Bayer CropScience

Document Title

Summary of the toxicological and metabolism studies for Iodosulfuron-methyl-sodium

Data Requirements

EU Regulation 1107/2009 & EU Regulation 283/2013
Document MCA
Section 5: Toxicological and metabolism studies

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

Date

2015-05-27

Author(s)

[redacted]

Bayer CropScience

OWNERSHIP STATEMENT

Version history

Date	Data points containing amendments or additions[1]	Document identifier or version number
May 2015	Addition of position papers (5.6.1 & 5.6.2) upon RMS request	

[1] Note how the amendments or additions are represented (italics/colour etc)

Table of Contents

CA 5 - TOXICOLOGICAL AND METABOLISM STUDIES ON THE ACTIVE SUBSTANCE

This document contains only summaries of studies, which were not available at the time of the first Annex I inclusion of iodosulfuron-methyl-sodium and were therefore not evaluated during the first EU review of this compound. In order to facilitate discrimination between new and original information, the old information is written in grey letters. All studies, which were already submitted by Bayer for the first Annex I inclusion, are contained in the Monograph, its Addenda and in the original (baseline) dossier provided by Bayer CropScience and are not summarised in this document.

The Acceptable Daily Intake (ADI) established in the first EU review of iodosulfuron-methyl-sodium was based on the lowest NOAEL observed, specifically 3.0 mg/kg bw/day in the rat chronic / oncogenicity study. The conventional safety / uncertainty factor of 100 was applied, deriving an

ADI of 0.03 mg/kg bw.

An ARfD was not allocated in the inital EU review of iodosulfuron-methyl-sodium because it was considered not necessary. On the basis of its toxicological profile, iodosulfuron-methyl-sodium is considered unlikely to present an acute hazard.

CA 5.1 - Studies on absorption, distribution, metabolism and excretion in mammals

CA 5.1.1 - Absorption, distribution, metabolism and excretion by oral route

Report:	[redacted];[redacted];[redacted];1996;M-142006-01
Title:	Biostability after a single oral administration of 500 mg/kg body weight to a male and female rat (Phenyl-U-14C) ; Code: Hoe 115008
Report No:	A58314
Document No:	M-142006-01-1
Guidelines:	**EU (=EEC): 94/79; JMAF: ; OECD: ; USEPA (=EPA): F 85-1, F § 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1996;M-140088-01
Title:	Absorption, distribution and elimination - rat, oral high dose (500 mg/kg body weight) 14C-Hoe 115008
Report No:	A56254
Document No:	M-140088-01-1
Guidelines:	**JMAF: ; OECD: ; USEPA (=EPA): 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];[redacted];1996;M-140089-01
Title:	Blood levels following single oral administration of 500 mg/kg body weight to male and female rats 14C-Hoe 115008
Report No:	A56255
Document No:	M-140089-01-1
Guidelines:	**JMAF: ; OECD: ; USEPA (=EPA): 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-141310-01
Title:	Metabolism - rat, oral high dose (500 mg/kg body weight) 2-14C-triazinyl Code: Hoe 115008
Report No:	A57609
Document No:	M-141310-01-1
Guidelines:	**EU (=EEC): 94/79/EC; OECD: 417; USEPA (=EPA): F 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1997;M-141311-01
Title:	Metabolism - rat, oral high dose (500 mg/kg body weight) U-14C-phenyl Code: Hoe 115008
Report No:	A57610
Document No:	M-141311-01-1
Guidelines:	**EU (=EEC): 94/79; JMAF: ; OECD: 417; USEPA (=EPA): F 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];1996;M-141309-01
Title:	Absorption, distribution and elimination - rat, oral low dose (10 mg/kg body weight) Triazinyl-2-14C Code: Hoe 115008
Report No:	A57608
Document No:	M-141309-01-1
Guidelines:	**EU (=EEC): 94/79/EC; OECD: 417; USEPA (=EPA): Subdiv. F§ 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];1996;M-142005-01
Title:	Blood levels following single oral and intravenous administration of 10 mg/kg body weight to male and female rats; 14C-Hoe 115008
Report No:	A58310
Document No:	M-142005-01-1
Guidelines:	**EU (=EEC): 94/79; OECD: 417; USEPA (=EPA): F§ 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];1997;M-141312-01
Title:	Metabolism - rat, oral low dose (10 mg/kg body weight) 2-14C-triazinyl Code: Hoe 115008
Report No:	A57611
Document No:	M-141312-01-1
Guidelines:	**EU (=EEC): 94/79; JMAF: ; OECD: 417; USEPA (=EPA): F 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];1998;M-180570-01
Title:	Dose absorption, distribution, elimination - oral low (6 mg/kg b.w.) and high (200 mg/kg b.w.) dose (Phenyl-U-14C)-AE F115008
Report No:	C000382
Document No:	M-180570-01-1
Guidelines:	**EU (=EEC): 94/79/EC; JMAF: ; OECD: 417; USEPA (=EPA): Subdiv. F§ 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];1998;M-148018-01
Title:	Dog metabolism - oral high (200 mg/kg body weight) and low dose (6 mg/kg body weight) U-14C-phenyl-AE F115008
Report No:	A67649
Document No:	M-148018-01-1
Guidelines:	**EU (=EEC): 94/79; JMAF: ; OECD: 417; USEPA (=EPA): Subdiv. F § 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];1998;M-180572-01
Title:	Rat absorption, distribution, elimination - repeated oral dose (7 x 100 mg/kg bw) (Phenyl-U-14C) Code: AE F115008
Report No:	C000383
Document No:	M-180572-01-1
Guidelines:	**EU (=EEC): 94/79; JMAF: ; OECD: 417; USEPA (=EPA): F 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];1998;M-180530-01
Title:	Rat metabolism - Repeated oral dose (7 x 100 mg/kg body weight) U-14C-phenyl-AE F115008
Report No:	C000362
Document No:	M-180530-01-1
Guidelines:	**EU (=EEC): 94/79/EC; JMAF: ; OECD: 417; USEPA (=EPA): Subdiv. F§ 85-1;Deviation not specified**
GLP/GEP:	**yes**

The toxicological profile of iodosulfuron-methyl-sodium was already investigated and evaluated. The absorption, distribution (including blood and plasma kinetics) metabolism and excretion of AE F115008 was investigated in Wistar rats using oral and intravenous low doses of 10 mg/kg bw and oral high doses of 500 mg/kg bw. The influence of the label position was examined using two different labels (U-^{14}C-phenyl- and 2-^{14}C-triazinyl-label). Repeated oral administration of doses of 100 mg/kg bw for 7 consecutive days was investigated as well (U-^{14}C-phenyl-label only, as cleavage of the sulfonylurea bridge proved to be a minor metabolic pathway after single dosing). The metabolite pattern was investigated in urine, faeces and cage washings by adequate analytical methods.
After specific toxic effects in the dog had become obvious absorption, distribution, elimination and in particular metabolism were also examined in Beagle dogs using an oral low dose of 6 mg/kg bw which was close to the 90 day NOAEL as well as an oral high dose of 200 mg/kg bw. The high dose was close to a dose level with clear toxic effects in the dog subchronic toxicity studies. The metabolite pattern was investigated in urine, faeces and plasma by adequate analytical methods.

The test substance was rapidly absorbed and rapidly excreted in rats and dogs following oral administration. No indication for cumulative properties was seen. Radioactivity in major organs was low. In rats elimination via urine ranged between 95% (single oral low dose) and 70% or 80% in males and females respectively (single oral high dose) of the administered radioactivity. Faecal excretion was about 5% (single oral low dose) and 26% in males and 14% in females (single oral high dose). The main part of the radioactivity was eliminated within 48 hours and elimination was nearly complete within 72 hours after dose administration. No radioactivity was exhaled during the first 24 hours after administration of a single high dose.
Absorption, plasma kinetics and elimination (elimination in urine > 70% of the administered radioactivity) in dogs were comparable to those in rats.

After repeated oral exposure to 100 mg/kg bw more than 80% of the totally administered radioactivity were found in rat urine.
The pharmacokinetics of AE F115008 in the plasma of rats indicated a biphasic elimination with a fast initial elimination (half-lives ranged between 4 and 7 hours depending on test conditions) in which the main part of the radioactivity was excreted and a second slow elimination of a minor part of the radioactivity (38 - 60 hours).

Metabolic pathway
In the metabolism studies the major part of the radioactivity (>80% in studies with single application) was excreted as parent compound in rats and dogs. AE F115008 was metabolised in mammals by hydrolysis of the methylester of the benzoic acid function to AE F145740 and O-demethylation at the 1,3,5-triazine leading to AE F145741 after single and repeated oral dosing. Oxidative hydroxylation of the 6-methyl-group of the 1,3,5-triazinyl-moiety was also observed. Breakdown of the sulfonylurea bridge possibly due to amidases leads to AE F114368 and 2-aminosulfonyl-4-iodo-benzoic acid (AE 0031850) which cyclised to AE F143133. The cleavage of the iodine-phenyl-bond resulting in methyl 2-[3-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)ureidosulfonyl]benzoate (AE F075736) and methyl 2-[3-(4-hydroxy-6-methyl-1,3,5 triazin-2-yl)ureidosulfonyl] benzoate (AE F161778) was observed to be a minor metabolic reaction in animals. Metabolites identified in the dog study were the same as those found in rats.
Overall the studies show no significant difference in the metabolic profile between sexes, dose levels or following repeated dosing in the rat or between the rat and the dog.

The metabolism pathway proposed in mammals is given in the following scheme. The postulated intermediates are shown in brackets. The arrows do not only represent a one-step enzymatic reaction, but may mean complex metabolic transformations leading to the compounds shown in Figure 5.1-1.

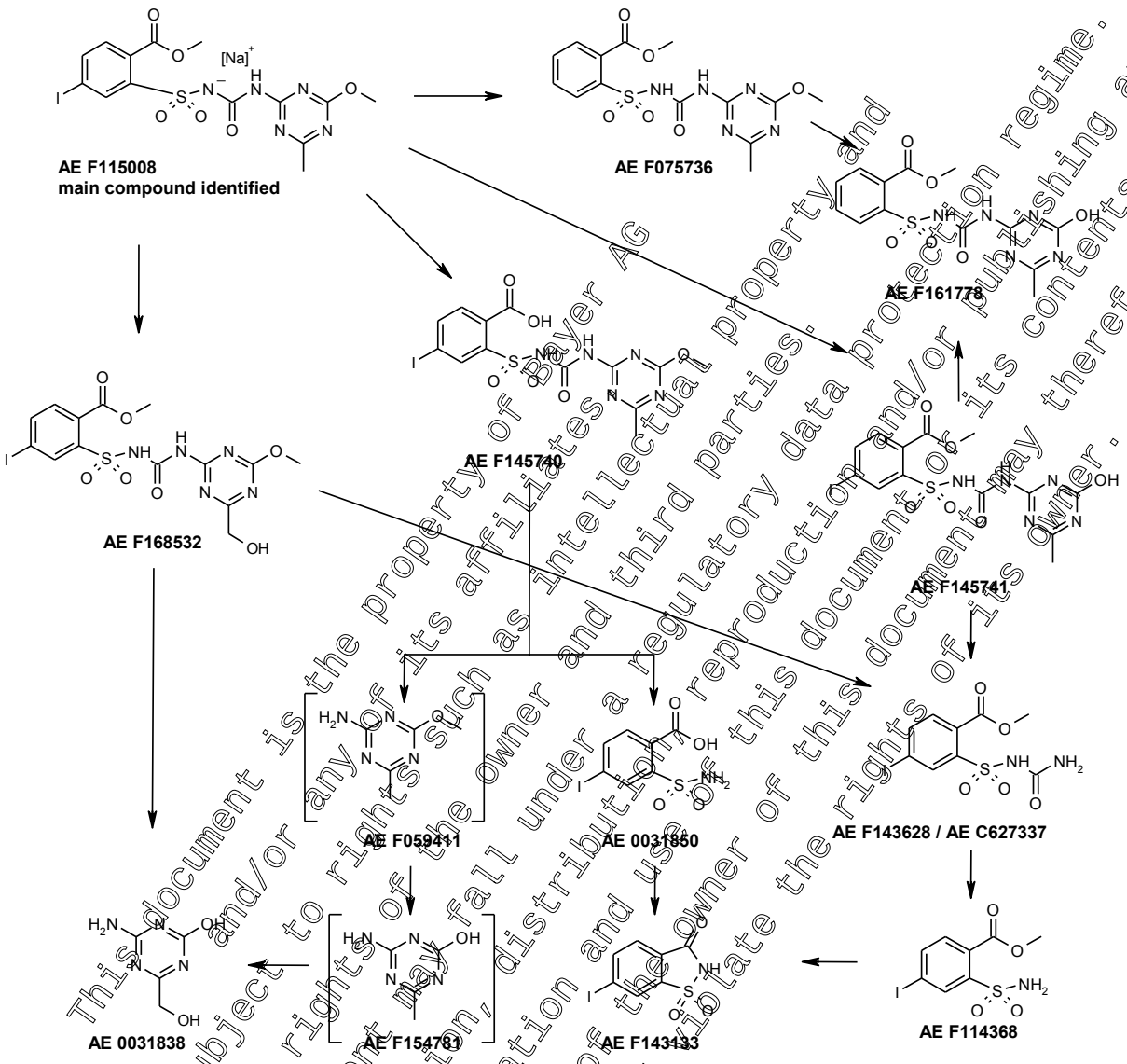


Figure 5.1-1: Metabolic profile of iodosulfuron-methyl-sodium in the rat and dog

Report:	[redacted]; [redacted] 2013; M-470475-01
Title:	[Triazinyl-2-^{14}C]iodosulfuron-methyl-sodium: Metabolic stability and profiling in liver microsomes from rats and humans for inter-species comparison
Report No:	EnSa-13-0828
Document No:	M-470475-01-1
Guidelines:	**Regulation (EC) No 1107/2009 (Europe) amended by the Commission Regulation (EU) No. 283/2013 (Europe)** **US EPA OCSPP 870.SUPP;not specified**
GLP/GEP:	**yes**

The comparative metabolism of ^{14}C-iodosulfuron-methyl-sodium was investigated in *in-vitro* systems by incubating the test item with liver microsomes from male Wistar rats (RLM) and from humans (HLM) in the presence of NADPH cofactor.

The results of the tests with demonstrated that the *in-vitro* metabolism of ^{14}C-iodosulfuron-methyl-sodium when incubated with liver microsomes was found to be different between rats and humans. No metabolism was observed in rat microsomes. The human microsomal incubations produced a single metabolite (metabolite I-2) that accounted for around 52% of the applied radioactivity.
In a second study (EnSa-13-0692), the metabolite was identified.

Materials and Methods

Test System

Pooled liver microsomes from male Wistar rats (RLM) and humans (HLM) were incubated with [triazinyl-2-^{14}C]-iodosulfuron-methyl-sodium in the presence of NADPH cofactor. The 15 µM test item concentration was chosen in order to have enough sample material for possible identification of metabolites by chromatographic or spectroscopic methods. The sampling times were 0 and 1 hour after test start. The test duration of 1 hour for the test item was considered as reasonable because positive results were obtained from the enzymatic reaction of testosterone to hydroxy-testosterone already after 10 minutes. Samples were analyzed following protein precipitation by reversed phase HPLC with radiochemical detection (HPLC RAD).

Results

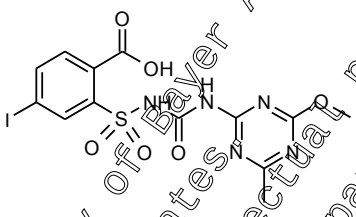
The recovery of radioactivity was measured in the microsome incubations and amounted to >92% for the 1-hour samples.
The metabolic activity of the microsomes was clearly demonstrated by determining 6β-hydroxytestosterone that was formed from testosterone by testosterone 6β-hydroxylase. This biochemical reaction is well known for the CYP3A microsomal enzyme.

The results of the tests demonstrated that the in-vitro metabolism of ^{14}C-iodosulfuron-methyl-sodium when incubated with liver microsomes was different between rats and humans:
No metabolism was observed in the rat microsomal incubations. The human microsomal incubations produced a single metabolite (metabolite I-2) that accounted for 51.7% of the relative percentage (calculated from peak area values).
No detectable metabolites were found after the 1 hour incubation period of the different microsome preparations with the test item.
Further experiments to identify the chemical structure of metabolite I-2 were then performed.

Report:	[redacted];[redacted];2013;M-465993-01
Title:	[Triazinyl-2-14C]Iodosulfuron-methyl-sodium: Isolation and identification of metabolite(s) from an in-vitro studywith human liver microsomes
Report No:	EnSa-13-0692
Document No:	M-465993-01-1
Guidelines:	**Regulation (EC) No 1107/2009 (Europe)** **amended by the Commission Regulation (EU) No. 283/2013 (Europe)** **US EPA OCSPP 870.SUPP;none**
GLP/GEP:	**yes**

In the study "[triazinyl-2-^{14}C]-iodosulfuron-methyl-sodium: Metabolic Stability and Profiling in Liver Microsomes from Rats and Humans for Inter-Species Comparison (M-470475-01-1, point KCA

5.1.1/13)", a single metabolite (I-2) was detected in the testing solution of ^{14}C-iodosulfuron-methylsodium with human liver microsomes (HLM, pool from both genders) after an incubation period of 60 minutes. This metabolite accounted for around 52% of the total relative percentage and didn't occur in the incubation with rat liver microsomes.
In this additional study, metabolite I-2 was identified as "iodosulfuron-methylbenzoic acid" (AE F145740) by spectroscopic methods (LC-MS) as shown below:



I-2 (AE F145740)

The relatively high abundance of the metabolite "iodosulfuron-methyl-benzoic acid" formed in human liver microsomes indicated a higher importance for this phase I biotransformation reaction in humans that is obviously not as present in rat microsomes.
Whereas "iodosulfuron-methyl-benzoic acid" was not formed in rat liver microsomes, it was however detected in the excreta of the *in-vivo* rat ADME-studies in low amounts.
Rats excreted the majority of the dose as unchanged parent via the urine (48.7-86.3%) or faeces (1.1-11.1%). Minor routes of metabolism for iodosulfuron-methyl included - beside others - hydrolysis of the methylester to form "Iodosulfuron-methyl-benzoic acid" (AE F145740; 0.9- 4.5%). No additional toxicological studies are necessary.

Overall conclusion
In the comparative *in vitro* study "Metabolic Stability and Profiling in Liver Microsomes from Rats and Humans for Inter-Species Comparison (M-470475-01-1), a single metabolite (I-2) was detected in the testing solution of ^{14}C-iodosulfuron-methylsodium with human liver microsomes (HLM, pool from both genders) after an incubation period of 60 minutes. This metabolite accounted for around 52% of the total relative percentage and didn't occur in the incubation with rat liver microsomes. In an additional study, metabolite I-2 was identified as "iodosulfuron-methylbenzoic acid" (AE F145740) by spectroscopic methods (LC-MS). Although this metabolite was not formed in rat liver microsomes, it was however detected in the excreta of the *in-vivo* rat ADME-studies in low amounts. No additional toxicological studies are necessary.

CA 5.1.2 - Absorption, distribution, metabolism and excretion by other routes

Report:	[redacted];[redacted];[redacted];1998;M-182308-01
Title:	Dermal absorption in the rat (14C)-AE F115008
Report No:	C007303
Document No(s):	M-182308-01-1
Guidelines:	**EU (=EEC): 87/302, 91/414; USEPA (=EPA): OPPTS 870.7600;Deviation not specified**
GLP/GEP:	**yes**

Following dermal administration of 14C-AE F115008 to rats only limited systemic absorption was observed (1.2 % using 100-fold diluted spray solution and 5.6 % absorption after application of a concentrated formulation.

CA 5.2 - Acute toxicity

The acute toxicity of iodosulfuron-methyl-sodium was assessed in an earlier EU review of iodosulfuron-methyl-sodium, however these data are summarized here for reference in gray type. Further information is available in the Baseline dossier provided by Bayer CropScience and in the Monograph. A full summary of the new phototoxicity study is appended below in section 5.2.7.

Type of study (Reference)	Species	Results	Classification acc. Reg EC 1272/2008
Acute oral toxicity ([redacted], 1993b M-132162-01-1)	Rat	LD50 (M+F) > 2678 mg/kg bw	Unclassified
Acute dermal toxicity ([redacted], 1993a M-132113-01-1)	Rat	LD50 (M+F) > 2000 mg/kg bw	Unclassified
Acute inhalation toxicity ([redacted], 1996b M-140802-01-1)	Rat	LC50 > 2.81 mg/L	Unclassified
Skin irritation ([redacted], 1993a M-132114-01-1)	Rabbit	Non-irritating	Unclassified
Eye irritation ([redacted], 1993b M-132115-01-1)	Rabbit	Non-irritating	Unclassified
Skin sensitization (Magnusson & Kligman) ([redacted], 1996a M-140993-01-1)	Guinea pig	Non-sensitizing	Unclassified
Phototoxicity in vitro ([redacted], 2013 M-	BALB/c 3T3 cells	Negative	Not relevant

The acute toxicity of iodosulfuron-methyl-sodium after oral, dermal, or inhalation exposure was relatively low. Clinical signs of intoxication were seen after oral and inhalation exposure, and were were non-specific in most cases. No clinical signs were observed after dermal administration. Iodosulfururon-methyl-sodium was not irritating to either skin or eye, and was not sensitizing to the skin.

CA 5.2.1 – Oral

Report:	[redacted];1993;M-132162-01
Title:	Acute oral toxicity in the male and female Wistar rat Hoe 115008 substance, technical Code: Hoe 115008 00 ZC97 0001
Report No:	A51192
Document No:	M-132162-01-1
Guidelines:	**EU (=EEC): ; JMAF: ; OECD: ; USEPA (=EPA): Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.2.2 – Dermal

Report:	[redacted];1993;M-132113-01
Title:	Acute dermal toxicity in the male and female Wistar rat Hoe 115008 substance, technical Code: Hoe 115008 00 ZC97 0001
Report No:	A51142
Document No:	M-132113-01-1
Guidelines:	**EU (=EEC): ; JMAF: ; OECD: ; USEPA (=EPA): Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.2.3 – Inhalation

Report:	[redacted];1996;M-140802-01
Title:	Acute aerosol inhalation toxicity in the male and female SPF Wistar rat 4-hour LC50 Code: Hoe 115008 00 ZC89 0001
Report No:	A97043
Document No(s):	M-140802-01-1
Guidelines:	**EU (=EEC): 92/69 B.1; JMAF: ; OECD: 403; USEPA (=EPA): 81-3;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.2.4 - Skin irritation

Report:	[redacted]; [redacted];1993;M-132114-01
Title:	Primary dermal irritation in the rabbit Hoe 115008 substance, technical Code: Hoe 115008 00 ZC97 0001
Report No:	A51143
Document No:	M-132114-01-1
Guidelines:	**EU (=EEC): ; JMAF: ; OECD: ; USEPA (=EPA): Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.2.5 - Eye irritation

Report:	[redacted]; [redacted];1993;M-132115-01
Title:	Primary eye irritation in the rabbit Hoe 115008 substance, technical Code: Hoe 115008 00 ZC97 0001
Report No:	A51144
Document No:	M-132115-01-1
Guidelines:	**EU (=EEC): ; JMAF: ; OECD: ; USEPA (=EPA): Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.2.6 - Skin sensitization

Report:	[redacted]; [redacted];1996;M-140993-01
Title:	Sensitizing properties in the Trybright-White guinea pig in a maximization test Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A57254
Document No(s):	M-140993-01-1
Guidelines:	**EU (=EEC): 92/69; B.6; JMAF: ; OECD: 406; USEPA (=EPA): §81-6;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.2.7 - Phototoxicity

According to the new data requirements (Commission Regulation (EU) No. 283/2013 of 1 March 2013, Official Journal of the European Union, L 93/1, 3.4.2013), the conduct of a phototoxicity study is required under certain conditions.

The circumstances in which a phototoxicity study, according to the new data requirements, is required are “where the active substance absorbs electromagnetic radiation in the range 290-700 nm and is

liable to reach the eyes or light-exposed areas of the skin, either by direct contact or through systemic distribution. If the Ultraviolet / visible molar extinction / absorption coefficient of the active substance is less than 10 L x mol^{-1} x cm^{-1}, no toxicity testing is required.

As the Ultraviolet / visible molar extinction / absorptioin coefficient of the active substance exceeds the trigger of 10 L x mol^{-1} x cm^{-1}, a cytotoxicity study has been performed in vitro using BALB/c 3T3 cells.

Report:	[redacted];[redacted];2013;M-479598-01
Title:	Iodosulfuron-methyl sodium TC: Cytotoxicity assay in vitro with BALB/c 3T3 cells: Neutral Red (NR) test during simultaneous irradiation with artificial sunlight
Report No:	1579600
Document No:	M-479598-01-1
Guidelines:	**Commission regulation (EC) No. 440/2008 B 41, dated May 30, 2008; Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on Photosafety testing, EMEA, CPMP/SWP/398/01, adopted 27 June 2002, into operation in Dec 2002.; OECD Guideline for Testing of Chemicals: Guideline: 432: In vitro 3T3 NRU phototoxicity test (Revised and approved by the National Co-ordinators in May 2002, approved by Council April 2004);not specified**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material:

Name:	Iodosulfuron-methyl-sodium
Synonyms:	AE F115008, BCS-BB66887
Description:	Light beige powder
Lot/Batch no:	ELIR003050
Purity:	93.0%, w/w
Stability of test compound:	guaranteed for study duration; expiry date: 2015-09-11
2. Vehicle and or positive control:	Solvent control: Earle's Balanced Salt Solution (EBSS) Positive control: chlorpromazine (Sigma) dissolved in EBSS
3. Test system:	BALB/c 3T3 cell clone 31
Culture medium:	Dulbecco's Minimal Essential Medium (DMEM) supplemented with 10% (v/v) NCS.
Cell cultures:	Thawed stock cultures were propagated at 37 ± 1.5 °C in 75 cm^2 plastic flasks. Seeding was done with about 1 x 10^6 cells per flask in 15 mL DMEM, supplemented with 10 % NCS. Cells were sub-cultured twice weekly. The cell cultures were incubated at 37 ± 1.5 °C in a 7.5 ± 0.5% carbon dioxide atmosphere.

B. Study design and methods

1. Treatment

Dose:

Test item	+/– UV	Final concentrations in µg/mL*
IMS*	+/–	7.81, 15.6, 31.3, 62.5, 125.0, 250.0, 500.0, 1000
Positive control**	-	6.25, 12.5, 25, 37.5, 50, 75, 100, 200
	+	0.125, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0
Solvent control	+/–	EBSS containing 1 % (v/v) DMSO

*iodosulfuron-methyl-sodium, ** chlorpromazine

The test item iodosulfuron-methyl-sodium was dissolved in EBSS.

Seeding of cultures: 2 x 10^4 cells per well were seeded in 100 µL culture medium in two 96 well plates

Replicates: 2 (one for irradiation exposure, one for treatment in the dark)

Treatment & irradiation: 24 h after seeding the cultures were washed with EBSS. 100 µL solved test item added per well for pre-incubation of the plates for 1 hour in the dark. Afterwards one plate was irradiated at 1.65 mW/cm^2 (4.95 J/cm^2) for 50 min ± 2 min at 26 °C, the other plate was stored for 50 min ± 2 min at 20-31 °C in the dark. Test item was removed and both plates were washed twice with EBSS. Fresh culture medium was added and the plates were incubated about 22 hours at 37 ± 1.5 °C and 7.5 ± 0.5 % CO_2.

Cytotoxicity determination: For measurement of Neutral Red uptake the medium was removed and 0.1 mL serum-free medium containing 50 µg Neutral Red / mL were added to each well. The plates were incubated for another 3 hours at 37°, before the medium was removed completely and the cells were washed with EBSS. For extraction of the dye 0.15 mL of a solution of 49% (v/v) deionised water, 50% (v/v) ethanol and 1% (v/v) acetic acid were added to each well. After approximately 10 minutes at room temperature and a brief agitation, the plates were transferred to a microplate reader (Versamax®, Molecular Devices) equipped with a 540 nm filter to determine the absorbance of the extracted dye. This absorbance showed a linear relationship with the number of surviving cells.

Number of measurements: Iodosulfuron-methyl-sodium and positive control: each concentration was measured 6 times
Solvent control: 12 times

2. Evaluation

The mean absorption (OD_{540}) value per concentration was calculated. The ED_{50}* values were determined by curve fitting by software. The Photo-irritancy factor (PIF), as well as the Mean Phototoxic effect (MPE) was calculated according to OECD guideline 432.

*ED_{50} = effective dose where only 50% of the cells survived

Evaluation criteria: If PIF < 2 or MPE < 0.1 no phototoxic potential is predicted
If PIF > 2 and < 5 or MPE > 0.1 and < 0.15 a probable phototoxic potential is predicted

If PIF > 5 or MPE > 0.15 a phototoxic potential is predicted.

II. Results and discussion

In the range finding experiment (RFE) no cytotoxic effects were observed after exposure of the cells to the test item iodosulfuron-methyl-sodium, neither in the presence nor in the absence of irradiation to artificial sunlight. Therefore, ED_{50}-values and PIF could not be calculated. The resulting MPE-value was -0.069.

In the main experiment (ME) no cytotoxic effects were observed after exposure of the cells to the test item iodosulfuron-methyl-sodium, neither in the presence nor in the absence of irradiation to artificial sunlight. Therefore, ED_{50}-values and PIF could not be calculated. The resulting MPE-value was -0.140.

The mean of solvent control values of the irradiated versus the non-irradiated group met the acceptance criteria. The positive control chlorpromazine induced phototoxicity in the expected range in the presence of irradiation.

The results are summarized in Table CA 5.2.7-1 and Table CA 5.2.7-2 below.

Table CA 5.2.7-1: OD_{540} values Neutral Red assay of the main experiment

Con-centration [µg/mL]	OD_{540} with artificial sunlight			OD_{540} without artificial sunlight			
	Mean	SD	% of solvent control	Con-centration [µg/mL]	Mean	SD	% of solvent control
Treatment with iodosulfuron-methyl-sodium							
Solvent control	0.5137*	0.0335	100.00	**Solvent control**	0.5644*	0.0481	100.00
7.81	0.5530	0.0205	107.64	7.81	0.5388	0.0385	95.45
15.63	0.5497	0.0173	107.00	15.63	0.5317	0.0287	94.20
31.25	0.5686	0.0549	110.69	31.25	0.5407	0.0661	95.79
62.50	0.5439	0.0321	105.88	62.50	0.5412	0.0555	95.89
125.0	0.5413	0.0386	105.37	125.0	0.5223	0.0350	92.54
250.0	0.5271	0.0599	102.61	250.0	0.4953	0.0253	87.75
500.0	0.5472	0.0392	106.52	500.0	0.4935	0.0209	87.43
1000	0.5115	0.0304	99.56	1000	0.4905	0.0348	86.90
Treatment with positive control chlorpromazine							
Solvent control	0.4810*	0.0365	100.00	**Solvent control**	0.5288*	0.0297	100.00
0.125	0.5149	0.0522	107.05	6.25	0.4489	0.0287	84.89
0.250	0.4249	0.0450	88.34	12.50	0.1264	0.0147	23.90
0.500	0.3042	0.0303	62.25	25.00	0.0477	0.0017	9.02
0.750	0.1478	0.0454	30.73	37.50	0.0483	0.0010	9.13
1.000	0.0674	0.0137	14.01	50.00	0.0474	0.0009	8.95
1.500	0.0627	0.0078	13.03	75.00	0.0478	0.0006	9.03
2.000	0.0626	0.0017	13.01	100.00	0.0483	0.0012	9.14
4.000	0.0684	0.0031	14.21	200.00	0.0508	0.0013	9.61

* mean OD_{540} out of 12 wells

Table CA 5.2.7-2: Summary of results of the Neutral Red assay

	Substance	ED_{50} (+UV) [µg/mL]	ED_{50} (–UV) [µg/mL]	PIF	MPE	% viability of solvent control of irradiated vs. non-irradiated plate
Range finding experiment	Iodosulfuron-methyl-sodium	--	--	--	-0.069	93.2
	Positive control	1.19	17.16	14.41	0.442	93.7
Main experiment	Iodosulfuron-methyl-sodium	--	--	--	-0.140	91.0
	Positive control	0.57	9.47	16.72	0.415	91.0

ED_{50} = effective dose where only 50% of the cells survived
PIF = Photo-Irritation Factor
MPE = Mean Phototoxic effect

III. Conclusions

In conclusion, in this study and under the experimental conditions reported, the test item iodosulfuron-methyl-sodium does not possess any phototoxic potential.

CA 5.3 - Short-term toxicity

The short-term toxicity of iodosulfuron-methyl sodium was assessed in an earlier EU review of the active substance, however these data are summarized here for reference in gray type. Further information is available in the Baseline Dossier provided by Bayer CropScience and in the Monograph.

Study duration (Reference)	Species	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Critical effects
90-day dietary ([redacted], 1997 M-142651-01-1)	Rat	13.8 / 14.4 mg/kg bw/day (M / F)	67 / 74 mg/kg bw/day (M / F)	Decr body wt, decr RBC parameters
90-day dietary ([redacted], 1997 M-143075-01-1)	Mouse	119 / 139 mg/kg bw/day (M / F)	119 / 139 mg/kg bw/day (M / F)	Hepatotoxicity
28-day dietary ([redacted], 1998 M-181089-01-1)	Dog	<39 / 41 mg/kg bw/day (M / F)	39 / 41 mg/kg bw/day (M / F)	Decr body wt, decr RBC parameters
90-day dietary ([redacted], 1998 M-180321-01-1)	Dog	8.1 / 8.4 mg/kg bw/day (M / F)	49 / 51 mg/kg bw/day (M / F)	Decr body wt, peripheral anemia
12-month dietary ([redacted], 1998 M-181091-01-1)	Dog	7.37/ 7.25 mg/kg bw/day (M / F)	41.8 / 43.7 mg/kg bw/day (M / F)	Bone marrow hyperplasia, extramed. hematopoiesis

In rats, toxicologically significant effects of iodosulfuron-methyl-sodium occurred from 1000 ppm (67 / 74 mg/kg bw/day in males and females respectively) and above, and included reduced red blood cell

parameters, decreased body weight gains, and slight hepatocyte enlargement. The NOAEL in the 90-day rat dietary study was 13.8 / 15.4 mg/kg bw/day in males and females respectively.

In mice, administration of iodosulfuron-methyl-sodium exerted toxicologically significant effects on the liver from 700 ppm (119 / 139 mg/kg bw/day in males and females respectively), with increased liver weight and hepatocyte enlargement observed eventually in both sexes. Other observations included lipofuscin accumulation in the liver as well as other signs of hepatotoxicity. No NOAEL was derived from the mouse 90-day study, with the LOAEL at 119 / 139 mg/kg bw/day in males and females respectively.

In the dog, dietary concentrations from approximately 40-50 mg/kg bw/day caused dose-dependent hematotoxic effects; at high doses (approximately 300 mg/kg bw/day), findings included hyperplasia of hematopoietic tissues and extramedullary hematopoiesis, both accompanied by a gradually-developing peripheral anemia. Other findings included decreased body weight gain. The NOAEL in the 90-day and 12-month dietary studies in the dog were very similar, at 8.1 / 8.4 mg/kg bw/day in males and females in the 90-day study and 7.37 / 7.25 mg/kg bw/day in males and females in the 12-month study.

Report:	[redacted], 1998;M-181091-01
Title:	Dog 12 month oral (dietary) toxicity study AE F115008 (Hoe 115008) code:AE F115008 00 ZC93 0001
Report No:	C000689
Document No(s):	M-181091-01-1
Guidelines:	**EU (=EEC): 91/414/EEC 5.8.1; JMAF: 4200; USEPA (=EPA): 83-1;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.3.1 - Oral 28-day study

Report:	[redacted], 1998;M-181089-01
Title:	Dog 28-day dietary range-finding study Hoe 115008 (AE F115008) technical substance Code: Hoe 115008 00 ZC93 0001
Report No:	C000688
Document No(s):	M-181089-01-1
Guidelines:	**EU (=EEC): CA 5.3.1.3; JMAF: 4200; USEPA (=EPA): 82-1;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.3.2 - Oral 90-day study

Report:	[redacted];[redacted];1997;M-142651-01
Title:	90-day dietary repeat dose study on rat with 4 week regression Hoe 115008 93.8 % w/w Code: Hoe 115008 00 ZC93 0001
Report No:	A58942
Document No(s):	M-142651-01-1
Guidelines:	**EU (=EEC): 78/831 Ann. V Part B; OECD: 408 Sect. 4; USEPA (=EPA): F 82-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-180321-01
Title:	Dog 90-day oral (dietary) toxicity study Hoe 115008 (AE F115008) technical substance Code: Hoe 115008 00 ZC89 0001
Report No:	C000173
Document No(s):	M-180321-01-1
Guidelines:	**EU (=EEC): AIIA/CA 5.3.2.2; JMAF: 4200; USEPA (=EPA): 82-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1997;M-143075-01
Title:	Mouse 90-day dietary repeat dose study (report and addendum) Hoe 115008 93.8 % w/w Code: Hoe 115008 00 ZC93 0001
Report No:	A59001
Document No(s):	M-143075-01-1
Guidelines:	**EU (=EEC): 78/831 Ann. V IIIB; JMAF: 4200; OECD: 408; USEPA (=EPA): F 82-1;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.3.3 - Other routes

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.4 - Genotoxicity testing

The genotoxicity of iodosulfuron-methyl-sodium was assessed in an earlier EU review of the active substance, however these data are summarized here for reference in grey type. Further information is available in the Baseline Dossier provided by Bayer CropScience and in the Monograph.

Study (Reference)	Purity (%)	Test system	Concentration / Dose levels	Results
Bacterial reverse mutation test (Ames test) ([redacted], 1993 M-132017-01-1)	97.4	*S. typhimurium*, strains TA 100, TA 1535, TA 1537, TA 98 *E. coli*, strain WP2uvra	4-5000 µg/plate, ± S9 mix	Negative
Mammalian cell gene mutation (HPRT test) ([redacted], 1996 M-141032-01-1)	88.7	HPRT locus V79 Chinese hamster cells	100-2649 µg/ml, ± S9 mix	Negative
DNA damage and repair (UDS test) ([redacted], 1996 M-141073-01-1)	88.7	Rat primary hepatocytes	0.03-3000 µg/ml	Negative
Chromosomal aberration *in vitro* ([redacted], 1996 M-141224-01-1)	88.7	Lung fibroblasts of Chinese hamster V79	1000-1500 µg/ml, without S9; 1500-2649 µg/ml, with S9	Negative
Chromosomal aberration (micronucleus test) *in vivo* ([redacted], 1996 M-140992-01-1)	88.7	SHOE:NMRI mice (male and female)	500, 1000, 2000 mg/kg bw	Negative

Testing for potential genotoxic properties of iodosulfuron-methyl-sodium in several *in vitro* and *in vivo* test systems on different endpoints gave consistently negative results.

CA 5.4.1 - In vitro studies

Report:	[redacted]; [redacted]; 1993;M-132017-01
Title:	Mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli Hoe 115008 substance, technical Code: Hoe 115008 00 ZC97 0001
Report No:	A51035
Document No:	M-132017-01-1
Guidelines:	**EU (=EEC): -OECD: ; USEPA (=EPA):;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted]; [redacted]; 1996;M-141224-01
Title:	In vitro mammalian chromosome aberration test in V79 Chinese hamster cells Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A57511
Document No:	M-141224-01-1
Guidelines:	**EU (=EEC): 92/69/B.10.; OECD: 473; USEPA (=EPA): 798.5375;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted]; [redacted];1996;M-141703-01
Title:	Detection of DNA strand breaks in primary hepatocytes of male rats in vitro UDS test in primary rat hepatocytes Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A57977
Document No:	M-141703-01-1
Guidelines:	**EU (=EEC): 88/302,L 133.; OECD: 482; USEPA (=EPA): Subd.F;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted]; [redacted];1996;M-141032-01
Title:	In vitro mammalian cell gene mutation test HPRT-test with V79 Chinese Hamster cells Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A57293
Document No:	M-141032-01-1
Guidelines:	**EU (=EEC): 87/302,L133; OECD: 476; USEPA (=EPA): 40,700 to end;Deviation not specified**
GLP/GEP:	**yes**

No new studies have been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

According to the new data requirements (Commission Regulation (EU) No. 283/2013 of 1 March 2013; Official Journal of the European Union, L 93/1, 3.4.2013) (1), the conduct of a phototoxicity study and a photomutagenicity study is required for plant protection active ingredients under certain conditions.

According to the new data requirements, as listed under point 5.2.7, the circumstances in which a phototoxicity study is required are "where the active substance absorbs electromagnetic radiation in the range 290-700 nm and is liable to reach the eyes of light-exposed areas of skin, either by direct contact or through systemic distribution. If the ultraviolet / visible molar extinction / absorption coefficient of the active substance is less than 10 L x mol-1 x cm-1, no toxicity testing is required."

For photomutagenicity, the requirements as specified under point 5.4 are as follows: "Special testing requirements in relation to photomutagenicity may be indicated by the structure of a molecule. If the ultraviolet / visible molar extinction / absorption coefficient of the active substance and its major metabolites is less than 1000 L x mol-1 x cm-1, photomutagenicity testing is not required." Based on this text, it is the understanding of Bayer CropScience that a photomutagenicity study may be triggered based on the molecular structure and related photochemical properties, but not automatically by the molar extinction / absorption coefficient. This is in clear contrast to the requirement for a phototoxicity study, which is only triggered by the molar extinction / absorption coefficient.

A study was performed with iodosulfuron-methyl-sodium to determine the UV spectrum in pure water, in water adjusted to pH 1 with hydrochloric acid, and in water adjusted to pH 13 with sodium hydroxide (2).

The UV-visible absorption spectra of iodosulfuron-methyl-sodium yielded two peaks in the case of neutral pure water and basic medium, while in acidic conditions there were three peaks of absorption.

Table CA 5.4.1-1 shows the molar extinction coefficients of these peaks as well as the molar extinction coefficients measured at 290, 295, and 310 nm for all three experiments.

Table CA 5.4.1-1. Maximum molar extinction coefficients for iodosulfuron-methyl-sodium in neutral, acidic, and basic media

Solvent	Wavelength	Molar extinction coefficient (L / mol * cm)
Water	199	38752
	237	23423
	290	1720
	295	1183
	310	62
Water / sodium hydroxide pH 13.0	218	24744
	236	27561
	290	4300
	295	2913
	310	238
Water / hydrogen chloride pH 1.0	202	37518
	229	34209
	289	3582
	290	3589
	295	3454
	310	1025

A phototoxicity study was conducted with iodosulfuron-methyl sodium (data point KCA 5.2.7) and was clearly negative at all concentrations of iodosulfuron-methyl sodium tested.

The quantum yield of phototransformation for iodosulfuron-methyl-sodium has been calculated to be $\Phi = 2.68 * 10^{-2}$. This quantum yield shows a low turnover of the energy of photons into chemical reactivity. Since light absorption itself is not responsible for any phototoxic reactions, but rather the subsequent steps in the energy cascade, i.e. the dissipation of the energy transferred to the molecule, the likelihood for iodosulfuron-methyl sodium to undergo photochemical reactions is very low due to its low quantum yield.

The intensity of sunlight reaching the surface of the earth depends on the wavelength and the specific absorption by the atmosphere. This atmospheric absorption is responsible for the phenomenon that, in contrast to the physical relation of increasing radiation energy with decreasing wavelengths, the energy of sunlight decreases with decreasing wavelength below 480 nm under environmental conditions, as with wavelengths below 480 nm fewer photons penetrate the atmosphere and each the surface of the earth.

The American Society for Testing and Materials (ASTM) has published wavelength-dependent irradiance data and solar spectra measured at the surface of the globe (ASTM G-173-03 Reference Spectra; http://rredc.nrel.gov/solar/spectra/am1.5/). The most relevant spectrum for Europe is that for a 37° sun-facing, tilted surface, for the wavelength range 280-1000 nm at sea level altitude.

Atmospheric absorption below 290-295 nm leads to intransparency, so that no sunlight at wavelengths below 295 nm reaches the surface, due to complete absorption of light by the ozone layer in the stratosphere. The absorption is already efficient above 290 nm, so that the sunlight in the UV B range (280-320 nm) has only low spectral irradiance (light intensity).

Thus, significant photochemical effects below 295 nm in the natural environment are not expected as the sunlight energy below 295 nm is too low. Likewise, phototoxic and photomutagenic effects of a substance which are directly linked to photoreactions and initiated by sunlight are not expected in this range.

Mean intensities of the global solar spectrum during spring and summer have been collected by Atlas Material Testing GmbH. These intensity data given for different types of solar energy and different sun elevation angles are shown in Table CA 5.4.1-2.

Table CA 5.4.1-2. Global irradiation intensity data, with intensity given as Watt m^{-2} nm^{-1}

Type of sunlight	Wavelength, nm		Sun elevation angle				
	From	To	90°	41.8°	30°	20°	10°
UV B	290	320	3.5	1.4	0.7	0.3	0.1
UV A	320	400	61.9	35.6	24.0	14.1	5.7
Vis	400	780	591.3	346.4	239.9	143.4	53.2
IR	780	3000	443.3	272.4	193.3	120.7	48.6

It is clear from this data that solar energy below 320 nm which reaches the surface of the earth is very low. As shown in Table CA 5.4.1-1, the extinction coefficient of iodosulfuron-methyl sodium is below 1000 L mol-1 cm-1 at 310 nm in unbuffered and basic media, and very near the threshold of 1000 L mol-1 cm-1 at 310 nm in acidic media.

In summary, iodosulfuron-methyl sodium has a very low quantum yield, a low extinction coefficient at wavelengths at which there is a significant amount of energy reaching the earth, and was completely negative in the phototoxicity study. With these factors, and in the absence of a validated guideline for photomutagenicity, it is the position of Bayer CropScience that a photomutagenicity study is not required.

CA 5.4.2 - In vivo studies in somatic cells

Report:	[redacted]; [redacted];1996;M-140992-01
Title:	Mammalian erythrocyte micronucleus test in male and female NMRI mice Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A57253
Document No:	M-140992-01-1
Guidelines:	**EU (=EEC): 92/69, L 383 A B.12; OECD: 474; USEPA (=EPA): 798.5395;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.4.3 - In vivo studies in germ cells

As all five genotoxicity studies were negative and no evidence for carcinogenicity was observed in long-term experiments in the rat and mouse, genotoxicity tests using germ cells were not triggered.

CA 5.5 - Long-term toxicity and carcinogenicity

The carcinogenicity and chronic toxicity of iodosulfuron-methyl-sodium was assessed in an earlier EU review of the active substance, however these data are summarized here for reference in gray type. Further information is available in the Baseline Dossier provided by Bayer CropScience and in the Monograph.

Study (Reference)	Species	Dose levels	NOAEL	LOAEL and findings
Combined chronic toxicity / carcinogenicity ([redacted], 1998B M-181889-01-1)	Rat	0, 70, 700, 7000 ppm M: 0, 2.96, 29.7, 331 mg/kg bw/day F: 0, 3.91, 39.1, 452 mg/kg bw/day	70 ppm M: 2.96 mg/kg bw/day F: 3.91 mg/kg bw/day	Decreased body weight
Oncogenicity study ([redacted], 1998f M-181896-01-1)	Mouse	0, 35, 350, 1750 ppm M: 0, 5.15, 54.2, 279 mg/kg bw/day F: 0, 5.72, 57.6, 277 mg/kg bw/day	35 ppm M: 5.15 mg/kg bw/day F: 5.72 mg/kg bw/day	Hepatotoxicity

In the rat, administration of iodosulfuron-methyl-sodium at dietary concentrations from 700 ppm for up to 24 months caused decreases in body weight gain and terminal body weight in both males and females. No findings were noted in clinical biochemistry, organ weight, or macro- or micropathology. A NOEL of 70 ppm (2.96 / 3.91 mg/kg bw/day in males and females respectively) was determined.

In the mouse, hepatotoxicity similar to that observed in the 90-day study was also seen in the 18-month dietary toxicity study, with centrilobular hepatocyte enlargement, increased mononuclear cell infiltration, pigment deposition, and lipofuscin storage noted generally from 350 ppm. A NOEL of 35 ppm (5.15 / 5.72 mg/kg bw/day) was established for this study.

Tumor incidence was not increased in either the rat or the mouse after lifetime administration of iodosulfuron-methyl-sodium.

Report:	[redacted];1998;M-181889-01
Title:	Rat dietary combined chronic toxicity and oncogenicity study AE F115008 (Hoe 115008) Code: AE F115008 00 1C89 0001
Report No:	C001157
Document No(s):	M-181889-01-1
Guidelines:	**EU (=EEC): 67/548 Annex V, Part B ;BMAF: 4200; OECD: 453; USEPA (=EPA): F 83-1, 83-2;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-181896-01
Title:	Mouse dietary 18 month oncogenicity study AE F115008 (Hoe 115008) Code: AE F115008 00 1C89 0001
Report No:	C001158
Document No(s):	M-181896-01-1
Guidelines:	**EU (=EEC): 88/302, Ann. V, B;BMAF: 4200; OECD: 451; USEPA (=EPA): F 83-2;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.6 - Reproductive toxicity

The reproductive and developmental toxicity of iodosulfuron-methyl sodium was assessed in an earlier EU review of the active substance, however these data are summarized here for reference in gray type. Further information is available in the Baseline Dossier provided by Bayer CropScience and in the Monograph.

Study type (Reference)	Species	Dose levels	NOAEL and findings at LOAEL
2-generation study ([redacted], 1998 M-182647-01-1)	Rat	0, 50, 500, 5000 ppm	Parental: NOAEL = 500 ppm (~ 50 mg/kg bw/day) Findings: decr body wt Offspring: NOAEL = 500 ppm (~ 50 mg/kg bw/day) Findings: incr peri- / post-natal mortality, decr body wt
Developmental toxicity study ([redacted], 1996 M-141359-01-1)	Rat	0, 100, 315, 1000 mg/kg bw/day	Maternal: NOAEL = 315 mg/kg bw/day Findings: decr body wt Fetal: NOAEL = 315 mg/kg bw/day Findings: skeletal retardation
Developmental toxicity study ([redacted], 1996 M-141358-01-1)	Rabbit	0, 25, 100, 400 mg/kg bw/day	Maternal: NOAEL = 25 mg/kg bw/day Findings: decr body wt, clinical signs Fetal: NOAEL = 100 mg/kg bw/day Findings: skeletal retardation

In the rat 2-generation reproduction study, administration of iodosulfuron-methyl-sodium at dietary concentrations of up to 5000 ppm (from approximately 300 to approximately 1100 mg/kg bw/day, depending on the phase of the study) did not have any effect on fertility, reproduction, mating behavior, or offspring development. Parental toxicity, indicated by decreased body weight gain, was noted at 5000 ppm in both the first and second generation beginning in the pre-mating phase and continuing through the study. At 5000 ppm, offspring toxicity was limited to an increased number of dead pups at birth, increased perinatal mortality, increased incidence of renal pelvis dilation, and decreased pup body weight and body weight gain. The NOAEL in this study for both adult and offspring was 500 ppm (approximately 50 mg/kg bw/day).

In the rat developmental toxicity study, maternal findings were only noted at 1000 mg/kg bw/day and included decreased food consumption and decreased body weight. The only fetal findings observed in the study were delayed ossification, occasional blood in the abdominal cavity, and distended renal pelvis in some fetuses. The NOAEL in both dams and fetuses was 315 mg/kg bw/day.

In the rabbit developmental toxicity study, dams showed decreased body weight gain at doses of 100 mg/kg bw/day and above. The maternal NOAEL was therefore 25 mg/kg bw/day. In the fetuses at 400 mg/kg bw/day only, there was a slight decrease in ossification of sternebrae, suggesting a slight delay in embryofetal development. The fetal NOAEL for this study was 100 mg/kg bw/day.

There were no teratogenic effects observed in either the rat or the rabbit developmental toxicity studies.

CA 5.6.1 - Generational studies

Report:	[redacted]q; [redacted];1998;M-182647-01
Title:	Range finding feeding-reproduction study for a two-generation reproduction toxicity study in rats Hoe 115008 substance technical Code: Hoe 115008 00 ZC89 0001
Report No:	C001447
Document No(s):	M-182647-01-1
Guidelines:	**JMAF: 1985; OECD: Sec.4, 416, 1983; USEPA (=EPA): §83-4, 1984;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted]; [redacted];1998;M-182825-01
Title:	Two-generation feeding-reproduction toxicity study in rats Hoe 115008 substance technical Code: Hoe 115008 00 ZC89 0001
Report No:	C001514
Document No(s):	M-182825-01-1
Guidelines:	**JMAF: 59 NoSan 200, 1985; OECD: 416; USEPA (=EPA): §83-4;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

Report:	[redacted]; [redacted];2014;M-502267-01
Title:	Regulatory toxicology - Position paper - Iodosulfuron-methyl-sodium - Response to initial questions from Kemi during 2014 re-registration process
Report No:	M-502267-01-1
Document No(s):	M-502267-01-1
Guidelines:	**not specified;not specified**
GLP/GEP:	**n.a.**

A question was raised by KEMI regarding the toxicology section of the AIR-3 dossier for iodosulfuron-methyl-sodium and was addressed in the position paper which will be summarized here.

Question from KEMI:

> In the two generation toxicity study in the rat ([redacted], 1998, Study No. C001514) increased incidence of dilated renal pelvis was noted at the dose level of 5000 ppm in both F1 and F2 pups. Increased incidence of renal pelvis was also noted in the developmental toxicity study in the rat ([redacted], 1996, Report No. A57677) at the highest dose level (1000 ppm). It is stated by the study author that incidences were within the historical range of the rat strain used. However no historical control data is available to support this statement. Furthermore increased incidences of blood in the abdominal cavity was noted at the highest dose level in the rat developmental toxicity study. The incidence of this finding was also considered to be within the range of historical control data according to study author, but no historical control data is available. Could you please submit historical control data for the findings noted in the studies mentioned above?

The only two-generation reproduction studies in the company internal archives which were conducted in the same laboratory using the same strain of animals from the same source were the range-finding

study and definitive study conducted with iodosulfuron-methyl-sodium ([redacted], 1998, Study No. C001514). The laboratory has been closed in the intervening years and although historical control data was requested from the last owners of the laboratory such data was not received.

Dilated renal pelvis was observed in two adult animals and two pups in the control group of the range-finding study conducted with iodosulfuron-methyl-sodium. In the two-generation reproduction study, it was observed in one F1 adult in the control group.

Developmental toxicity studies conducted in the rat were extracted from the company internal archive and filtered for those studies conducted in the same lab and using the same strain of animal from the same source as the rat developmental toxicity study conducted with iodosulfuron-methyl-sodium. Data for dilated renal pelvis and blood in the abdominal cavity were collected from the resulting 20 studies including [redacted], 1996, Report No. A57677.

Data collated from these 20 studies shows that the incidence of dilated renal pelvis in the rat developmental toxicity study with iodosulfuron-methyl-sodium is within the historical control incidence when considered on a litter basis (6 litters affected at 1000 mg/kg bw/day, vs 7 litters affected in one study in the historical database) or slightly outside the historical control incidence when considered on a fetal basis (12 fetuses affected at 1000 mg/kg bw/day, vs 9 fetuses affected in one study in the historical database). This study was conducted at the same now-closed laboratory as was the two-generation reproduction study, and similarly although historical control data was requested it was not received. It is possible that other studies from this laboratory were referred to for compilation of the historical control database referenced in these two reports, but are not in our internal archive.

Dilated renal pelvis is a relatively common finding in the Wistar rat. One publication (Burton et al., 1979) showed incidence in adults of 13.8% in males and 4.5% in females, with overall incidence of 11.3%. O'Donoghue and Wilson (1977) report an incidence in males in an established colony of approximately 30%, which spontaneously reverted in that same colony "virtually to nothing" within apparently a very short time.

The incidental occurrence of dilated renal pelvis in the rat is a normal morphological variation and is not by itself an indicator of pathological effects of a compound in the renal tract. Dilation of the renal pelvis which is not accompanied by pathological findings in the renal parenchyma (changes to the transitional cell epithelium, renal tubular damage, inflammatory infiltrate, etc) is generally not of any toxicological significance. The sporadic observation of dilated renal pelvis in the two-generation reproduction study was not accompanied by other significant macroscopic findings in the kidney or the rest of the urinary tract.

The potential effect of chronic administration of iodosulfuron-methyl-sodium in the rat can be examined the rat two-year chronic / oncogenicity study ([redacted], 1988), in which animals were fed diets containing iodosulfuron-methyl-sodium at up to 7000 ppm for up to two years. There were no relevant increases in pathological findings in either the kidney or the urinary bladder in this study.

In summary,

- Dilated renal pelvis is a fairly frequent finding in the Wistar rat;
- There are no findings in long-term studies with iodosulfuron-methyl-sodium which suggest that dilated renal pelvis observed in either the two-generation reproduction study or the developmental toxicity study is a toxicologically relevant finding;
- The incidence of dilated renal pelvis in the two-generation reproduction study shows no relationship to dose; and
- The incidence of dilated renal pelvis in the F1 adults is much lower than that which would normally be expected if its incidence in the rat developmental toxicity study were permanent.

Based on these findings, the incidence of dilated renal pelvis in the rat developmental toxicity study and the two-generation reproduction study conducted with iodosulfuron-methyl-sodium is not an indication of a toxic effect of the active ingredient.

The incidence of blood in the abdominal cavity in the rat developmental toxicity study (5 litters, 6 fetuses affected at 1000 mg/kg bw/day) is within the historical range (7 litters, 10 fetuses).

CA 5.6.2 - Developmental toxicity studies

Report:	[redacted];[redacted];1996;M-140665-01
Title:	Range finding embryotoxicity study after oral administration in Wistar rats Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A56889
Document No(s):	M-140665-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Report:	[redacted];[redacted];1996;M-141359-01
Title:	Oral developmental toxicity (teratogenicity) study - rat Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A57677
Document No(s):	M-141359-01-1
Guidelines:	**EU (=EEC): 88/302; JMAFF: ; OECD: 414; USEPA (=EPA): Subd.F,83-3;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];2014;M-502267-01
Title:	Regulatory toxicology - Position paper - Iodosulfuron-methyl-sodium - Response to initial questions from Kemi during 2014 re-registration process
Report No:	M-502267-01-1
Document No(s):	M-502267-01-1
Guidelines:	**not specified;not specified**
GLP/GEP:	**n.a.**

A question was raised by KEMI regarding the toxicology section of the AIR-3 dossier for iodosulfuron-methyl-sodium and was addressed in the position paper which will be summarized here.

Question from KEMI:

> In the two generation toxicity study in the rat ([redacted], 1998, Study No. C001514) increased incidence of dilated renal pelvis was noted at the dose level of 5000 ppm in both F1 and F2 pups. Increased incidence of renal pelvis was also noted in the developmental toxicity study in the rat ([redacted], 1996, Report No. A57677) at the highest dose level (1000 ppm). It is stated by the study author that incidences were within the historical range of the rat strain used. However no historical control data is available to support this statement. Furthermore increased incidences of blood in the abdominal cavity was noted at the highest dose level in the rat developmental toxicity study. The incidence of this finding was also considered to be within the range of historical control data according to study author, but no historical control data is available. Could you please submit historical control data for the findings noted in the studies mentioned above?

The only two-generation reproduction studies in the company internal archives which were conducted in the same laboratory using the same strain of animals from the same source were the range-finding study and definitive study conducted with iodosulfuron-methyl-sodium ([redacted], 1998, Study No. C001514). The laboratory has been closed in the intervening years and although historical control data was requested from the last owners of the laboratory such data was not received.

Dilated renal pelvis was observed in two adult animals and two pups in the control group of the range-finding study conducted with iodosulfuron-methyl-sodium. In the two-generation reproduction study, it was observed in one F1 adult in the control group.

Developmental toxicity studies conducted in the rat were extracted from the company internal archive and filtered for those studies conducted in the same lab and using the same strain of animal from the same source as the rat developmental toxicity study conducted with iodosulfuron-methyl-sodium. Data for dilated renal pelvis and blood in the abdominal cavity were collected from the resulting 20 studies including [redacted], 1996, Report No. A57677.

Data collated from these 20 studies shows that the incidence of dilated renal pelvis in the rat developmental toxicity study with iodosulfuron-methyl-sodium is within the historical control incidence when considered on a litter basis (6 litters affected at 1000 mg/kg bw/day, vs 7 litters affected in one study in the historical database) or slightly outside the historical control incidence when considered on a fetal basis (12 fetuses affected at 1000 mg/kg bw/day, vs 9 fetuses affected in one study in the historical database). This study was conducted at the same now-closed laboratory as was the two-generation reproduction study, and similarly although historical control data was requested it was not received. It is possible that other studies from this laboratory were referred to for compilation of the historical control database referenced in these two reports, but are not in our internal archive.

Dilated renal pelvis is a relatively common finding in the Wistar rat. One publication (Burton et al., 1979) showed incidence in adults of 13.8% in males and 4.5% in females, with overall incidence of 11.3%. O'Donoghue and Wilson (1977) report an incidence in males in an established colony of

approximately 30%, which spontaneously reverted in that same colony "virtually to nothing" within apparently a very short time.

The incidental occurrence of dilated renal pelvis in the rat is a normal morphological variation and is not by itself an indicator of pathological effects of a compound in the renal tract. Dilation of the renal pelvis which is not accompanied by pathological findings in the renal parenchyma (changes to the transitional cell epithelium, renal tubular damage, inflammatory infiltrate, etc) is generally not of any toxicological significance. The sporadic observation of dilated renal pelvis in the two-generation reproduction study was not accompanied by other significant macroscopic findings in the kidney or the rest of the urinary tract.

The potential effect of chronic administration of iodosulfuron-methyl-sodium in the rat can be examined the rat two-year chronic / oncogenicity study ([redacted], 1988), in which animals were fed diets containing iodosulfuron-methyl-sodium at up to 7000 ppm for up to two years. There were no relevant increases in pathological findings in either the kidney or the urinary bladder in this study.

In summary,

- Dilated renal pelvis is a fairly frequent finding in the Wistar rat;
- There are no findings in long-term studies with iodosulfuron-methyl-sodium which suggest that dilated renal pelvis observed in either the two-generation reproduction study or the developmental toxicity study is a toxicologically relevant finding;
- The incidence of dilated renal pelvis in the two-generation reproduction study shows no relationship to dose; and
- The incidence of dilated renal pelvis in the F1 adults is much lower than that which would normally be expected if its incidence in the rat developmental toxicity study were permanent.

Based on these findings, the incidence of dilated renal pelvis in the rat developmental toxicity study and the two-generation reproduction study conducted with iodosulfuron-methyl-sodium is not an indication of a toxic effect of the active ingredient.

The incidence of blood in the abdominal cavity in the rat developmental toxicity study (5 litters, 6 fetuses affected at 1000 mg/kg bw/day) is within the historical range (7 litters, 10 fetuses).

Report:	[redacted];2015;M-508521-01
Title:	Regulatory toxicology - Position paper - Iodosulfuron-methyl-sodium - Response to further questions from Kemi during re- registration process
Report No:	M-508521-01-1
Document No(s):	M-508521-01-1
Guidelines:	**not specified;not specified**
GLP/GEP:	**n.a.**

A further question was raised by KEMI regarding the toxicology section of the AIR-3 dossier for iodosulfuron-methyl-sodium and was addressed in the position paper which will be summarized here.

Question from KEMI:

1. In the rat developmental toxicity study ([redacted] 1996, Report no. A57677) increased incidence of retarded ossification, haematomas in the liver and distended ureter was noted in pups of the high dose group. Could you please submit historical control data for the following findings:
   - Slight or non-ossification of skull
   - Weakly or non-ossification of sacral vertebral arch
   - Weakly or non-ossification of sternebrae
   - Non-ossified forepaw metacarpale 5
   - Haematoma in the liver and distended ureter
2. In the rabbit developmental toxicity study ([redacted] 1996, Report no. A57676) increased incidence of non or weakly ossified sternebrae was noted in the high dose group. Could you please submit historical control data for this finding.

Developmental toxicity studies conducted in the rat were extracted from the company internal archive and filtered for those studies conducted in the same lab and using the same strain of animal from the same source as the rat developmental toxicity study conducted with iodosulfuron-methyl-sodium.

In the rat, the incidence of weakly or non-ossified sacral vertebral arch and of non-ossified or weakly ossified sternebra(e) was within the historical control data on both a fetal and a litter basis. The incidence of slight or non-ossification of individual skull bones exceeded the historical control incidence on both a litter and a fetal basis. However, it should be noted that the incidence of this finding was quite high in the control group of the iodosulfuron-methyl-sodium (16 litters, 49 fetuses) when compared to maximum incidence in the historical control data (18 litters, 55 fetuses). The incidence of non-ossified metacarpale 5 at the high dose of 1000 mg/kg bw/day slightly exceeded the historical control data on a fetal basis only (87 fetuses at 1000 mg/kg bw/day vs 79 fetuses in the historical data).

These observations are indicative of slightly delayed skeletal development rather than of a frank effect of iodosulfuron-methyl-sodium on fetal development. Although both fetal and maternal body weight are similar between the high dose and the control groups at the end of the study, maternal body weight showed a clear effect at both 315 and 1000 mg/kg bw/day during the treatment period. It is highly likely that this decreased body weight during compound administration slightly delayed normal fetal development thus leading to slight delays in fetal skeletal ossification.

The incidence of both haematoma in the liver and of distended ureter slightly exceeded the historical control incidence, although these findings were not statistically significant in any dose group. The low incidence even at the high dose group suggests a lack of toxicological relevance.

For the rabbit, developmental toxicity studies conducted in the rabbit were extracted from the company internal archive and filtered for those studies conducted at the same lab using the same strain of animal from the same source as the rabbit developmental toxicity studies conducted with iodosulfuron-methyl-sodium. The incidence of weakly or non-ossified sternebrae at the top dose slightly exceeded the historical control data when considered on the basis of fetal incidence (46 fetuses affected in the study conducted with iodosulfuron-methyl-sodium versus 34 fetuses in the historical control data). Maternal body weight at the top dose was significantly reduced throughout the treatment period, and it is probably that this decreased maternal body weight led to slight delays in fetal growth and development.

Report:	[redacted]; [redacted];1996;M-140510-01
Title:	Range finding embryotoxicity study after oral administration in Himalayan rabbits Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A56721
Document No(s):	M-140510-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Report:	[redacted]; [redacted];1996;M-141358-01
Title:	Rabbit oral developmental toxicity (teratogenicity) study Hoe 115008 substance, technical Code: Hoe 115008 00 ZC89 0001
Report No:	A57676
Document No(s):	M-141358-01-1
Guidelines:	**EU (=EEC): 88/302; JMAF: ; OECD: 414,Sect.4; USEPA (=EPA): Subd.F,83-3;Deviation not specified**
GLP/GEP:	**yes**

No new study has been performed, and there are no new scientific findings that influence the regulatory interpretation of the official evaluation of the active substance.

CA 5.7 - Neurotoxicity studies

No indication of neurotoxicity was observed in any of the studies conducted with iodosulfuron-methyl-sodium in rat, mouse, or dog, and thus neurotoxicity studies were not required. No new study has been performed that would alter this conclusion.

CA 5.7.1 - Neurotoxicity studies in rodents

No indication of neurotoxicity was observed in any of the studies conducted with iodosulfuron-methyl-sodium in rat, mouse, or dog, and thus neurotoxicity studies were not required. No new study has been performed that would alter this conclusion.

CA 5.7.2 - Delayed polyneuropathy studies

No indication of neurotoxicity was observed in any of the studies conducted with iodosulfuron-methyl-sodium in rat, mouse, or dog, and thus neurotoxicity studies were not required. No new study has been performed that would alter this conclusion.

CA 5.8 - Other toxicological studies

CA 5.8.1 - Toxicity studies of metabolites

The toxicity of several metabolites of iodosulfuron-methyl-sodium was assessed in an earlier EU review of the active substance, however these data are summarized here for reference in gray type. Further information is available in the Baseline Dossier provided by Bayer CropScience and in the Monograph.

AE F059411 (2-amino-4-methoxy-6-methyl-S-triazine) is a metabolite of iodosulfuron-methyl-sodium. Testing for acute oral toxicity of AE F059411 shows that the LD50 value in rats and the

symptoms of toxicity are similar to the acute toxic profile of iodosulfuron-methyl-sodium itself. The Ames test on AE F059411 was negative. Thus, AE F059411 does not pose any particular hazard potential different from that of the active substance.

The metabolite AE F114368 was only detected during metabolism studies at minor amounts, and mainly in the fecal samples. Testing for acute oral toxicity of AE F114368 shows that the LD50 value in rats and the symptoms of toxicity are quite similar to the acute toxic profile of iodosulfuron-methyl-sodium itself. The Ames test on AE F114368 was negative. Thus, AE F114368 does not pose any particular hazard potential different from that of the active substance.

The metabolite AE F143133 was only detected during metabolism studies at minor amounts in urine samples. Testing for acute oral toxicity of AE F143133 shows that the LD50 value in rats and the symptoms of toxicity are quite similar to the acute toxic profile of iodosulfuron-methyl-sodium itself. The Ames test on AE F143133 was negative. Thus, AE F143133 does not pose any particular hazard potential different from that of the active substance.

Report:	[redacted];[redacted];1989;M-182294-01
Title:	Acute oral toxicity study in rats with 2-amino-4-methoxy-6-methyl-s-triazine
Report No:	C001299
Document No:	M-182294-01-1
Guidelines:	**OECD: 401; USEPA (=EPA): TSCA 40, § 81-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-182299-01
Title:	Letter of access to use HLA Study No. 2319-132 for registration purposes 2-Amino-4-methoxy-6-methyl-s-triazin
Report No:	C001736
Document No:	M-182299-01-2
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Report:	[redacted];[redacted];[redacted];1998;M-181601-01
Title:	Bacterial reverse mutation test AE F059411 substance, technical Code: AE F059411 00 1C99 0001
Report No:	C000993
Document No(s):	M-181601-01-1
Guidelines:	**EU (=EEC): B.13 + B.14,92/69; OECD: 471, 1997; USEPA (=EPA): 798.5265,798.5100;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-182408-01
Title:	Acute oral toxicity in the male and female Sprague Dawley rat AE F114368 substance, technical Code: AE F114368 00 1C99 0001
Report No:	C001147
Document No(s):	M-182408-01-1
Guidelines:	**EU (=EEC): B.1., 92/69/EEC, 67/548/EEC ; JMAF: 1985; OECD: 401; USEPA (=EPA): F §81-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];[redacted];1998;M-181800-01
Title:	Bacterial reverse mutation test AE F114368 substance, technical Code: AE F114368 00 1C99 0001
Report No:	C001107
Document No(s):	M-181800-01-1
Guidelines:	**EU (=EEC): 92/69, L383, B14 + B13; OECD: 471, 21-Jul-1997; USEPA (=EPA): 798.5265, 798.5100;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-182169-01
Title:	Acute oral toxicity in the male and female Sprague Dawley rat AE F143133 substance, technical Code: AE F143133 00 1C98 0001
Report No:	C001252
Document No(s):	M-182169-01-1
Guidelines:	**EU (=EEC): B.1., 92/69/EEC, 67/548/EEC; JMAF: 1985; OECD: 401, 1981 update 1987; USEPA (=EPA): §81-2;540/9-82-025;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-182410-01
Title:	Bacterial reverse mutation test AE F143133 substance, technical Code: AE F143133 00 1C98 0001
Report No:	C001348
Document No(s):	M-182410-01-1
Guidelines:	**EU (=EEC): B.13. 14., L 383 A, 92/69/EEC; OECD: 471, 21.07.98; USEPA (=EPA): OPPTS 870.5100;Deviation not specified**
GLP/GEP:	**yes**

Further information on impurities wrongly assigned to this point in the baseline dossier, have been transferred to confidential information in document IIA.

CA 5.8.2 - Supplementary studies on the active substance

The toxicity of several impurities of iodosulfuron-methyl-sodium was assessed in an earlier EU review of the active substance, however these data are summarized here for reference in grey type. Further information is available in the Baseline Dossier provided by Bayer CropScience and in the Monograph.

The substance AE F114844 is the free acid and the last precursor stage of iodosulfuron-methyl-sodium. All studies in which iodosulfuron-methyl-sodium was administered by the oral route can also be used for the hazard assessment of AE F114844 as iodosulfuron-methyl-sodium will be present as the protonated free acid. The acute dermal toxicity and potential for mutagenicity of AE F114844 were determined separately. The acute dermal toxicity of AE F11844 was similar to that of the active substance iodosulfuron-methyl-sodium, and the Ames test was also negative. It can thus be stated that AE F114844 does not pose any hazard different from that of iodosulfuron-methyl-sodium itself.

Report:	[redacted];[redacted];1998;M-182172-01
Title:	Acute dermal toxicity in the male and female Sprague Dawley rat AE F114844 substance, technical Code: AE F114844 00 1C97 0001
Report No:	C001253
Document No(s):	M-182172-01-1
Guidelines:	**EU (=EEC): B.3., 92/69, 67/548; JMAF: 1985; OECD: 402, 1987; USEPA (=EPA): §81-2, 540/9-82-025;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1998;M-182403-01
Title:	Bacterial reverse mutation test AE F114844 substance, technical Code: AE F114844 00 1C97 0001
Report No:	C001344
Document No(s):	M-182403-01-1
Guidelines:	**EU (=EEC): B.13., B.14; 92/69/EEC, 1383 A; OECD: 471, 1997; USEPA (=EPA): OPPTS 870.5100;Deviation not specified**
GLP/GEP:	**yes**

For further information on impurities, please refer to confidential information in document JCA.

A mechanistic study to determine the reversibility of hematological effects observed after oral administration of iodosulfuron-methyl-sodium was conducted in the dog. A further endpoint of the study was to determine the possibility of potentiation of effects between iodosulfuron-methyl-sodium and the safener mefenpyr-diethyl. Dietary administration for four weeks of iodosulfuron-methyl-sodium alone at approximately 400 mg/kg bw/day, or in combination with mefenpyr-diethyl at varying doses, caused in some groups decreased body weight and / or food consumption, and decreased red cell parameters. There was no potentiation by mefenpyr-diethyl of the effects observed after iodosulfuron-methyl-sodium administration. The hematological findings observed in treated animals were shown to be fully reversible after cessation of treatment.

Report:	[redacted];[redacted];2001;M-454791-01
Title:	4-week toxicity study by oral route (dietary admixture) in beagle dogs followed by a 12-week treatment-free period
Report No:	21602 TSK
Document No:	M-454791-01-1
Guidelines:	**EEC Recommendation No. 96/54/EEC, B32, 30 September 1996;not specified**
GLP/GEP:	**yes**

I. MATERIALS AND METHODS

A. *MATERIALS:*

1. Test Material:

AE F115008

Description:	beige powder
Lot/Batch:	CR21436/02/950601
Purity:	87.1
CAS:	
Stability of test compound:	not stated in the report

AE F107892

Description:	brownish viscous liquid
Lot/Batch:	C01H8MV008
Purity:	95.2
CAS:	
Stability of test compound:	not stated in report

2. Vehicle and /or positive control: none

3. Test animals:

Species:	Dog
Strain:	Beagle
Age:	approximately 6 months old
Weight at dosing:	6.6-8.7 kg
Source:	[redacted], New York
Acclimation period:	8 days acclimation
Diet:	Dog diet 125 C2 (P2.5), [redacted] France
Water:	tap water
Housing:	individual housing in kennels with wood shavings
Environmental conditions –	
Temperature:	20 ± 5°C
Humidity:	50 ± 20%
Air changes:	at least 12 air changes per hour
Photoperiod:	12 hours light / 12 hours dark

B. *STUDY DESIGN:*

1. In life dates: 12 April 2001 – 25 July 2001

2. Animal assignment and treatment

During the pre-treatment period, the animals were selected according to the results of the clinical and laboratory examinations and allocated to groups according to a computerized stratification procedure.

The dose levels selected for iodosulfuron-methyl-sodium and mefenpyr-diethyl were chosen based on the results in previous 28- and 90-day studies with each compound. Iodosulfuron-methyl-sodium had been shown to have a marked effect on several hematological parameters (including erythrocyte count, hemoglobin concentration, and packed cell volume), while the effect of mefenpyr-diethyl at a similar dose in mg/kg bw/day had a much less severe effect. Nevertheless, concerns were raised regarding the possibility that mefenpyr-diethyl could potentiate the hematological effects of iodosulfuron-methyl-sodium, and thus this study was designed to test the effects observed when both compounds were administered together.

Both iodosulfuron-methyl-sodium and mefenpyr-diethyl were noted to have hematological effects at approximately 300-400 mg/kg bw/day, and thus the doses were selected in order to elicit clear effects with iodosulfuron-methyl-sodium alone, to test whether low doses of iodosulfuron-methyl-sodium and mefenpyr-diethyl administered together would have any effect on hematology, and to examine whether the effects due to a high dose of either iodosulfuron-methyl-sodium or mefenpyr-diethyl could be altered by co-administration of a low dose of the other compound. The resulting study design is shown in Table CA 5.8.2-01.

Table CA 5.8.2-01. Target doses, in mg/kg bw/day, of iodosulfuron-methyl-sodium and

mefenpyr-diethyl administered to male dogs for 28 days.

	Target dose, in mg/kg bw/day	
Group	**Iodosulfuron-methyl-sodium**	**Mefenpyr-diethyl**
Control	0	0
High-dose IMS*	400	0
Low-dose IMS / low-dose MFP	100	100
High-dose IMS / low-dose MFP	400	100
Low-dose IMS / high-dose MFP	100	400

* IMS = iodosulfuron-methyl-sodium; MFP = mefenpyr-diethyl

Animals in the group receiving iodosulfuron-methyl-sodium at 100 mg/kg bw/day and mefenpyr-diethyl at 400 mg/kg bw/day showed a marked body weight loss and were thus transferred to control diet for one week to allow them to regain condition. It was hypothesized that the taste and / or smell of the mefenpyr-diethyl were causing rejection of the feed and that the body weight loss was not a direct result of the administration of either test substance. This was tested by providing the animals with a diet containing only mefenpyr-diethyl to provide a high dose, again causing inappetance and body weight loss. This group was withdrawn from the hematological assessment prior to blood sampling on study day 14.

3. Diet preparation

iodosulfuron-methyl-sodium and mefenpyr-diethyl were mixed into dog diet at the concentrations shown in Table CA 5.8.2/05-02.

Table CA 5.8.2-02. Dietary concentrations of iodosulfuron-methyl-sodium and mefenpyr-diethyl in diets fed to male dogs for 28 days.

	Dietary concentration, in ppm	
Group	**Iodosulfuron-methyl-sodium**	**Mefenpyr-diethyl**
Control	0	0
High-dose IMS*	11000	0
Low-dose IMS / low-dose MFP	3000	3000
High-dose IMS / low-dose MFP	11000	3000
Low-dose IMS / high-dose MFP	3000	11000

* IMS = iodosulfuron-methyl-sodium; MFP = mefenpyr-diethyl

For each concentration, a premix of the total amount of each test substance was prepared with approximately 1000g of the diet using a pestle and mortar, or a mixer to incorporate mefenpyr-diethyl into the diet. The final mix was prepared by dispersing the premix in the remaining diet in a mixer for a period of 10 minutes. The dietary admixtures were made every week and stored at room temperature, protected from light in closed plastic bags. Each day, prior to delivery to the animal rooms, the dietary admixtures were mixed with water, adding 500ml of water for 300g of diet.

4. Statistics

Data to be statistically analyzed was first tested for normality of the distribution using the Kolmogorov-Lilliefors test. If the distributions were shown to be normal, the homogeneity of variances between groups was tested with the Bartlett test; the data was then assessed for statistical relevance using the Dunnett test if the variances were homogeneous, or the Dunn test if they were not homogeneous. If the distributions were not normal, the value was transformed logarithmically, then re-tested for normality of the distribution using the Kolmogorov-Lilliefors test. If this transformation rendered the distribution normal, the data was then tested as described above. Data which was not rendered into a normal distribution with logarithmic transformation was then tested for statistical significance using the Dunn test.

C. *METHODS:*

1. Observations

Each animal was checked at least twice a day including during weekends and public holidays for mortality or signs of morbidity, and clinical signs were recorded at least once a day.

2. Body weight

The body weight of each animal was recorded twice before allocation of the animals to treatment groups, on the first day of treatment, and once a week until the end of the study.

3. Food consumption

The quantity of food consumed was recorded for each animal by weighing the quantity given and that remaining the following morning.

4. Hematology

Blood samples were taken without anesthesia, prior to feeding and following an overnight fast of at least 14 hours, once a week during the pre-treatment period, on study days 1 (the first day of treatment) and 7 for all animals, and on study days 14, 21, 28, 42, 56, and 70 for all animals except the group receiving a low dose of iodosulfuron-methyl-sodium and a high dose of mefenpyr-diethyl.

5. Sacrifice and pathology

Animals were not sacrificed at the end of the study, but were returned to stock.

II. RESULTS AND DISCUSSION

A. OBSERVATIONS:

1. Clinical signs of toxicity

In animals receiving iodosulfuron-methyl-sodium at 11000 ppm and mefenpyr-diethyl at 3000 ppm, thin appearance was noted in three animals during the treatment period and into the beginning of the post-treatment period. Hypoactivity was noted in one dog in this group from week 3 to 4 of the treatment period.

In animals receiving iodosulfuron-methyl-sodium at 3000 ppm and mefenpyr-diethyl at 11000 ppm, a thin appearance was noted in two of the animals from weeks 4 to 6.

2. Mortality

No deaths occurred during the study.

B. BODY WEIGHT AND BODY WEIGHT GAIN:

As shown in Table CA 5.8.2-03, the only statistically significant effect on body weight was noted during the last week of the treatment period, in dogs which had initially received a high dose of mefenpyr-diethyl in conjunction with a low dose of iodosulfuron-methyl-sodium; this marked decrease in body weight was related to the inappetance caused by inclusion of a high concentration of mefenpyr-diethyl in the diet. However, both this group and the group receiving a high dose of iodosulfuron-methyl-sodium together with a low dose of mefenpyr-diethyl showed biologically significant decreases in body weight at several points during the treatment period. The effects on body weight and body weight gain largely disappeared during the reversibility period.

Table CA 5.8.2-03. Body weight and body weight gain, during the pre-treatment, treatment, and reversibility phase of the study, in dogs administered iodosulfuron-methyl-sodium alone or with mefenpyr-diethyl via the diet.

		Dietary concentration, in ppm				
Iodosulfuron-methyl-sodium		**0**	**11000**	**3000**	**11000**	**3000**
Mefenpyr-diethyl		**0**	**0**	**3000**	**3000**	**11000**
Body weight, g	Week -4	7.2	7.2	7.2	7.2	7.2
	Week -1	7.5	7.6	7.6	7.4	7.6
	Week 1	7.6	7.8	7.8	7.6	7.8
	Week 2	7.7	8.4	7.7	7.5	6.9
	Week 3	7.9	8.4	8.0	7.6	7.4
	Week 4	7.9	8.3	8.2	7.1	6.5*
	Week 5	8.2	8.5	8.4	7.0	7.3
	Week 6	8.1	8.3	8.5	7.4	7.6
	Week 7	8.1	8.4	8.7	7.5	7.8
	Week 8	8.4	8.7	9.0	7.8	8.2
	Week 9	8.4	8.8	9.1	8.0	8.2
	Week 10	8.3	8.9	9.2	8.1	8.5
	Week 11	8.2	9.0	9.3	8.2	8.5
Body weight gain, kg	Week -4 to Week 1 (pre-treatment)	0.4	0.6	0.6	0.4	0.6
	Week 1 to Week 5 (treatment)	0.6	0.7	0.6	-0.6	-0.5
	Week 5 to Week 11 (reversibility)	0.0	0.5	0.9	1.0	1.2

* statistically significant at $p < 0.05$.

C. FOOD CONSUMPTION:

Food consumption was statistically significantly decreased on several occasions in the groups receiving both iodosulfuron-methyl-sodium and mefenpyr-diethyl in the diet. In the group receiving 3000 ppm of both compounds, food consumption was only statistically significantly decreased on the first two days of treatment, and returned to normal levels by study day 11. Food consumption, in g/animal/day, is shown in Table CA 5.8.2-04.

Table CA 5.8.2-04. Food consumption in g/animal/day, during the pre-treatment, treatment, and reversibility phase of the study, in dogs administered iodosulfuron-methyl-sodium alone or with mefenpyr-diethyl via the diet.

		Dietary concentration, in ppm				
Iodosulfuron-methyl-sodium		**0**	**11000**	**3000**	**11000**	**3000**
	Mefenpyr-diethyl	**0**	**0**	**3000**	**3000**	**11000**
Pre-treatment	Day -7	736.4	796.4	799.9	801.3	801.3
Treatment	Day 1	800.4	630.2	213.0**	360.7*	104.9**
	Day 8	810.5	770.3	737.8	606.8	802.4[a]
	Day 15	798.0	686.8	796.4	494.0	132.1**[b]
	Day 22	794.8	645.4	795.1	397.4	796.5[a]
Reversibility	Day 29	798.6	799.0	801.9	808.2	805.1
	Day 36	803.1	796.4	795.2	801.6	801.0
	Day 43	824.1	825.1	816.4	825.3	835.1
	Day 50	803.7	803.0	804.4	804.2	804.2
	Day 57	805.3	808.7	818.8	825.6	826.8*
	Day 64	807.8	808.3	803.5	807.6	800.2
	Day 71	799.8	798.7	799.1	800.1	801.0
	Day 76	802.7	806.2	795.8	808.4	802.9

* statistically significant at $p < 0.05$; ** statistically significant at $p < 0.01$
a animals transferred to normal diet during this week.
b animals administered diet containing mefenpyr-diethyl at 11000 ppm during this week.

D. BLOOD ANALYSIS:

Because of the marked body weight effects observed in the group receiving 3000 ppm iodosulfuron-methyl-sodium and 11000 ppm mefenpyr-diethyl, blood samples were not taken from these animals after week 2, and the hematological results from the first samples are not included in the following discussion.

Statistically significant decreases in one or more red cell parameters were noted in all treated groups during the treatment period. A trend towards recovery was evident from study day 42 (14 days after the end of treatment) and recovery was total by study day 70 (6 weeks after the end of treatment). Hematological data from all phases of the study is shown in Table CA 5.8.2-05.

Table CA 5.8.2-05. Selected hematological parameters measured during the pre-treatment (PT), treatment (TRT), and reversibility (REV) phase of the study in dogs administered iodosulfuron-methyl-sodium alone or in combination with mefenpyr-diethyl via the diet.

		Dietary concentration in ppm			
Iodosulfuron-methyl-sodium		**0**	**11000**	**3000**	**11000**
Mefenpyr-diethyl		**0**	**0**	**3000**	**3000**
RBC, T/L	Day -27 (PT)	5.62	5.71	5.99	5.91
	Day -13 (PT)	6.11	6.03	6.22	6.06
	Day 1 (TRT)	6.36	6.65	6.70	6.36
	Day 14 (TRT)	6.14	5.00**	5.88	4.99**
	Day 28 (TRT)	6.36	4.58**	5.81	4.95**
	Day 42 (REV)	6.52	5.87	6.24	5.65*
	Day 56 (REV)	6.25	6.15	6.55	5.86
	Day 70 (REV)	6.35	6.51	6.63	6.15
HB, g/DL	Day -27 (PT)	13.6	13.3	13.5	13.6
	Day -14 (PT)	14.4	13.9	13.9	14.0
	Day 1 (TRT)	14.6	15.1	14.8	14.4
	Day 14 (TRT)	14.6	11.5**	13.2	11.4**
	Day 28 (TRT)	14.6	10.3**	12.9	11.2**
	Day 42 (REV)	15.1	13.3*	14.1	12.7*
	Day 56 (REV)	14.4	13.8	14.5	12.9
	Day 70 (REV)	14.6	14.7	14.7	13.6
PCV	Day -27 (PT)	0.40	0.40	0.41	0.41
	Day -14 (PT)	0.44	0.42	0.42	0.42
	Day 1 (TRT)	0.45	0.46	0.45	0.44
	Day 14 (TRT)	0.43	0.34**	0.40	0.34**
	Day 28 (TRT)	0.44	0.31**	0.39*	0.33**
	Day 42 (REV)	0.46	0.41	0.42	0.38*
	Day 56 (REV)	0.44	0.42	0.44	0.40
	Day 70 (REV)	0.44	0.45	0.46	0.42
Reticulocytes, per 1000	Day -27 (PT)	5	3	4	5
	Day -14 (PT)	3	3*	3**	5
	Day 1 (TRT)	4	9*	7	6
	Day 14 (TRT)	6	3	7	1*
	Day 28 (TRT)	5	3	3	1**
	Day 42 (REV)	4	6	3	6
	Day 56 (REV)	3	3	2	4
	Day 70 (REV)	6	11	6	10

* statistically significant at $p < 0.05$; ** statistically significant at $p < 0.01$.

III. CONCLUSION

Hematological changes observed in the peripheral anemia included decreases in erythrocyte count, hemoglobin concentration, packed cell volume, and reticulocyte count. The effects observed in the group administered iodosulfuron-methyl-sodium at 11000 ppm were no different from those observed in the group administered iodosulfuron-methyl-sodium at 11000 ppm with mefenpyr-diethyl at 3000 ppm.

The anemia noted during the study was dose-related, reversible, and due to the test substance iodosulfuron-methyl-sodium as this anemia was observed with the same severity with or without co-administration of mefenpyr-diethyl.

CA 5.8.3 - Endocrine disrupting properties

Iodosulfuron-methyl-sodium did not cause any effects in endocrine organs or tissues in any of the studies presented in this dossier, and thus does not possess any endocrine disrupting properties.

CA 5.9 - Medical data

CA 5.9.1 - Medical surveillance on manufacturing plant personnel and monitoring studies

Report:	[redacted];[redacted];1998;M-182378-01
Title:	Medical data. Medical surveillance of manufacturing plant personnel. Proposed first aid measures Jodosulfuron Code: AE F153008
Report No:	C001333
Document No:	M-182378-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Report:	[redacted];[redacted];2014;M-476230-01
Title:	Occupational medical experiences with iodosulfuron-methyl-sodium
Report No:	M-476230-01-1
Document No:	M-476230-01-1
Guidelines:	**US EPA FIFRA Guideline Requirement; N/A;not applicable**
GLP/GEP:	**no**

There have been no significant changes in medical advice or in occupational findings between the initial report in 1998 and the more recent report from 2014. The available occupational data and the medical advice to be followed after exposure to iodosulfuron-methyl sodium is described in data points KCA 5.9.7 below.

CA 5.9.2 - Data collected on humans

No data can be retrieved on humans and iodosulfuron-methyl-sodium. No poisoning cases have been reported.

CA 5.9.3 - Direct observations

None available.

CA 5.9.4 - Epidemiological studies

None available.

CA 5.9.5 - Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests

There are no reports of poisoning in humans. Animal experiments with high doses showed unspecific symptoms like irregular breathing, weakness, salivation. Although it is a sulfonylurea compound, iodosulfuron-methyl-sodium does not influence glucose metabolism.

CA 5.9.6 - Proposed treatment: first aid measures, antidotes, medical treatment

First aid:

- Remove patient from exposure / terminate exposure
- Thorough skin decontamination with copious amounts of water and soap, if available with polyethylene glycol 300 followed by water
    - NOTE: most formulations with this active ingredient can be decontaminated with water (and soap), so for formulations polyethylene glycol 300 is not required.
- Flushing of the eyes with lukewarm water for 15 minutes
- Induction of vomiting does not seem to be required in regard of the low toxicity. It should only be considered if a large amount has been swallowed, if the ingestion was less than one hour ago, and if the patient is fully conscious. Induced vomiting can remove maximum 50% of the ingested substance.
    - NOTE: Induction of vomiting is forbidden, if a formulation containing organic solvents has been ingested.

Treatment:

- Gastric lavage does not seem to be required in regard of the low toxicity of the compound.
- The application of activated charcoal and sodium sulphate (or other cathartic) might be considered in significant ingestions.
- As there is no antidote, treatment has to be symptomatic and supportive.

CA 5.9.7 - Expected effects of poisoning

No persistent effects are expected.