data requirement had been addressed under Point 7.1.3.3 of the existing Dossier and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that the potential for mobility of isoxaflutole residues to ground water can be adequately assessed by the simulation of vulnerable scenarios representative for the EU. The simulations are able to cover a range of worse cases rather than to be limited to soil and climatic conditions reflected by lysimeter studies.

Separate lysimeter studies with isoxaflutole are therefore regarded as not necessary.

CA 7.1.4.3   Field leaching studies

Field leaching studies with the active substance isoxaflutole were not performed.

This data requirement had been addressed under Point 7.1.3.3 of the existing Dossier and evaluated within the process of Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that the potential for mobility of isoxaflutole residues to ground water can be adequately assessed by the simulation of vulnerable scenarios representative for the EU. The simulations are able to cover a range of worse cases rather than to be limited to soil and climatic conditions reflected by lysimeter studies.

Separate field leaching studies with isoxaflutole are therefore regarded as not necessary.

CA 7.2   Fate and behaviour in water and sediment

CA 7.2.1   Route and rate of degradation in aquatic systems (chemical and photochemical degradation)

CA 7.2.1.1 Hydrolytic degradation

Report:	███████████x; ██████; ████████;1994;M-162558-01
Title:	Hydrolysis 14C-RPA201772
Report No:	R002384
Document No(s):	Report includes Trial Nos.: 93-180 M-162558-01-1
Guidelines:	USEPA (=EPA): N, 161-1;Deviation not specified
GLP/GEP:	yes

The <u>hydrolysis of isoxaflutole</u> was investigated in

- sterile aqueous buffer solution at pH 5, 7 and 9 after application of phenyl-UL-^{14}C-labeled active substance and incubation at 25°C (KCA 7.2.1.1 /01).

The data requirement was addressed under Points 2.9.1 and 7.2.1.1 of the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

Consequently there is no detailed description of this existing data in this update.

The evaluation revealed that the hydrolytic behavior of isoxaflutole is well understood. Therefore, no additional hydrolysis studies are necessary. The half-lives of isoxaflutole under conditions of sterile aqueous buffer hydrolysis have been summarized in Table 7.2.1.1-1.

Hydrolysis was shown to be dependent on pH resulting in half-lives of 11.1 days at pH 5 to decrease to values of 20.1 hours (pH 7) and 3.2 hours (pH 9) at 25°C.

Table 7.2.1.1-1: Half-lives of isoxaflutole in sterile aqueous buffer at 25°C

pH	Half-life
5	11.1 days
7	0.84 days (20.1 hours)
9	0.13 days (3.2 hours)

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As a result of a pH-dependent rearrangement, the diketonitrile compound RPA 202248 was formed as the sole product of hydrolytic transformation and observed at maximum values of 58.3% of AR at pH 5, 53.9% at pH 7 and 95.5% at pH 9. Since no further transformation products were observed, RPA 202248 was shown to be stable under conditions of hydrolysis in sterile aqueous buffer solution.

The proposed pathway of hydrolytic degradation of isoxaflutole in sterile aqueous buffer is summarized in Figure 7.2.1.1-1.

Figure 7.2.1.1-1: Proposed hydrolysis pathway of isoxaflutole in sterile aqueous buffer
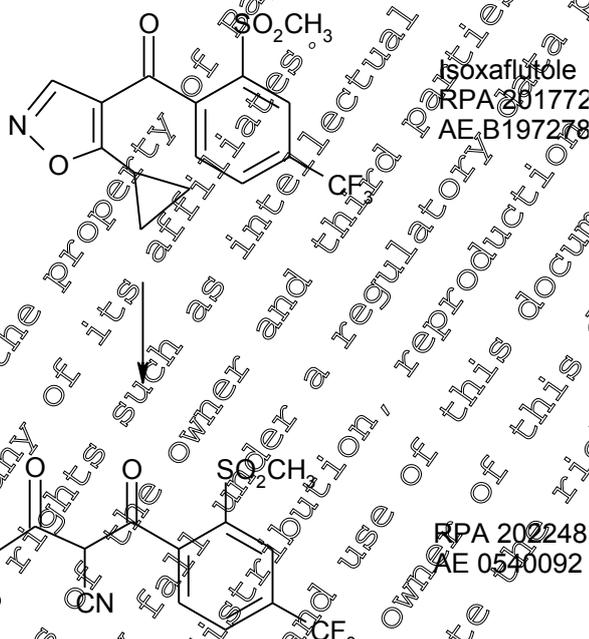
CA 7.2.1.2 Direct photochemical degradation

Report:	;1995;M-162794-01
Title:	Photodegradation in water 14C-RPA201772 (isoxaflutole)
Report No.:	R002507
Document No(s):	Report includes Trial Nos.:
	94-11
	M-162794-04-1
Guidelines:	**USEPA (=EPA); N, 161-2;Deviation not specified**
GLP/GEP:	yes

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Report:	;; ;1995;M-189753-01
Title:	Isoxaflutole - Quantum yield and environmental half-life in water
Report No:	R014778
Document No(s):	Report includes Trial Nos.: 95-80 M-189753-01-1
Guidelines:	**BBA: Part IV, 6-1, First level, (1990) ; ECETOC: Technical Report No.12, (1994); UBA: (1990);Deviation not specified**
GLP/GEP:	**yes**

Report:	9; ;2002;M-214288-01
Title:	Photolysis in distilled water RPA202248
Report No:	C027919
Document No(s):	Report includes Trial Nos.: 36662 CX/02/066 M-214288-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

The direct photolysis of isoxaflutole was investigated in

- sterile aqueous buffer at pH 5 following application of phenyl-UL-^{14}C-labeled active substance and irradiation at 25°C at 50°North latitude light intensity in July (KCA 7.2.1.2 /01).

The point was addressed under Points 2.9.2 and 7.2.1.2 of the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently there is no detailed description of this existing data in this update.

The evaluation revealed that photolytic degradation of isoxaflutole was moderate to result in a photolytic half-life of 6.7 days when being referenced to natural sunlight at summer solstice and latitudes of 20° to 50°N.
The active substance was degraded from 98.5% AR at start to 39.3% at the end of irradiation while degradation in dark controls was insignificant (88.5% AR) following the same incubation time. Photo-degradation products were extensively formed to result in at least 18 minor components each observed at levels below 5% AR in the course of the study.

Two components, reported as Met 14[11] and Met 20, were observed at maximum values of 9.3% (Met 14) and 16.8% AR (Met 20) thus approaching or exceeding the trigger of 10%. Structure elucidation resulted in the two compounds included in the proposed photolysis pathway of isoxaflutole in sterile aqueous buffer as summarized in Figure 7.2.1.2-1.

It should be noted that the formation of the two structures Met 14 and Met 20 resulted from opening of the two ring systems, the isoxazole ring and the cyclopropane ring. In effect, these structures are closely related to the major soil and aquatic metabolite RPA 202248 rather than to the parent molecule.

Efforts for synthesis of Met 14 and Met 20 failed, however, the high structural similarity of RPA 202248 justifies that any potential effects to aquatic organisms are related to RPA 202248 rather than to the parent compound.

Photolytic processes would contribute to the elimination of isoxaflutole from the aquatic environment to some extent when just concluding on the results of the sterile aqueous buffer photolysis study.

In total, direct photolysis processes do not contribute significantly to the overall elimination of isoxaflutole from the aquatic environment. This conclusion comes when considering additional fast and significant pathways of degradation in the aquatic environment:

The contribution of abiotic hydrolysis (KCA 7.2.1.1 /01) is already significantly higher (DT$_{50}$ of 0.84 days in water at pH 7) than the potential portion coming from photolytical processes (DT$_{50}$ of 6.7 days) at the same pH. This rough comparison did not consider the contribution of biotical-induced hydrolysis as documented by a DT$_{50}$ of 0.65 days in non-sterile natural water (KCA 7.2.2.2 /01) or a DT$_{50}$ of 0.34 to 0.53 days in water of total sediment/water systems (KCA 7.2.2.3 /01).

These general considerations may be taken into account when assessing the probability of occurrence and potential effects of metabolites Met 14 and Met 20 since these compounds do result from direct transformation of the active substance isoxaflutole only. Other metabolites as those originating from biotic processes (i.e. RPA 202248, RPA 203328 and RPA 205834) were observed each below 3% AR and thus to a minor extent in the course of the study.

The overall conclusion is that it is extremely unlikely to observe any direct photo-degradation product in the outdoor aquatic environment originating from the active substance isoxaflutole directly.

Figure 7.2.1.2-1: Proposed photolysis pathway of isoxaflutole in sterile aqueous buffer

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[11] Numbering followed that in chromatograms thus synonymous with Peak 14 and Peak 20.

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Isoxaflutole (RPA 201772)

RPA 205834 (minor)

Met 14 (MW: 377) (minor)

RPA 202248 (minor)

Met 20 (MW: 359)

RPA 203328 (minor)

Report:	████████████████████████████; 1995;M-189753-01
Title:	Isoxaflutole / Quantum yield and environmental half-life in water
Report No:	R014778
Document No(s):	Report includes Trial Nos.: 95-80 M-189753-01-1
Guidelines:	**BBA: Part IV, 6-1, First level, (1990) ; ECETOC: Technical Report No.12, (1994); UBA: (1990);Deviation not specified**
GLP/GEP:	**yes**

The underlined quantum yield of isoxaflutole was determined by:

- irradiation of non-labelled active substance in aqueous solution at 25°C for 600 seconds (ECETOC method), paralleled by the determination of the photon concentration by actinometry (KCA 7.2.1.2 /02).

The point was addressed under Points 2.9.2 and 7.2.1.2 of the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

Consequently there is no detailed description of this existing data in this update.

The evaluation revealed a quantum yield of 7.83 x 10^{-4}. This value was used for the calculation of environmental half-lives of isoxaflutole in water according to the method of Frank and Kloepffer. The resulting values are summarized in Table 7.2.1.2-01.

Table 7.2.1.2-1: Environmental half-lives of isoxaflutole in water according to the method of Frank and Kloepffer

Month	Half-life	
	(hours)	(days)
January	9082	378
February	3922	163
March	1768	73.7
April	983	41.0
May	769	32.0
June	673	28.0
July	719	30.0
August	702	29.3
September	1190	49.6
October	2325	96.9
November	6532	272
December	18466	769

In addition, the behavior of metabolite RPA 202248 was investigated under conditions of photolysis in distilled water. The study summarized briefly below contains new supplemental information on the behavior of RPA 202248 in a non-buffered aqueous system.

Report:	⊒; ,2002,M-214288-01
Title:	Photolysis in distilled water RPA202248
Report No:	C027919
Document No(s):	Report includes Trial Nos.:
	36662
	CX/02/066
	M-214288-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

The photolysis of RPA 202248 was investigated in distilled water at $25 \pm 2°C$ under artificial sunlight (xenon lamp, cut-off wave length below 290 nm) for 7 days, equivalent to a maximum period of 10 days of natural sunlight. The investigations were performed with non-labelled RPA 202248 at the two test concentrations 0.05 mg/L and 0.5 mg/L.

Analysis by HPLC/MS/MS showed that no decline had occurred in irradiated or dark control samples.

It was therefore concluded that RPA 202248 was stable under the conditions of aquatic photolysis. Photolytic processes thus do not contribute to the overall elimination of RPA 202248 from the aquatic environment.

CA 7.2.1.3   Indirect photochemical degradation

Being regarded as higher tier option no studies on the behavior of isoxaflutole and its residues under conditions of indirect photochemical degradation have been performed.

Being a new potential data requirement the point was not addressed in the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

CA 7.2.2   Route and rate of biological degradation in aquatic systems

CA 7.2.2.1   "Ready biodegradability"

Report:	███████████████████████████;1996;M-211235-01
Title:	Determination of ready biodegrability: Carbon dioxide (CO2) evolution test (modified Sturm test) with isoxaflutole.
Report No:	C026345
Document No:	M-211235-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**yes**

The ready biodegradability of isoxaflutole was investigated experimentally by:

- incubation of non-labelled active substance at a concentration of 30 mg a.s./L in an activated sludge of pH 7.4 to 7.7 under the conditions of a modified Sturm test at 20 to 22°C (KCA 7.2.2.1 /01).

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The data requirement was addressed under Point 7.2.1.3.1 of the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.
Consequently there is no detailed description of this existing data in this update.

The evaluation revealed that isoxaflutole can be regarded as not readily biodegradable. This finding was confirmed by the results of biological degradation tests performed in surface water (KCA 7.2.2.2 /01) and the existing sediment/water study (KCA 7.2.2.3 /01).

CA 7.2.2.2   Aerobic mineralisation in surface water

Being a new data requirement this point had not been addressed in the existing Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

Report:	4; ;2013;M-459354-02; Amended: 2013-07-02
Title:	[14C] Isoxaflutole: Aerobic mineralization in surface water
Report No:	D62847
Document No:	M-459354-02-1
Guidelines:	**OECD Guidelines for the Testing of Chemicals, Guideline 309, April 13, 2004;not applicable**
GLP/GEP:	**yes**

Executive Summary
The mineralisation of phenyl-UL-^{14}C-labeled active substance isoxaflutole was investigated in non-sterile natural water at pH 7.5 at test concentrations of 10.9 µg a.s./L (low dose) and 108.5 µg a.s./L (high dose). Samples were incubated at 23.3 ±0.75 °C in the dark for a maximum of 58 days.
Microbial activity of the test water was demonstrated by incubation of phenyl-UL-^{14}C-labeled benzoic acid serving as reference. The mean recovered radioactivity ranged from 100.1 to 104.8% AR for treated samples of both doses.
Values of the test substance in the test water decreased rapidly from 87.5% of AR for the low dose (93.3% for high dose) at time zero to 1.2% (5.4% for high dose) after five days of incubation with no detects in the following.
Isoxaflutole was transformed to the major and predominant product RPA 202248. Formation of other transformation products including volatile components and carbon dioxide was minimal accounting for less than 2.5% in maximum for a single component in the course of the study.
Values of the DT_{50} of isoxaflutole under conditions of mineralization testing were calculated to be 0.68 days (low dose) and 0.99 days (high dose). No DT_{50}-values could be determined for metabolite RPA 202248 since insufficient degradation was observed under the conditions of the test.

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I. Material and Methods

A. Materials

1. Test Material: [Phenyl-UL-^{14}C]Isoxaflutole

Specific radioactivity: 4.34 MBq/mg

Radiochemical purity: >99%

Chemical purity: not reported

Sample ID: KML 9369 / 253323/A

2. Test water

The natural water used for the test was freshly collected (0 to 15 cm depth) from a lake at Moehlin, Aargau (AG), Switzerland. Water samples were characterized as summarized in Table 7.2.2.2-1.

Table 7.2.2.2-1: Physico-chemical characteristics of test water

Water	Pond Water
pH	7.49
Colour	not reported
Concentration of dissolved oxygen at collection (mg/L)	7.44
Total hardness (°dH)	12.0
Biological oxygen demand (mg/L)	<4.0
Total organic carbon (TOC, mg/kg)	13.05
Dissolved Organic Carbon (DOC, mg/L)	14.05
Total phosphorus (mg/L)	0.21
Total nitrogen (mg/L)	3.76
Nitrate NO_3^- (mg/L)	6.54
Nitrite NO_2^- (mg/L)	<0.8
Ammonium NH_4^+ (mg/L)	2.94

Before start of incubation the test water was passed through a 0.2 mm sieve.

B. Study design

1. Experimental conditions: Samples of 300 mL test water each were filled into all-glass incubation flasks and pre-equilibrated prior to treatment at approximate study conditions (darkness, 20 °C). The test was performed with phenyl-UL-^{14}C-isoxaflutole at initial concentrations of 11.08 µg/L (low dose) and 109.4 µg/L (high dose). For the potential generation of metabolites, samples were also incubated that had received an exaggerated dose of 1000 µg/L. Following application the samples were attached to flow-through systems allowing moisturized air to pass through and with traps to collect ^{14}C-carbon dioxide and other volatiles (2 M aqueous potassium hydroxide and ethylene glycol). Samples were incubated at 22.3 ± 0.75 °C in the dark for 57 days in maximum.

In addition, samples containing untreated water, solvent controls and biological controls were incubated under the same conditions and removed for analysis at selected time points. Solvent controls and biological controls contained the reference substance phenyl-UL-^{14}C-benzoic acid.

2. Sampling: Duplicate samples each of both test concentrations were removed for analysis after 0, 1, 2, 5, 14, 28 and 57 days of incubation.

Samples for determination of microbial activity (biological controls) were investigated after 0, 5 and 14 days of incubation. Solvent controls were taken for analysis after 14 days of incubation. Finally, sterile controls were removed for analysis after 55 days.

The complete samples were immediately processed and HPLC analysis was usually performed the same day. Therefore no additional investigations of storage stability were necessary.
The pH, oxygen concentration and the redox potential was determined at each sampling interval.

3. Analytical procedures: The water was analysed directly without a concentration step prior to analysis. The ^{14}C-material balance was established for each sample following analysis of the water and determination of volatile radioactivity in the traps. For high dose samples and following quantitation of radioactivity in water by LSC, analysis was performed by reversed phase HPLC and ^{14}C-flow-through detection techniques. Samples of the low dose were analysed by TLC followed by ^{14}C-detection (phosphor imaging).
Based on the lowest integrable peak, the LOD was estimated to be about 1.0% of AR for a compound in low dose and about 1.2% AR for those in the high dose samples.

4. Kinetic evaluation: The kinetic evaluation was performed for the active substance isoxaflutole and its readily formed metabolite RPA 202248 with the software KinGUI following FOCUS kinetic guidance (2006) to obtain best fits to the measured data.

II. Results and Discussion

The temperature was maintained at 23.3 ± 0.75 °C during the test. Biological activity of the test water was confirmed by the degradation of reference substance phenyl-UL-^{14}C-benzoic acid within 14 days of incubation. The pH, oxygen concentration and redox potential of the test water was shown to be within the same range for treated samples and for untreated controls.
The material balances and distribution of radioactivity are summarized for irradiated samples and dark controls in Table 7.2.2.2-2 (low dose) and Table 7.2.2.2-3 (high dose). The mean material balances were 102.4% ± 1.9% AR for low dose samples and 102.0% ± 2.2% for the high dose. The complete material balances indicate no significant losses of radioactivity from samples in the course of the test including processing till analysis.
Formation of ^{14}C-carbon dioxide or other volatile components was negligible to account for less than 0.2% of AR for both concentrations tested.
Biotransformation of phenyl-UL-^{14}C-labeled isoxaflutole was fast to result in a decline of values from 87.5% AR at time zero to 1.2% after 5 days for the low dose and from 93.3% AR at time zero to 5.4% after 5 days for the high dose. Degradation of active substance was quantitative also in sterile controls as it is documented by a value below the LOD after 55 days of incubation.
Formation of minor fractions added up to maximum values of 3.8% after 57 days distributed into two components with none present at more than 2.1% AR for the two test concentrations in the course of the study.
RPA 202248 was observed as the major and predominant transformation product at maximum values of 101.3% AR by day 5 at the low dose and 102.9% by day 14 at the high dose. RPA 202248 was also in sterile samples. This serves as an indication that the transformation of isoxaflutole to RPA 202248 is driven chemically by pH (sterile controls) or by both, biotical and chemical, as demonstrated from incubation of the microbial viable samples.

The kinetic evaluation of the data underlined the fast degradation of isoxaflutole to form RPA 202248 to result in DT_{50}-values of 0.68 days for the low dose and 0.99 days for the high dose. The values were derived from the SFO kinetic model as the best fits to measured data. No experimental value of the DT_{50} could be calculated for RPA 202248 since no decline was observed under the conditions of the test. The results of kinetic evaluations are summarized in Table 7.2.2.2-4.

Table 7.2.2.2-2: Degradation of [phenyl-UL-^{14}C]isoxaflutole in aerobic natural water treated at low dose, expressed as percentage of total applied radioactivity

Component		Sampling interval (days)						
		0	**1**	**2**	**5**	**14**	**28**	**57**
Isoxaflutole	Mean*	87.5	45.6	2.6	1.2	0.0	0.0	0.0
	SD	±0.3	±0.9	±0.5	±1.2	±0.0	±0.0	±0.0
RPA 202248 (Diketonitrile, M1)	Mean*	14.7	59.0	96.5	101.3	98.7	98.5	99.9
	SD	±0.9	±1.2	±1.0	±1.2	±2.2	±0.8	±0.2
Unknown M2	Mean*	0.0	0.0	1.6	0.0	2.1	0.7	2.1
	SD	±0.0	±0.0	±1.6	±0.0	±0.4	±0.1	±0.1
Unknown M3	Mean*	0.0	0.0	0.4	0.0	1.2	0.8	1.7
	SD	±0.0	±0.0	±0.4	±0.0	±0.0	±0.1	±0.0
Total radioactivity in water	Mean*	102.3	104.6	101.1	102.5	102.0	100.0	103.7
	SD	±0.5	±0.3	±1.3	±0.0	±2.6	±0.8	±0.2
[14]CO$_2$	Mean*	n.a.	0.2	0.1	<0.1	<0.1	<0.1	<0.1
	SD	n.a.	±0.1	±0.0	±0.0	±0.0	±0.0	±0.0
Other volatiles	Mean*	n.a.	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	SD	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total radioactivity (%)	Mean*	102.3	104.8	101.3	102.5	102.1	100.1	103.7
	SD	±0.5	±0.3	±1.5	±0.0	±2.6	±0.8	±0.1

Values given as percentages of initially applied radioactivity
SD = standard deviation   * Mean values of two replicates
n.a. = not analysed or not applicable

Table 7.2.2.2-3: Degradation of [phenyl-UL-^{14}C]isoxaflutole in aerobic natural water treated at high dose, expressed as percentage of total applied radioactivity

Component		Sampling interval (days)						
		0	**1**	**2**	**5**	**14**	**28**	**57**
Isoxaflutole	Mean*	93.3	58.3	19.5	5.4	0.0	0.0	0.0
	SD	±1.7	±1.2	±3.5	±0.4	±0.0	±0.0	±0.0
RPA 202248 (Diketonitrile, M1)	Mean*	11.0	43.6	83.6	93.3	102.9	102.8	101.0
	SD	±2.5	±0.6	±2.9	±0.8	±0.1	±0.2	±1.3
Unknown M2	Mean*	n.d.	n.d.	n.d.	2.4	n.d.	n.d.	n.d.

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	SD	n.a.	n.a.	n.a.	±1.2	n.a.	n.a.	n.a.
Total radioactivity	Mean*	104.3	101.9	103.0	99.9	102.9	102.8	101.0
in water	SD	±0.8	±1.8	±0.6	±2.4	±0.1	±0.2	±1.3
$^{14}CO_2$	Mean*	n.a.	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	SD	n.a.	±0.0	±0.0	±0.0	±0.0	±0.0	±0.0
Other volatiles	Mean*	n.a.	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	SD	n.a.	±0.0	±0.0	±0.0	±0.0	±0.0	±0.0
Total radioactivity (%)	Mean*	104.3	101.9	103.1	99.9	102.9	102.9	101.0
	SD	±0.8	±1.8	±0.6	±2.4	±0.1	±0.2	±1.3

Values given as percentages of initially applied radioactivity
SD = standard deviation; * Mean values of two replicates
n.a. = not analysed or not applicable; n.d. = not detected.

Table 7.2.2.2-4: Kinetic evaluation of the degradation of [phenyl-UL-^{14}C]isoxaflutole in aerobic natural water under conditions of OECD 309 testing

Compound / Dose	Kinetic Model	DT$_{50}$ (days)	DT$_{90}$ (days)	Error for Chi^2	r^2
Isoxaflutole / Low	**SFO**	**0.68**	**2.27**	**16.14**	**0.974**
	FOMC	0.63	2.10	19.06	0.972
Isoxaflutole / High	**SFO**	**0.99**	**3.29**	**8.76**	**0.987**
	FOMC	0.89	2.94	11.60	0.985
RPA 202248 / Low	SFO	n.c.	n.c.	n.c.	n.c.
	FOMC	n.c.	n.c.	n.c.	n.c.
RPA 202248 / High	SFO	n.c.	n.c.	n.c.	n.c.
	FOMC	n.c.	n.c.	n.c.	n.c.

Best fits are marked bold

n.c. = not calculable due to no decline of values seen in the course of the study

III. Conclusion

The overall biotransformation including mineralization of isoxaflutole and its residues formed in non-sterile natural water was insignificant under the 'pelagic' conditions of the test.

RPA 202248 was observed as the single and predominant major transformation product thus requiring consideration in environmental risk assessments.

The DT_{50} of isoxaflutole in water under conditions of aerobic mineralisation testing was calculated to be 0.68 days for the low dose and 0.99 days for the high dose tested thus indicating some dependency of transformation rate upon the test concentration.

No experimental value of the DT_{50} could be calculated for RPA 202248 since no decline was observed under the conditions of the test.

Overall the results are well in line with observations made in existing water/sediment tests.

CA 7.2.2.3   Water/sediment study

Report:	i; :1995;M-158508-01
Title:	RPA 201772: Degradation and retention in two water / sediment systems
Report No:	R000377
Document No:	M-158508-01-1
Guidelines:	**BBA: Part IV, Section 5.1, (1990);not specified**
GLP/GEP:	**yes**

Report:	s; :2013;M-464901-01
Title:	Isoxaflutole: Kinetic modelling evaluation of water sediment degradation study data to derive total system DT50 values
Report No:	VC/13/008A
Document No:	M-464901-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Report:	n; ;2013;M-464903-01
Title:	Isoxaflutole: Kinetic modelling evaluation of water sediment degradation study data to derive water phase DT50 values
Report No:	VC/13/008B
Document No:	M-464903-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

The degradation of isoxaflutole under conditions of water/sediment testing was investigated in:

- two contrasting sediments and their associated water following application of phenyl-UL-^{14}C-labelled active substance and incubation at 20°C (KCA 7.2.2.3 /01).

The data requirement was addressed under Point 7.2.1.3.2 of the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

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Consequently there is no detailed description of this existing data in this update.

The evaluation revealed that isoxaflutole was degraded rapidly to form metabolites RPA 202248 and RPA 205834 as major metabolites (maximum of 70.3% AR and 26.4%, respectively). The formation of RPA 202248 and RPA 205834 was observed in parallel from the active substance. As a result of biotic processes, both initially and fast formed metabolites could thus serve as predecessors for the benzoic acid RPA 203328. In addition, RPA 207048 was observed as a minor component below 5% AR in the water or the sediment. Being transient this compound was likely to be formed by deamination of the predecessor compound RPA 205834.

Half-lives for degradation ranged from 0.34 to 0.53 days for isoxaflutole while values of the DT_{50} were estimated to 255 to 700 days for RPA 202248 and 52 to 97 days for RPA 205834. No DT_{50} was estimated for RPA 203328.

Due to their occurrence as major metabolites in water/sediment testing, RPA 202248, RPA 205834 and RPA 203328 had been defined as residues to be considered within the existing environmental risk assessments for surface water.

The results of degradation tests in water/sediment systems under conditions of the laboratory resulted in the metabolic pathway summarized in Figure 7.2.2.3-1.

The data from existing water/sediment tests were kinetically re-evaluated according to actual FOCUS guidance (2006) in documents KCA 7.2.2.3 /02 and KCA 7.2.2.3 /03 summarized in more detail below.

Figure 7.2.2.3-1: Proposed pathway of metabolism of isoxaflutole in water/sediment systems

Isoxaflutole
RPA 201772
(AE B197278)

RPA 202248
(AE 0540092)

RPA 205834
(AE 0692291)

RPA 203328
(AE B197555)

RPA 207048
(AE 0893029)
(minor)
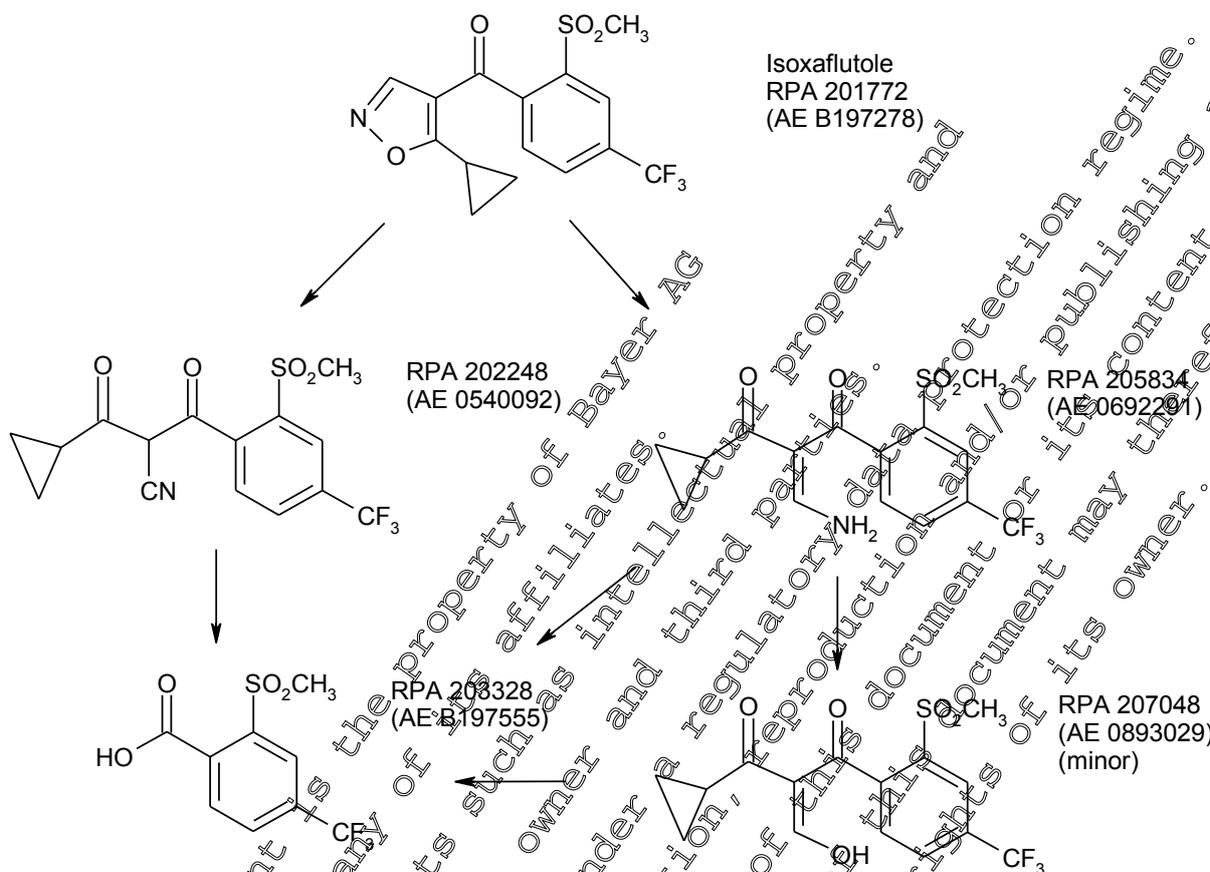
Report:	6; ;2013;M-464901-01
Title:	Isoxaflutole: Kinetic modelling evaluation of water sediment degradation study data to derive total system DT50 values
Report No:	VC/13/008A
Document No:	M-464901-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Executive Summary

The kinetics of degradation of isoxaflutole in total systems was evaluated from data of tests performed in two water/sediment systems with phenyl-UL-^{14}C-radiolabeled active substance (KCA 7.2.2.3 /01).

The kinetic evaluation followed FOCUS guidance to derive values for the degradation in total sediment water systems from best fits to measured data for use as modeling endpoints in aquatic exposure assessments and for comparison against trigger endpoints. Separate analysis was performed for isoxaflutole and its metabolites RPA 202248 (AE 0540092) and RPA 205834 (AE 0692291) at Level I for the total systems with results summarised in Table 7.2.2.3-1 and Table 7.2.2.3-2.

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For modelling endpoints the kinetic evaluation resulted in an 'all-SFO' fit of residue data for the ▮ ▮ system. Best fits were obtained for the ▮ system from combination of the Hockey Stick model for parent substance with the SFO model for the metabolites. A geometric mean value for the DegT$_{50}$ of 0.36 days was calculated for the parent compound isoxaflutole. For metabolites the values are 237 days for RPA 202248 and 76.2 days for RPA 205834. The evaluation resulted in average formation fractions of 0.71 for formation of RPA 202248 and 0.23 for the formation of RPA 205834 each from the parent compound.

For persistence endpoints and for the ▮ system the kinetic evaluation resulted in an 'all-SFO' fit for residue data. Best fits were obtained for the ▮ system from combination of Hockey Stick model for parent substance with SFO models for the metabolites. A worst case DegT$_{50}$ in total system of 0.57 days was derived for the parent compound isoxaflutole (▮ system). For metabolites the values are 334 days for RPA 202248 and 81.4 days for RPA 205834. Worst case values for the DegT$_{90}$ in total systems are 1.9 days for the parent compound, more than 1000 days for RPA 202248 and 270 days for RPA 205834.

Table 7.2.2.3-1: Modeling endpoints; half-lives and formation fractions for the degradation of isoxaflutole residues in total water/sediment systems according to FOCUS Level I

Compound	System	Label	DegT$_{50}$ (days)	ffm
Isoxaflutole	▮	1	0.57	-
	▮	1	0.23	-
	Mean (geometric)		**0.36**	-
RPA 202248	▮	1	334	0.75
	▮	1	168	0.68
	Mean (geometric)		**237**	-
	Average		-	**0.71**
RPA 205834	▮	1	81.4	0.25
	▮	1	71.5	0.22
	Mean (geometric)		**76.2**	-
	Average		-	**0.23**

Label 1 = phenyl; ffm = formation fraction

Table 7.2.2.3-2: Persistence endpoints; half-lives for the degradation of isoxaflutole residues in total water/sediment systems according to FOCUS Level I

Compound	System	Label	ffm	DegT$_{50}$ (days)	DegT$_{90}$ (days)
Isoxaflutole	▮	1	-	0.57	1.9
	▮	1	-	0.21	1.2
RPA 202248	▮	1	0.75	334	>1000
	▮	1	0.68	168	559
RPA 205834	▮	1	0.25	81.4	270
	▮	1	0.22	71.5	237

Label 1 = phenyl; ffm = formation fraction

I. Material and Methods

The kinetic evaluation was based on data of a water/sediment study (KCA 7.2.2.3/01) conducted with phenyl-UL-^{14}C-labeled isoxaflutole in a sandy (⬛⬛⬛⬛⬛) and a loamy sediment (⬛⬛⬛⬛⬛) and their associated water at 20°C in the dark for a maximum of 100 days.

Data pre-processing
Generally, replicates were taken into account separately. The data were checked for consistency and clear outliers. Data for non-extractable residues (NER) and CO_2 were not fitted within the evaluation (open system).

For the residues in the total sediment/water systems the following procedure was applied:
- For data processing of day zero samples, radioactivity assigned to metabolites, non-extractable residues (NER) and CO_2 was added to the parent compound and thus metabolite concentrations were set to 0 %. Parent compound was attributed to the water phase only thus resulting in a value of zero for the sediment phase, since the test substance was applied to the water phase.
- Residues values below the limit of detection (LOD = 0.01% of AR) were set to 0.5 times the LOD for the first non-detect at the end of the curve. The curve could be cut at this time point in case of no later detects. For metabolites, the last non-detect at the beginning of a curve was set to 0.5 times the LOD for occurrences later than day 0.

Kinetic models
The kinetic evaluation of water/sediment data was performed according to FOCUS Level I to result in degradation kinetics in total systems.

No evaluations according to Level II were performed since not regarded as mandatory. For lower-tier calculations or the comparison with persistence triggers a Level I evaluation of the dissipation may be often appropriate.

Contrary to the parent, for metabolites it may be often neither feasible nor meaningful to differentiate between SFO and the bi-phasic models using Level I and a simultaneous fit of the complete metabolic pathway (i.e. considering formation and decline of metabolites). A bi-phasic approach would result in too many free parameters needed to describe such systems. Even for SFO the number of free parameters is often at the limit and the use of bi-phasic kinetics could easily multiply the number of free parameters.

The inferring of kinetic degradation parameters followed the proposed metabolic pathway as given in Figure 7.2.2.3-1.

Each compound was represented by one compartment as the total of measured occurrences in water and sediment with no values associated with a sink compartment. Between compartments transformation reactions were assumed to proceed only one-way. The initial amount of the parent compound was free fitted and the initial amount for metabolites was fixed to a value of zero. All data were weighted equally thus corresponding to an absolute error model.

At least four kinetic models consisting of single first-order (SFO), first-order multiple-compartment (FOMC, Gustafson-Holden), double first-order in parallel (DFOP), and the hockey-stick (HS) model were available, in principle, according to the set of models proposed by FOCUS.

While best-fits should be taken to derive trigger or persistence endpoints SFO should be used to derive modeling input parameters if an acceptable fit can be obtained.

Before use of bi-phasic kinetic models FOMC, DFOP and HS the following major cases were taken into account:

1. A check whether a degradation or dissipation to 10% of the initial amount M_0 was reached within experimental period, then the estimation of the DT_{50} could be simplified according to the relation $DT_{50} = DT_{90}/(\ln(10)/\ln(2))$. By this method the equivalent SFO-curve meets the bi-phasic curve at the time $DT_{90\ bi-phasic}$ and consequently the residue values at earlier times are over-predicted.

2. In case a value of 10% for M_0 was not reached within the runtime of the study FOMC should not be used to derive modelling endpoints.

3. In case a value of 10% for M_0 was not reached within the runtime of the study, the DT_{50} could be derived for DFOP and HS models from the slower part of the bi-phasic curve using the relation $DT_{50} = \ln(2)/k_2$.

Statistical evaluation

The identification of the most appropriate kinetic model for the description of experimental data according to FOCUS is mainly based on the three criteria of visual assessment of fits of calculated transformation curves to experimental data, the value of error of Chi-square (χ^2) test and a single-sided significance t-test.

The choice of the appropriate kinetic model was primarily based on visual assessment of the fit and the Chi^2- (χ^2-) error.

Within the current evaluation, single first-order (SFO) kinetics had been tested first, since SFO is being used as the simplest kinetic model almost exclusively in environmental exposure models. In case the SFO fit should not be visually acceptable or in case of a significant exceedance of value for χ^2-error of 15%, bi-phasic models were tested. Finally the model was chosen which was visually acceptable and provided a significantly better fit in terms of the χ^2-error.

The approach avoided the use of over-parameterised models simply and only being chosen on the basis of a marginally better fit. Finally it should be noted that a value of χ^2-error below 15% should only be considered as guidance and not as an absolute cut-off criterion. This is true, in particular, for the modelling of metabolite data with errors for χ^2 being higher, but with fits still representing a reasonable description of their formation and degradation behaviour.

II. Results and Discussion

The kinetic evaluation of water-sediment data was performed according to FOCUS Level I to result in degradation kinetics in total systems (Table 7.2.2.3-3 and Table 7.2.2.3-4). No evaluations according to Level II were performed.

For the two data sets under investigation, the application of an all-SFO kinetic model to the parent substance and metabolite data resulted in acceptable fits for the ▮▮▮▮▮▮ system.

For the ▮▮▮▮▮▮ data, the fits could be optimised by a bi-phasic approach applying the Hockey Stick model to the parent substance data and the SFO model for the metabolites RPA 202248 and

RPA 205834. Apart from low Chi^2-errors there was also no sign of systematic variations of the residuals. Consequently, no further testing of other kinetic models was considered necessary.

Table 7.2.2.3-3: Modelling endpoints, half-lives for the degradation of isoxaflutole and metabolites in total systems Level I

Compound	System	DegT$_{50}$ (days)	DegT$_{90}$ (days)	ffm	Chi^2 (%)	t-test	VA
Isoxaflutole	■	0.57	1.9	-	5.9	2.67e-05	Very good
	■	0.23	0.78	-	10.8	1.04e-05	Good
	Mean (geometric)	**0.36**					
RPA 202248	■	334	1000	0.75	7.4	0.005830	Very good
	■	168	559	0.68	8.6	0.000254	Good
	Mean (geometric)	**237**					
	Average			**0.71**			
RPA 205834	■	81.4	270	0.25	16.4	0.000343	Good
	■	71.5	237	0.22	23.6	0.001603	Good
	Mean (geometric)	**76.2**					
	Average			**0.23**			

ffm = formation fraction; Chi^2 = Chi square error; t-test = t-probability test; VA = Visual Assessment

■ : SFO model for parent substance, SFO for metabolites

■ : Hockey Stick model for parent substance, SFO for metabolites

Table 7.2.2.3-4: Persistence endpoints, half-lives for the degradation of isoxaflutole and metabolites in total systems Level I

Compound	System	DegT$_{50}$ (days)	DegT$_{90}$ (days)	ffm	Chi^2 (%)	t-test	VA
Isoxaflutole	■	0.57	1.9		5.9	2.67e-05	Very good
	■	0.21	1.2	-	2.3	k1 5.06e-08 k2 0.00729	Excellent
RPA 202248	■	334	1000	0.75	7.4	0.005830	Very good
		168	559	0.68	8.6	0.000254	Good
RPA 205834	■	81.4	270	0.25	16.4	0.000343	Good
		71.5	237	0.22	23.6	0.001603	Good

ffm = formation fraction; Chi^2 = Chi square error; t-test = t-probability test; VA = Visual Assessment

III. Conclusion

The degradation of phenyl-UL-^{14}C-labeled isoxaflutole under conditions of a water/sediment test was shown to proceed via the formation of metabolites RPA 202248 and RPA 205834.

For modelling endpoints the kinetic evaluation resulted in an 'all-SFO' fit of residue data for the ■ system. Best fits were obtained for the ■ system from combination of the Hockey Stick model for parent substance with the SFO model for the metabolites.

For persistence endpoints and for the ■ system the kinetic evaluation resulted in an 'all-SFO' fit for residue data. Best fits were obtained for the ■ system from combination of Hockey Stick model for parent substance with SFO models for the metabolites.

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For modelling endpoints the kinetic evaluation resulted in a geometric mean value for the $DegT_{50}$ of 0.36 days for the parent compound isoxaflutole. For metabolites the values are 237 days for RPA 202248 and 76.2 days for RPA 205834.

For evaluation against persistence triggers the worst case $DegT_{50}$ in total system is 0.57 days (██████ ██████ system) for parent compound isoxaflutole. For metabolites the values are 334 days for RPA 202248 and 81.4 days for RPA 205834. Worst case values for the $DegT_{90}$ in total systems are 1.9 days for the parent compound, more than 1000 days for RPA 202248 and 270 days for RPA 205834.

The results can therefore be used as input parameters for modelling in environmental risk assessments and for evaluation against persistence triggers.

Report:	██████████*; ████████;2013;M-464903-01
Title:	Isoxaflutole: Kinetic modelling evaluation of water sediment degradation study data to derive water phase DT50 values
Report No:	VC/13/008B
Document No:	M-464903-01-1
Guidelines:	**EU Council Directive 91/414/EEC, as amended by Commission Directive 95/36/EC of July 1995, Section 5, Point 7 and Commission Regulation (EC) No 1107/2009 of 21 October 2009;not applicable**
GLP/GEP:	**no**

Executive Summary

The kinetics of dissipation of isoxaflutole from water was evaluated from data of tests performed in two water/sediment systems with phenyl-UL-^{14}C-radiolabeled active substance (KCA 7.2.2.3 /01).

The kinetic evaluation followed FOCUS guidance to derive values for the dissipation from the water phase in sediment/water systems from best fits to measured data for use as modeling endpoints in aquatic exposure assessments and for comparison against trigger endpoints. Separate analysis was performed for isoxaflutole and its metabolites RPA 202248 (AE 0540092) and RPA 205834 (AE 0692291) at Level I for water with results summarised in Table 7.2.2.3-5 and Table 7.2.2.3-6.

For modelling endpoints the kinetic evaluation resulted in an 'all-SFO' fit of residue data for the ████ ████████ system. Best fits were obtained for the ███████████ system from combination of the SFO model for parent substance and RPA 202248 with the DFOP model for RPA 205834.

A geometric mean value for the $DisT_{50}$ of 0.36 days was calculated for the parent compound isoxaflutole. For metabolites the values are 62.2 days for RPA 202248 and 28.3 days for RPA 205834.

For persistence endpoints and for the ███████████ system the kinetic evaluation resulted in a SFO fit for residue data of parent substance, a Hockey Stick model for RPA 202248 and a DFOP fit for RPA 205834. Best fits were obtained for the ███████████ system from combination of Hockey Stick model for parent substance and RPA 202248 with the FOMC model for RPA 205834.

A worst case $DisT_{50}$ of 0.57 days in water (███████████ system) was calculated for the parent compound isoxaflutole. For metabolites the values are 57.1 days for RPA 202248 and 16.7 days for

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RPA 205834. Worst case values for the $DisT_{90}$ in total systems are 1.9 days for the parent compound, 328 days for RPA 202248 and 163 days for RPA 205834.

Table 7.2.2.3-5: Modelling endpoints, half-lives for the dissipation of isoxaflutole and metabolites from water systems Level I

Compound	System			Label	$DisT_{50}$ (days)
Isoxaflutole				1	0.57
				1	0.23
Mean (geometric)					**0.36**
RPA 202248				1	53.9
				1	71.8
Mean (geometric)					**62.2**
RPA 205834				1	33.9
				1	23.6
Mean (geometric)					**28.3**

Label 1 = phenyl

Table 7.2.2.3-6: Persistence endpoints, half-lives for the dissipation of isoxaflutole and metabolites from water, Level I

Compound	System			Label	$DisT_{50}$ (days)	$DisT_{90}$ (days)
Isoxaflutole				1	0.57	1.9
				1	0.21	1.2
RPA 202248				1	26.1	328
				1	57.1	289
RPA 205834				1	16.7	95.5
				1	15.7	163

Label 1 = phenyl

1 Material and Methods

The kinetic evaluation was based on data of a water/sediment study (IIA 7.2.2.3/01) conducted with phenyl-UL-^{14}C-labeled isoxaflutole in a sandy (▮▮▮▮▮▮▮▮) and a loamy sediment (▮▮▮▮▮▮▮) and their associated water at 20°C in the dark for a maximum of 100 days.

Data pre-processing
Generally, replicates were taken into account separately. The data were checked for consistency and clear outliers. Data for non-extractable residues (NER) and CO_2 were not fitted within the evaluation (open system).

For the residues in the water the following procedure was applied:

- For data processing of day zero samples, radioactivity assigned to metabolites, non-extractable residues (NER) and CO_2 was added to the parent compound and thus metabolite concentrations were set to 0 %. Parent compound was attributed to the water phase only thus resulting in a value of zero for the sediment phase, since the test substance was applied to the water phase.

- Residues values below the limit of detection (LOD = 0.01% of AR) were set to 0.5 times the LOD for the first non-detect at the end of the curve. The curve could be cut at this time point in case of no

later detects. For metabolites, the last non-detect at the beginning of a curve was set to 0.5 times the LOD for occurrences later than day 0.

Kinetic models

The current kinetic evaluation of water-sediment data was performed according to FOCUS Level I to result in dissipation kinetics in water.

No evaluations according to Level II were performed since not regarded as mandatory. For lower-tier calculations or the comparison with persistence triggers a Level I evaluation of the dissipation may be often appropriate.

Contrary to the parent, for metabolites it may be often neither feasible nor meaningful to differentiate between SFO and the bi-phasic models, using Level I and a simultaneous fit of the complete metabolic pathway (i.e. considering formation and decline of metabolites). A bi-phasic approach would result in too many free parameters needed to describe such systems. Even for SFO the number of free parameters is often at the limit and the use of bi-phasic kinetics could easily multiply the number of free parameters.

The inferring of kinetic degradation parameters followed the proposed metabolic pathway as given in Figure 7.2.2.3-1.

Each compound was represented by one compartment as the total of measured occurrences in water and sediment with no values associated with a sink compartment. Between compartments transformation reactions were assumed to proceed only one-way. The initial amount of the parent compound was free fitted and the initial amount for metabolites was fixed to a value of zero. All data were weighted equally thus corresponding to an absolute error model.

At least four kinetic models consisting of single first-order (SFO), first-order multiple-compartment (FOMC, Gustafson-Holden), double first-order in parallel (DFOP), and the hockey-stick (HS) model were available, in principle, according to the set of models proposed by FOCUS.

While best-fits should be taken to derive trigger or persistence endpoints SFO should be used to derive modeling input parameters if an acceptable fit can be obtained.

Before a use of bi-phasic kinetic models FOMC, DFOP and HS the following major cases were taken into account:

1. A check whether a degradation or dissipation to 10% of the initial amount M_0 was reached within experimental period, then the estimation of the DT_{50} could be simplified according to the relation $DT_{50} = DT_{90}/(\ln(10)/\ln(2))$. By this method the equivalent SFO-curve meets the bi-phasic curve at the time $DT_{90\,bi-phasic}$ and consequently the residue values at earlier times are over-predicted.

2. In case a value of 10% for M_0 was not reached within the runtime of the study, FOMC should not be used to derive modelling endpoints.

3. In case a value of 10% for M_0 was not reached within the runtime of the study, the DT_{50} could be derived for DFOP and HS models from the slower part of the bi-phasic curve using the relation $DT_{50} = \ln(2)/k_2$.

Statistical evaluation

The identification of the most appropriate kinetic model for the description of experimental data according to FOCUS is mainly based on the three criteria of visual assessment of fits of calculated

transformation curves to experimental data, the value of error of Chi-square (χ^2) test and a single-sided significance t-test.

The choice of the appropriate kinetic model was primarily based on visual assessment of the fit and the Chi^2- (χ^2-) error.

Within the current evaluation, single first-order (SFO) kinetics had been tested first, since SFO is being used as the simplest kinetic model almost exclusively in environmental exposure models. In case the SFO fit should not be visually acceptable or in case of a significant exceedance of value for χ^2-error of 15%, bi-phasic models were tested. Finally the model was chosen, which was visually acceptable and provided a significantly better fit in terms of the χ^2-error.

The approach avoided the use of over-parameterised models simply and only being chosen on the basis of a marginally better fit. Finally it should be noted that a value of χ^2-error below 15% should only be considered as guidance and not as an absolute cut-off criterion. This is true, in particular for the modelling of metabolite data with errors for χ^2 being higher but with fits still representing a reasonable description of their formation and degradation behaviour.

II. Results and Discussion

The current kinetic evaluation of water-sediment data was performed according to FOCUS Level I to result in dissipation kinetics in water. No evaluations according to Level II were performed.

For the two data sets under investigation the application of an 'all-SFO' kinetic model to the parent substance and metabolite data resulted in acceptable fits for the ▮▮▮▮▮▮▮ system with results summarised in Table 7.2.2.3-9 to Table 7.2.2.3-12.

For the ▮▮▮▮▮▮ data, the SFO model was acceptable for the parent compound isoxaflutole and metabolite RPA 202248. For the data of metabolite RPA 205834 the fits could be optimised by a bi-phasic approach applying the DFOP model. Apart from low Chi^2-errors there was also no sign of systematic variations of the residuals. Consequently, no further testing of other kinetic models was considered necessary.

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Table 7.2.2.3-10: Modelling endpoints, half-lives for the dissipation of isoxaflutole and metabolites from water systems Level I

Compound	System	DisT$_{50}$ (days)	DisT$_{90}$ (days)	Chi^2 (%)	t-test	VA
Isoxaflutole	▮	0.57	1.9	5.9	2.72e-05	Very good
	▮	0.23	0.78	10.8	1.20e-05	Good
	Mean (geometric)	**0.36**				
RPA 202248	▮	53.9	179	11.7	0.00563	Good
	▮	71.8	239	9.9	6.47e-05	Acceptable
	Mean (geometric)	**62.2**				
RPA 205834	▮	33.9*	113*	15.6	K2 0.00525	Very good
	▮	23.6	78.4	11.4	0.000774	Good
	Mean (geometric)	**28.3**				

ffm = formation fraction; Chi^2 = Chi square error; t-test = t-probability test; VA = Visual Assessment

* ▮▮▮▮: SFO model for parent substance and metabolite RPA 202248, DFOP for RPA 205834 with DT$_{50}$ back-calculated from slow phase

▮▮▮▮: SFO for parent substance, SFO for each metabolite

Table 7.2.2.3-12: Persistence endpoints, half-lives for the dissipation of isoxaflutole and metabolites from water, Level I

Compound	System	DisT$_{50}$ (days)	DisT$_{90}$ (days)	Chi^2 (%)	t-test	VA
Isoxaflutole	▮	0.57	1.9	5.9	2.72e-05	Very good
	▮	0.21	1.2	2.3	K1 5.13e-08 k2 0.00571	Excellent
RPA 202248	▮	26.1	328	6.2	k1 0.00398 k2 0.07538	Excellent
	▮	57.1	289	5.4	k1 0.00491 k2 4.61e-05	Very good
RPA 205834	▮	16.7	95.5	15.6	k1 0.48412 k2 0.00525	Very good
	▮	15.7	163	1.0	β contains zero	Excellent

ffm = formation fraction; Chi^2 = Chi square error; t-test = t-probability test; VA = Visual Assessment

▮▮▮▮: SFO model for parent substance, Hockey Stick for RPA 202248, DFOP for RPA 205834

▮▮▮▮: Hockey Stick model for parent substance and RPA 202248, FOMC for RPA 205834

III. Conclusion

The degradation of phenyl-UL-^{14}C-labeled isoxaflutole under conditions of a water/sediment test was shown to proceed via the formation of metabolites RPA 202248 and RPA 205834.

For modelling endpoints the kinetic evaluation of the dissipation from water resulted in an 'all-SFO' fit of residue data for the ▮▮▮▮ system. Best fits were obtained for the ▮▮▮▮ system from combination of the SFO model for parent substance and RPA 202248 with the DFOP model for RPA 205834.

For persistence endpoints and for the ▮▮▮▮▮▮▮ system the kinetic evaluation resulted in a SFO fit for residue data of parent substance, a Hockey Stick model for RPA 202248 and a DFOP fit for RPA 205834. Best fits were obtained for the ▮▮▮▮▮▮▮ system from combination of Hockey Stick model for parent substance and RPA 202248 with the FOMC model for RPA 205834.

For modelling endpoints the kinetic evaluation resulted in a geometric mean value for the $DisT_{50}$ of 0.36 days for the parent compound isoxaflutole. For metabolites the values are 62.2 days for RPA 202248 and 28.3 days for RPA 205834.

For evaluation against persistence triggers the worst case $DisT_{50}$ from water is 0.57 days (▮▮▮▮▮▮▮ system) for parent compound isoxaflutole. For metabolites the values are 57.1 days for RPA 202248 and 16.7 days for RPA 205834. Worst case values for the $DisT_{90}$ on total systems are 1.9 days for the parent compound, 328 days for RPA 202248 and 163 days for RPA 205834.

The results can therefore be used as input parameters for modelling in environmental risk assessments and for evaluation against persistence triggers.

CA 7.2.2.4 Irradiated water/sediment study

This point is regarded as a new optional data requirement in the EU. The degradation of isoxaflutole is well understood under standard conditions of water/sediment testing. In view of the overall limited potential of photolytic degradation as demonstrated under KCA 7.2.1.2/ 01 and KCA 7.2.1.2/ 03 the conduct of an irradiated water/sediment study is not regarded to result in a significantly better understanding of the behavior of isoxaflutole and its residues in the aquatic environment.

An irradiated water/sediment study was therefore not performed.

CA 7.2.3 Degradation in the saturated zone

This data requirement had been addressed under Point 7.2.1.4 of the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that the results of risk assessment in ground water demonstrated no significant risk for a contamination of sub-soils or the saturated zone by the parent compound and its metabolites, when applied according to good agricultural practice.

Therefore the separate investigations on the degradation in the saturated zone are not regarded as necessary.

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CA 7.3   Fate and behaviour in air

CA 7.3.1   Route and rate of degradation in air

Report:	4; ;1996;M-213115-01
Title:	Isoxaflutole - Estimation of the rate of photochemical transformation in the atmosphere under tropospheric conditions
Report No:	C022447
Document No(s):	Report includes Trial Nos.: 95-116 M-213115-01-1
Guidelines:	**OECD: Environment Monograph No. 61 (1992);Deviation not specified**
GLP/GEP:	**yes**

Report:	; ;2003;M-224922-01
Title:	Isoxaflutole: Estimation of degradation by photo-oxidation in air Model calculation according to Atkinson
Report No:	C038406
Document No(s):	Report includes Trial Nos.: CX/03/081 M-224922-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Report:	v; ;2003;M-224920-01
Title:	RPA202248: Estimation of degradation by photo-oxidation in air Model calculation according to Atkinson
Report No:	C038405
Document No(s):	Report includes Trial Nos.: CX/03/080 M-224920-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

This data requirement had been addressed under Point 7.2.2 of the Dossier submitted and evaluated within the process for Annex I inclusion as published in the corresponding Monograph of RMS The Netherlands (February 1997) and its amendments.

The evaluation revealed that based on rapid degradation in the atmosphere, isoxaflutole would not remain stable and thus available for long-range transport due to its susceptibility for reactions with photochemically produced hydroxyl radicals.

The existing calculation of the rate of transformation of isoxaflutole in air (KCA 7.3.1 /01) had been performed prior to the availability of the software AOPWIN introduced later by US EPA being regarded as the actual standard for this kind of calculation.
The rate of photochemical transformation of isoxaflutole in air has therefore been re-calculated as briefly described below (KCA 7.3.1 /02).

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In addition, the rate of transformation of the rapidly formed metabolite RPA 202248 in air was calculated following the same approach as presented for the active substance with results summarized below (KCA 7.3.1 /03).

The value for the vapour pressure of isoxaflutole had been determined to 3.2×10^{-7} Pa at 20°C as submitted under Point 2.3.1 of the existing Dossier.

Report:	k; ;2003;M-224922-01
Title:	Isoxaflutole: Estimation of degradation by photo-oxidation in air Model calculation according to Atkinson
Report No:	C038406
Document No(s):	Report includes Trial Nos.: CX/03/081 M-224922-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Executive Summary

The half-life time of isoxaflutole in air was estimated on the basis of structure-activity relationships for the degradation of chemicals in the atmosphere developed by Atkinson[12] and transferred into the computer program AOPWIN™ (v 1.91).

The half-life of isoxaflutole in air was estimated to 1.83 days based on a typical daylight concentration of 1.5×10^6 hydroxyl radicals/cm³ air and a 12 hour day.

The calculations showed that isoxaflutole is susceptible for reactions of hydroxyl radicals with various parts of the molecule thus contributing to the degradation of the substance in the atmosphere.

Nor isoxaflutole is available for longe-range transport neither the substance has a potential for accumulation in the atmosphere. Furthermore, the overall potential for occurrence of isoxaflutole in the atmosphere is additionally limited due to the low vapor pressure of the substance and its use in seed treatment.

I. Material and Methods

Based on an approach based on structure-activity relationship (SAR) by Atkinson, the half-life and chemical lifetime of isoxaflutole in air was estimated by use of the computer program AOPWIN™ (version 1.91, Syracuse Research Corp.).

The program allows for an estimatation of rate constants for the reaction of photolytically produced hydroxyl radicals with organic chemicals in the atmosphere. In case of presence of olefinic or acetylenic subgroups in the chemical under assessment the calculation includes estimations of rate constants for the reaction of ozone with these subgroups. From estimated rate constants half-lives of the chemical in the atmospheric are calculated based upon average concentrations of hydroxyl radicals. AOPWIN™ requires the input of chemical structure via a Smiles code and an estimate for the concentration of hydroxyl radicals in the atmosphere.

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[12] Atkinson, R.: Kinetics and mechanism of the gas-phase: Reactions of the hydroxyl radical with organic compounds under atmospheric conditions. Chem. Rev. 85, 69-201 (1985)

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Considering the chemical structure of isoxaflutole, its degradation in air will mainly be determined by reactions with hydroxyl radicals rather than from reaction with ozone due to the absence of susceptible moieties in the molecule.

The calculations were based on a typical concentration of 1.5×10^6 hydroxyl radicals/cm³ air for daylight and a 12 hour day (average daylight time for a whole year).

II. Results and Discussion

The half-life of isoxaflutole in air was calculated to 1.83 days based on a mean atmospheric hydroxyl radical concentration of 1.5×10^6 hydroxyl (OH) radicals/cm³ during 12 hours of daylight as summarized in Table 7.3.1-1.

Table 7.3.1-1: Half-life of isoxaflutole in air (AOPWIN, vers.1.91)

Parameter		Value
Time	(hours/day)	12
OH radical concentration	(radicals/cm³)	1.5×10^6
OH rate constant	(cm³ x molecule^{-1} x s^{-1})	5.85×10^{-12}
Half-life	(hours)	21.9
	(days)	1.83

Isoxaflutole can therefore be considered susceptible for degradation processes in air by reactions with photolytically generated hydroxyl radicals. These processes are expected to contribute significantly to the overall degradation of the substance in the atmosphere.

III. Conclusion

Being susceptible to photolytic reactions in the atmosphere it can be concluded that nor isoxaflutole is available for long-range transport neither has a potential for accumulation in the atmosphere. Furthermore, an overall potential for an occurrence of isoxaflutole in the atmosphere is additionally limited due to the low vapor pressure of the substance (3.2×10^{-7} Pa at 20°C).

Report:	███████u; ████████;2003;M-224920-01
Title:	RPA202248: Estimation of degradation by photo-oxidation in air Model calculation according to Atkinson
Report No:	C038405
Document No(s):	Report includes Trial Nos.:
	CX/03/080
	M-224920-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Executive Summary
The half-life time of RPA 202248 in air was estimated on the basis of structure-activity relationships for the degradation of chemicals in the atmosphere developed by Atkinson and transferred into the computer program AOPWIN™ (v 1.91).

The half-life of RPA 202248 in air was estimated to 0.62 to 1.42 days based on a typical daylight concentration of $1.5 \times 10^{+6}$ hydroxyl radicals/cm^3 air and a 12 hour day.

The calculations showed that RPA 202248 is susceptible for reactions of hydroxyl radicals with various parts of the molecule thus contributing to the degradation of the substance in the atmosphere.

The compound is thus not available for long-range transport and has neither a potential for accumulation in the atmosphere. Furthermore, the overall potential for occurrence in the atmosphere is additionally limited due to the low vapor pressure of the substance and its use in seed treatment.

I. Material and Methods

Based on an structure-activity relationship (SAR) approach by Atkinson, the half-life and chemical lifetime of isoxaflutole in air was estimated by use of the computer program AOPWIN™ (version 1.91, Syracuse Research Corp.).

The program allows for an estimation of rate constants for the reaction of light-induced hydroxyl radicals with organic chemicals in the atmosphere. In case of presence of olefinic or acetylenic subgroups in the chemical under assessment the calculation includes estimations of rate constants for the reaction of ozone with these subgroups. From estimated rate constants half-lives of the chemical in the atmospheric are calculated based upon average concentrations of hydroxyl radicals. AOPWIN™ requires the input of chemical structure *via* a Smiles code and an estimate for the concentration of hydroxyl radicals in the atmosphere.

The actual structure of the diketonitrile compound RPA 202248 can be described by at least two different forms that can exist in parallel und rapidly interconvert between these two forms. The forms have an 'enol-type' structural element as indicated by the strong acidic character of the molecule with a measured pKa of 2.7 (see KCA 2.8). It should be noted that the commonly used 'all-ketone' structure cannot explain this finding.

Enol form (I)   Enol form (II)
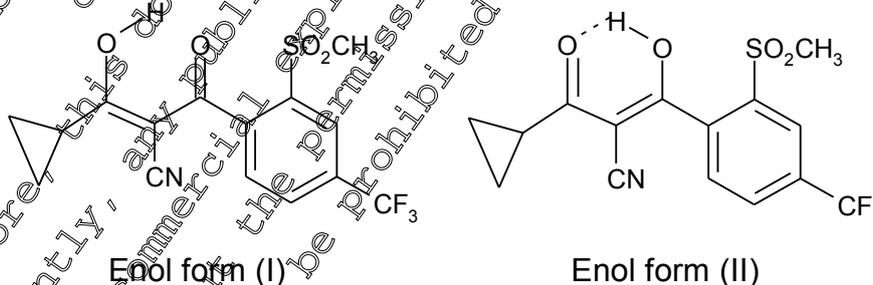
Considering these characteristics of RPA 202248, its degradation in air will be determined by reactions with hydroxyl radicals and with ozone with susceptible moieties being present in the molecule for both types of reaction. However, the ozone-induced reactions are slower contributing significantly less to the overall elimination from the atmosphere than reactions with hydroxyl radicals.

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The calculations given below were thus based on a typical concentration of 1.5×10^6 hydroxyl radicals/cm^3 air for daylight and a 12 hour day (average daylight time for a whole year).

II. Results and Discussion

Half-lives of two enol-forms of RPA 202248 in air were calculated to 0.62 to 1.42 days based on a mean hydroxyl radical concentration in the atmosphere of 1.5×10^6 hydroxyl (OH) radicals/cm^3 during 12 hours of daylight as summarized in Table 7.3.1-1.

Table 7.3.1-1: Half-lives of enol forms of RPA 202248 in air (AOPWIN, vers. 1.91)

Parameter		Value
Time	(hours/day)	12
OH radical concentration	(radicals/cm^3)	1.5×10^6
Enol form I		
OH rate constant	(cm^3 x molecule^{-1} x s^{-1})	7.53×10^{-12}
Half-life	(hours)	17.0
	(days)	1.42
Enol form II		
OH rate constant	(cm^3 x molecule^{-1} x s^{-1})	17.3×10^{-12}
Half-life	(hours)	7.4
	(days)	0.62

RPA 202248 can also be considered susceptible for degradation processes in air by reactions with photolytically generated hydroxyl radicals. These processes are expected to contribute significantly to the overall degradation of the substance in the atmosphere.

III. Conclusion

Being susceptible to photolytic reactions in the atmosphere it can be concluded that RPA 202248 is not available for long-range transport neither has a potential for accumulation in the atmosphere. Furthermore, an overall potential for an occurrence of RPA 202248 in the atmosphere is additionally limited due to the low vapor pressure of the substance (2.6×10^{-7} Pa at 20°C, see KCA 2.2).

CA 7.3.2　　Transport via air

Being a new potential requirement this had not been addressed in the Dossier submitted or evaluated within the process for Annex I inclusion.

In view of values for vapour pressure measured being below the triggers of 10^{-4} Pa for soil and 10^{-5} Pa for plant, no study on transport of the active substance isoxaflutole or RPA 202248 via air is regarded as necessary.

The combination of low half-life in the atmosphere (1.83 days) with a low vapour pressure (3.22×10^{-7} Pa at 20°C) results in a low value for the Henry constant (1.87×10^{-5} Pa x m3 x mole^{-1} at 20°C), indicating very low portioning from water to air. Consequently, isoxaflutole is clearly not subject to transport via air. Under conditions of the environment the active substance is subject to rapid transformation to form RPA 202248. This metabolite has the potential to form salts showing even lower potential for volatilization from soil or water surfaces than the parent active substance.

CA 7.3.3   Local and global effects

Being a new potential requirement this had not been addressed in the Dossier submitted or evaluated within the process for Annex I inclusion.

Isoxaflutole is applied to a limited number of crops (i.e. maize only) at a low field application rate. Following application residues are rapidly degraded. In combination with low potential for volatility these aspects indicate that residues are not present under outdoor conditions to form a risk for the environment short-term or long-term to set effects at local or global level.

The potential for local effects from use of isoxaflutole is considered in risk assessments performed following its use under field conditions, in particular by considering factors like spray drift. The combination of exposure assessments with potential effects measured in soil and surface water do thus cover the environmental compartments of interest. In contrast and since there is no aerial application envisaged, air is not a compartment regarded to be major compartment of potential for isoxaflutole occurrence following its intended use in the field.

The setting of global effects like contributions to global warming potential (GWP), ozone depleting potential (OPD), photochemical ozone creation potential (POCP) would require a high probability for the molecule assessed to evaporate and thus occur in the gas phase. This probability can be expressed by the volatility in terms of the vapour pressure and the Henry constant. The very low potential of isoxaflutole residues to occur in the atmosphere has been addressed before under KCA 7.3.2.

Any accumulation in the troposphere would require high volumes of active substance applied and a significant volatility combined with persistence in the gas phase. The latter characteristic has been addressed under KCA 7.3.2 to result in no long-term persistence of isoxaflutole residues in the atmosphere.

An acidification potential (AP) would require the generation of acidifying gases like sulfur dioxide or nitrogen oxides in a free form. An eutrophication potential (EP) would require the generation of ammonia or phosphorous compounds acting as nutrients.

There are no indications that the degradation of isoxaflutole residues in the environment via biological of physico-chemical processes would result in products that have a potential for acidification or

eutrophication of the environment. Even when this would be the case and to set a potential effect this would require amounts of active substance applied in the field being several orders of magnitude higher in comparison to the low seasonal application rates and from use in maize crops only.

CA 7.4 Definition of the residue

CA 7.4.1 Definition of the residue for risk assessment

The route and rate of degradation of isoxaflutole had been investigated after application of radiolabeled active substance to various soil, ground water and surface water test systems in the laboratory. Following the observation of metabolites and transformation products above the trigger values set in the relevant tests, these are potential residues to occur in the environment thus to be considered in the corresponding environmental risk assessments.

Residue definition for soil:
Besides the parent compound isoxaflutole metabolites RPA 202248 (AE 0540092) and RPA 203328 (AE B197555) had been considered in the existing environmental risk assessments due to their occurrence at >10% of AR in aerobic soil degradation tests.
A review of the data following new triggers set resulted in no need to consider compounds in addition to those addressed already.

Residue definition for ground water:
The risk assessment for ground water includes by default all components defined for the risk assessment in soil which is the active substance isoxaflutole and metabolites RPA 202248 and RPA 203328.

Residue definition for surface water:
The risk assessment for surface water includes by default the active substance isoxaflutole and those components defined for risk assessment in soil and ground water, i.e. metabolites RPA 202248 and RPA 203228.
In the existing surface water risk assessment metabolite RPA 205834 had been included additionally due to its occurrence at >10% of AR in maximum in water/sediment tests.

No additional transformation products of isoxaflutole were observed in sterile buffer hydrolysis and photolysis, tests on mineralization in surface water or sediment/water tests that would require consideration in surface water risk assessment.

CA 7.4.2 Definition of the residue for monitoring

Following risk assessments in soil, ground water and surface water according to the GAP defined, the environmental safety of all components under assessment could be demonstrated according to the requirements set.
It is therefore justified to define the parent compound isoxaflutole and its metabolite RPA 202248 as the relevant residue for monitoring in soil, ground water and surface water.

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CA 7.5   Monitoring data

No formal monitoring program was requested or required to address this point for isoxaflutole or residues in soil and water in the EU.

Moreover and specifically for isoxaflutole, there are no published data from formal monitoring programs outside BCS available that would indicate a specific concern or findings of isoxaflutole and its residues in remote environmental areas not being subject to the intended use.

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List of metabolites observed in environmental fate testing

In the original study reports on biotic or abiotic transformation of isoxaflutole the metabolites are denominated by different synonyms. In order to present a common system of nomenclature for the evaluation in the dossier a list of metabolites observed in environmental fate testing is included.

Report name Structure IUPAC name CAS name [CAS registry number]	Molecular formula molar mass Other names / codes	Occurrence
Isoxaflutole (parent substance) (5-cyclopropyl-1,2-oxazol-4-yl)-[2-methylsulfonyl-4-(trifluoromethyl)phenyl]methanone (IUPAC) Methanone,(5-cyclopropyl-4-isoxazolyl){2-(methylsulfonyl)-4-(trifluoromethyl)phenyl}-(9CI) (CAS) CAS no: 141112-29-0	$C_{15} H_{12} F_3 N O_4 S$ 359.32 g/mol **Isoxaflutole** (common name) RPA 201772 RPA 591428 AE B197278 BCS-AH21981	Parent substance used as test material in all reports
Diketonitrile 2-cyclopropylcarbonyl-3-(2-methylsulfonyl-4-trifluoromethylphenyl)-3-oxopropanenitrile (IUPAC) Benzenepropanenitrile, a-(cyclopropylcarbonyl)-2-(methylsulfonyl)-b-oxo-4-(trifluoromethyl)-(CAS) CAS no: 143701-75-1	$C_{15} H_{12} F_3 N O_4 S$ 359.32 g/mol RPA 202248 AE 0540092 BCS-AB59005 DKN	Soil, aerobic Soil, anaerobic Soil photolysis Abiotic hydrolysis
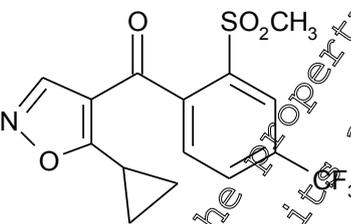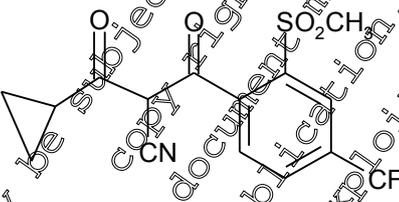
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Report name Structure IUPAC name CAS name [CAS registry number]	Molecular formula molar mass Other names / codes	Occurrence
Benzoic acid 2-mesyl-4-trifluoromethylbenzoic acid (IUPAC) Benzoic acid, 2-(methylsulfonyl)-4-(trifluoromethyl)- (CAS) CAS no: 142994-06-7	$C_9 H_7 F_3 O_4 S$ 268.22 g/mol RPA 203328 AE B197555 Pyrasulfotole-benzoic acid BCS-AB49990 BA TFT acid	Soil, aerobic Soil, anaerobic Soil photolysis
RPA 205834 Enamine-amidine tautomeric forms: 2-(1-aminomethylidene)-1-cyclopropyl-3-(2-mesyl-4-trifluoromethylphenyl)propane-1,3-dione (IUPAC) CAS no: n.a.	$C_{15} H_{14} F_3 N O_4 S$ 361.34 g/mol RPA 205834 AE 0692291 BCS-BY16134	Soil, aerobic Soil, anaerobic Water/Sediment
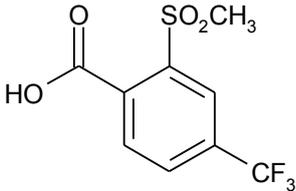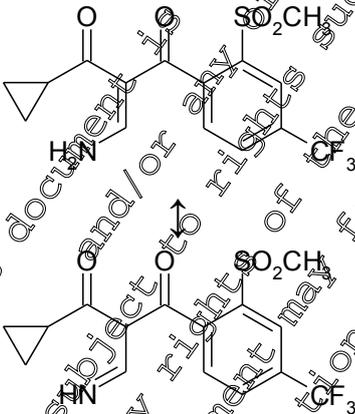
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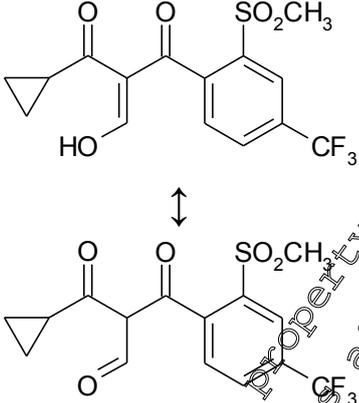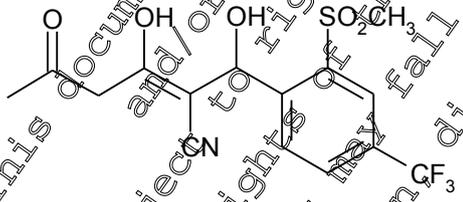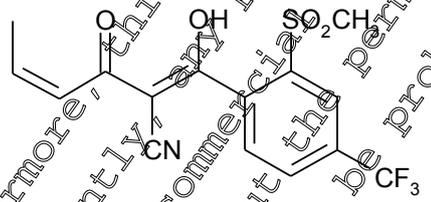
Report name Structure IUPAC name CAS name [CAS registry number]	Molecular formula molar mass Other names / codes	Occurrence
RPA 207048 Keto-enol tautomeric forms: 1-cyclopropyl-2-hydroxymethylene-3-(2-mesyl-4-trifluoromethylphenyl)propane-1,3-dione (IUPAC) CAS no: n.a.	$C_{15}H_{12}F_3O_5S$ 329.25 g/mol RPA 207048 AE Code: None BCS Code: None	Water/Sediment
Met 14 (2Z)-3-hydroxy-2-{hydroxy[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methyl}-5-oxohex-2-enenitrile (IUPAC) CAS no: n.a.	$C_{15}H_{14}F_3NO_5S$ 377 g/mol Peak 14 Met 14 AE Code: None BCS Code: None	Photolysis, buffer
Met 20 (2Z,4Z)-2-{hydroxy[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methylene}-3-oxohex-4-enenitrile (IUPAC) CAS no: n.a.	$C_{15}H_{12}F_3NO_4S$ 359 g/mol Peak 20 Met 20 AE Code: None BCS Code: None	Photolysis, buffer