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Document Title

Summary of the toxicological and metabolism studies for Foramsulfuron

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Data Requirements

EU Regulation 1107/2009 & EU Regulation 283/2013
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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

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Author(s)

[redacted]

Bayer CropScience

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Version history

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

[1] Changes will be made following the approach to showing revisions and version history outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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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 foramsulfuron and were therefore not evaluated during the first EU review of this compound. A short summary of the toxicological endpoints from the first EU review has been provided and adapted with the new information where necessary. 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 toxicology studies available at the time of the first Annex I inclusion of foramsulfuron were complete and conducted according to the state of the art at that time with regard to good laboratory practice, scientific and technical aspects and study guidelines. They covered all required endpoints, and showed that foramsulfuron had an overall favorable toxicological profile.

The following human reference values were adopted during the initial inclusion of foramsulfuron in Annex I:

- Acceptable Daily Intake (ADI): 0.5 mg/kg bw/d on the basis of the rabbit NOAEL of 50 mg/kg bw/day and a safety factor of 100.
- Acute Reference Dose (ARfD): not allocated / not considered necessary due to the low toxicity of foramsulfuron.

  Acceptable Operator Exposure Level (AOEL): 0.1 mg/kg bw/d on the basis of the rabbit NOAEL of 50 mg/kg bw/day, a safety factor of 100 and including a factor of 20% for absorption.

Since the inclusion of foramsulfuron into Annex I no new studies have been performed which have an impact on the ADI, ARfD or AOEL. The studies on which the endpoints are based are still considered to be acceptable to today's requirements. There were no changes in the technical basis for these reference values or in guidance on how to establish them. The revision of guidance on AOEL (SANCO 7531 rev 10 of July 2006) did not require revising of the AOEL. Therefore it is not necessary to revise any of these three reference values.

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

Since the absorption, distribution, metabolism and excretion in mammals are well described no further studies were necessary.

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

The metabolism of foramsulfuron showed that the main excretion product was unchanged foramsulfuron, excreted mainly in the faeces. Two metabolic routes were identified leading to the formation of AE F130619, an amine (4-amino-2-[3-(4, 6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-N,N-dimethylbenzamide, and the cleavage product AE F153745 (4-formylamino-N, N-dimethyl-2sulfamyl-benzamide) as minor metabolites. A number of unidentified, minor (<4 %, polar metabolites formed from the both the phenyl or pyrimidyl ring-labeled compound were also excreted.

The studies from the baseline dossier are listed below.

Report:	K[redacted]§;[redacted];;1999;M-187756-01
Title:	Preliminary toxicokinetic studies in the rat AE F130360
Report No:	C004339
Document No(s):	Report includes Trial Nos.: TOX96069A/B/C M-187756-01-1
Guidelines:	**EU (=EEC): 91/414, 94/79; JMAF: ; USEPA (=EPA): OPPTS 870.7485;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]∃;[redacted];;1999;M-187784-01
Title:	Rat - absorption, distribution, elimination following oral dosing at 10 and 1000 mg/kg body weight AE F130360
Report No:	C004352
Document No(s):	Report includes Trial Nos.: TOX96072 M-187784-01-1
Guidelines:	**EU (=EEC): 91/414, 94/79; JMAF: ; USEPA (=EPA): OPPTS 870.7485;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]y;[redacted];1998;M-148034-02;Amended: 2000-03-01
Title:	Study of excretion following oral administration to bile duct cannulated rats (14C)-AE F130360
Report No:	A67666
Document No(s):	Report includes Trial Nos.: TOX96073 TOX96703 M-148034-02-1
Guidelines:	**EU (=EEC): 91/414; JMAF: ; USEPA (=EPA): 85-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]•;[redacted];;1999;M-192393-01
Title:	Tissue distribution and clearance in the rat (14C)AE F130360
Report No:	C005639
Document No(s):	Report includes Trial Nos.: TOX96877 M-192393-01-1
Guidelines:	**EU (=EEC): 91/79/EEC; JMAF: 4200; USEPA (=EPA): OPPTS 870.7485;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]9;[redacted];;1999;M-188907-01
Title:	Metabolism in the rat following a single oral administration of 10 or 1000 mg/kg body weight AE F130360
Report No:	C004901
Document No(s):	Report includes Trial Nos.: TOX/96074 M-188907-01-1
Guidelines:	**EU (=EEC): 91/414, 94/79 ec; USEPA (=EPA): OPPTS 870.7485;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]2;[redacted];;1999;M-192228-01
Title:	Rat absorption, distribution and elimination - repeat oral dose (10 mg/kg day) Code: AE F130360
Report No:	C005527
Document No(s):	Report includes Trial Nos.: TOX/99/262-41 M-192228-01-1
Guidelines:	**EU (=EEC): 91/414/EEC; JMAF: 4200; USEPA (=EPA): OPPTS 870.7485;Deviation not specified**
GLP/GEP:	**yes**

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

According to the new data requirements (Commission regulation (EU) No 283/2013) an *in vitro* metabolism study was performed and is summarised below.

Report:	K[redacted]3;[redacted];;2013;M-470479-01
Title:	[Pyrimidine-2-14C]Foramsulfuron: Metabolic Stability and Profiling in Liver Microsomes from Rats and Humans for Inter-Species Comparison
Report No:	EnSa-13-0827
Document No:	M-470479-01-1
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 [Pyrimidine-2-14C]-Foramsulfuron (14C-Foramsulfuron) was investigated in animal in-vitro systems by incubating the test item with liver microsomes from male Wistar rats (RLM) and humans (HLM) 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).

The recovery of radioactivity was measured in the microsome incubations and amounted 94.8% (RLM) and 87.9% (HLM) for the 1 hour samples. These decreases were considered as non-relevant for the general outcome of the study.

The metabolic activity of the microsomes was 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 test with 14C-Foramsulfuron demonstrated that the test item was metabolically stable after incubation with RLM and HLM.

No detectable metabolites were found after the 1 hour incubation period of the different microsome preparations with the test item.

The results suggest that phase I metabolism is not involved in the biotransformation of Foramsulfuron in rat and human liver microsomes.

Materials and Methods

Test System

Pooled liver microsomes from male Wistar rats (RLM, batch 1010126, pool of 200 individuals) and humans (HLM, batch 1210153, pool of 50 donors from both genders) were purchased from Xenotech, LLC (USA).

Sample Preparation and Incubation

14C-Foramsulfuron was incubated separately with RLM and HLM (n=3) at 37 ± 1°C in a final volume of 500 µL. Incubations were performed in a thermomixer (Eppendorf) with shaking at 1000 rpm. The final incubation volume was 500 µL.

CONCLUSION

From the results of the present study, the following conclusions can be drawn:

- 14C-Foramsulfuron was metabolically stable after incubation with rat and human liver microsomes (RLM and HLM) at 37 °C for 1 hour, in the presence of NADPH cofactor.
- No detectable metabolites were found after the 1 hour incubation period of the different microsome preparations with the test item

The results suggest that phase I metabolism is not involved in the biotransformation of Foramsulfuron in rat and human liver microsomes.

CA 5.2 Acute toxicity

Foramsulfuron has been shown to have very low acute toxicity to mammals irrespective of the route of exposure. The oral LD_{50} was > 5000 mg/kg bw, with only non-specific clinical signs of piloerection, hunched posture and white, soft to liquid faeces as clinical signs. The dermal LD_{50} was > 2000 mg/kg bw with no systemic clinical signs, and the 4-hour inhalation LC_{50} was > 5.04 mg/L air which was the highest achievable concentration. This concentration did not cause mortality and the main clinical signs were non-specific, like wet fur, hunched posture and piloerection. There was no indication of any sex-specific susceptibility in any of the acute studies.

Foramsulfuron was not irritating to the rabbit skin. In the eye irritation test in rabbits, reversible slight to moderate reddening, slight chemosis and a slight to moderate discharge of the conjunctivae, was seen which was fully reversible within 48 hours post instillation. Based on EU criteria, classification and labelling of foramsulfuron as a skin or eye irritant is not required.

Due to the new data requirements a photoxicity study is required if the molar extinction coefficient is higher than 10 L x mol^{-1} x cm^{-1}. For foramsulfuron this is the case so that a photoxicity study was conducted and this showed that foramsulfuron does not possess any phototoxic potential.

The results of these studies are summarised in the table 5.2-1.

Table 5.2-1: Acute toxicity data of foramsulfuron

Study type	Species	Result	Reference
Acute oral toxicity	Rat	LD_{50} > 5000 mg/kg bw	XXXXXXX 1997 (M-141959-01-1) KCA 5.2.1/01
Acute dermal toxicity	Rat	LD_{50} > 2000 mg/kg bw	XXXXXXX 1997 (M-141960-01-1) KCA 5.2.2/01
Acute inhalation toxicity	Rat	LC_{50} >5.04 mg/l air (4-h nose-only, dust aerosol)	XXXXXXX 1998 (M-148009-01-1) KCA 5.2.3/01
Skin irritation	Rabbit	Non-irritant	XXXXXXX 1997 (M-143046-01-1) KCA 5.2.4/01
Eye irritation	Rabbit	Non-irritant	XXXXXXX 1997 (M-143047-01-1) KCA 5.2.5/01
Skin sensitization (M&K test)	Guinea pig	Non-sensitiser	XXXXXXX 1997 (M-141892-01-1) KCA 5.2.6/01
Phototoxicity	In vitro assay with BALB/c 3T3 cells	No phototoxic potential	[redacted] 2013 M-465937-01-1 KCA 5.2.7/01

Since the acute toxicity was low and also the local toxicity did not show any specific hazards, no further tests were deemed necessary. The acute oral, dermal, inhalation, skin and eye irritation and the skin sensitisation studies were submitted and evaluated for the first approval, so the studies are not summarised in this document. The studies are listed under points CA 5.2.1 to 5.2.6. A full study summary has been provided for the new phototoxicity study (CA 5.2.7)

CA 5.2.1 Oral

Report:	K[redacted]i[redacted];;1997;M-141959-01
Title:	Hoe 130360 (AE F130360); Code: Hoe 130360 00 ZC98 0001 - Rat acute oral toxicity
Report No:	A58207
Document No(s):	Report includes Trial Nos.: TOX96110 M-141959-01-1
Guidelines:	**OECD: 401; USEPA (=EPA): F 81-1;Deviation not specified**
GLP/GEP:	**yes**

CA 5.2.2 Dermal

Report:	K[redacted]5;[redacted];;1997;M-141960-01
Title:	Hoe 130360 (AE F130360); Code: Hoe 130360 00 ZC98 0001 - Rat acute dermal toxicity
Report No:	A58268
Document No(s):	Report includes Trial Nos.: TOX96111 M-141960-01-1
Guidelines:	**OECD: No. 402; USEPA (=EPA): F 81-2;Deviation not specified**
GLP/GEP:	**yes**

CA 5.2.3 Inhalation

Report:	K[redacted]g;[redacted];;1998;M-148009-01
Title:	Rat acute inhalation toxicity Code: AE F130360 00 1C94 0002
Report No:	A67640
Document No(s):	Report includes Trial Nos.: TOX96115 M-148009-01-1
Guidelines:	**EU (=EEC): B2, 67/548/EEC, Annex; JMAF: 1985; OECD: 403; USEPA (=EPA): F 81-3;Deviation not specified**
GLP/GEP:	**yes**

CA 5.2.4 Skin irritation

Report:	K[redacted]u;[redacted];1997;M-143046-01
Title:	Code: Hoe 130360 00 ZC98 0001 - Rabbit skin irritancy
Report No:	A59370
Document No(s):	Report includes Trial Nos.: TOX96112 M-143046-01-1
Guidelines:	**OECD: 404; USEPA (=EPA): F 81-5;Deviation not specified**
GLP/GEP:	**yes**

CA 5.2.5 Eye irritation

Report:	K[redacted]v;[redacted];;1997;M-143047-01
Title:	Code: Hoe 130360 00 ZC98 0001 - Rabbit eye irritancy
Report No:	A59371
Document No(s):	Report includes Trial Nos.: TOX96113 M-143047-01-1
Guidelines:	**OECD: 405; USEPA (=EPA): F 81-4;Deviation not specified**
GLP/GEP:	**yes**

CA 5.2.6 Skin sensitization

Report:	K[redacted]5;[redacted];;1997;M-141892-01
Title:	Hoe 130360 (AE F130360); Code: Hoe 130360 00 ZC98 0001 - Guinea-pig skin sensitization (Magnusson and Kligman test)
Report No:	A58182
Document No(s):	Report includes Trial Nos.: TOX96114 M-141892-01-1
Guidelines:	**OECD: 406; USEPA (=EPA): F 81-6;Deviation not specified**
GLP/GEP:	**yes**

CA 5.2.7 Phototoxicity

Due to the new data requirements a photoxicity study is required if the molar extinction coefficient is higher than 10 L x mol^{-1} x cm^{-1}. For foramsulfuron this is the case so that a photoxicity study was conducted. The test was conducted according to the guideline OECD 432 (Balb/c 3T3) and is described in detail below.

Report:	[redacted] <;[redacted] ;2013;M-465937-01
Title:	Foramsulfuron TC: Cytotoxicity assay in vitro with BALB/c3T3 cells: Neutral red (NR) test during simultaneous irritation with artificial sunlight
Report No:	1561300
Document No:	M-465937-01-1
Guidelines:	**Commission Regulation (EC) No. 440/2008, B41; Committee for Proprietary Medicinal Products (CPMP) CPMP/SWP/398/01; OECD 432; none**
GLP/GEP:	**yes**

Executive Summary

In this study the phototoxic potential of Foramsulfuron Technical (AE F130360) was evaluated. The test was performed using BALB/c 3T3 cells clone 31. In a first step a range finding experiment (RFE was conducted, the second step was the main experiment (ME). The following concentrations of the test item were used with and without irradiation in both experiments: 7.81, 15.63, 31.25, 62.5, 125, 250, 500, 1000 µg/mL. As solvent control EBSS (Earle's Balanced Salt Solution) was used. Chlorpromazine was used as positive control. One test group of cells treated with the test item was irradiated with artificial sunlight for 50 minutes with 1.6 to 1.7 mW/cm^2 UVA, resulting in an irradiation dose of 5 J/cm^2 UVA. Another test group of test item treated cells was kept in the dark for 50 minutes.

Cytotoxic effects did not occur after exposure of the test item to the cells, neither in the presence nor in the absence of irradiation with artificial sunlight in both experiments. Therefore, ED_{50}-values or a PIF could not be calculated. The resulting MPE values were 0.001 (RFE) and -0.002 (ME). Therefore, the test item is classified as not phototoxic.

I. MATERIALS AND METHODS

A. MATERIALS:

A1. Test Material: Foramsulfuron Technical (AE F130360)

- **Description:** White powder
- **Lot/Batch #:** AE F130360-01-02
- **Purity:** 97.3 % w/w
- **CAS #:** 173159-57-4
- **Stability of test compound:** The test material was found to be stable over a 2-year storage period
- **Solvent used:** EBSS (Earle's Balanced Salt Solution)

A2. Vehicle and/or positive control: Test material dosed as received

A3. Control Materials: **Negative:** EBSS
Positive: Chlorpromazine

A4. Test Cells: BALB/c 3T3 cells clone 31 (isolated from the muscle tissue of the mouse embryo)

A5. Culture Medium: Large stocks (Master Cell Stock) of the BALB/c 3T3 31 cell line (supplied by [redacted],

[redacted], Germany) are stored in liquid nitrogen in the cell bank of Harlan CCR. A working cell stock is produced by multiplying from the master cell stock. Thawed stock cultures were propagated at 37 ± 1.5 °C in 75 cm^2 plastic flasks. Seeding was done with about 1×10^6 cells per flask in 15 mL of Dulbecco's Minimal Essential Medium (DMEM), supplemented with 10% NCS. The 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.

A6. Test compound concentrations:

µg/mL of the test item, with and without irradiation: 7.81, 15.63, 31.25, 62.5, 125, 250, 1000.

B. TEST PERFORMANCE

B1. Seeding of the Cultures

2 x 10^4 cells per well were seeded in 100 µL culture medium (two plates, one was exposed to artificial sunlight, one was kept in the dark).

B2. Treatment

24 hours after seeding the cultures were treated with the test item. The treatment was performed according to the OECD guideline as follows:

- the cultures were washed with EBSS;
- 8 dilutions of the solved test item were tested on two 96-well plates (100 µL/well);
- both plates were pre-incubated for 1 hour in the dark;
- after one hour one 96-well plate was irradiated through the lid at 1.6 to 1.7 mW/cm2 (5 J/cm^2), for 50 ± 2 min at 20 - 30 °C, the other plate was stored for 50 ± 2 min at 20 - 30 °C in the dark;.
- after irradiation the test item was removed and both plates were washed twice with EBSS;
- fresh culture medium was added and the cells were incubated for 21.5 hours at 37 ± 1.5 °C and 7.5 ± 0.5% CO_2.

B3. Determination 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 returned to the incubator for another 3 hours to allow uptake of the vital dye into the lysosomes of viable cells. Thereafter, the medium was removed completely and the cells were washed with EBSS. Then 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 to extract the dye. After additional approx. 10 min 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.

B4. Data Recording

The data generated were recorded in the laboratory raw data file. The results are presented in tabular form, including experimental groups with the test item, solvent, and positive control. Arithmetic means ± standard deviation were calculated for every test group.

The ED_{50} values, the Photo-Irritancy-Factor (PIF), as well as the Mean Phototoxic Effect (MPE) were calculated using the software Phototox (Version 2.0) (distributed by [redacted], Germany, and recommended by the OECD guideline).

The ED_{50} values (effective dose where only 50% of the cells survived) were determined by curve fitting by the software.

The PIF is defined by the following equation:

$$PIF = \frac{ED_{50}(-UV)}{ED_{50}(+UV)}$$

If a chemical is only cytotoxic +UV and is not cytotoxic when tested –UV, the PIF cannot be calculated, although this result indicates a phototoxic potential. In such cases, a > PIF value can be calculated if the (-UV) cytotoxicity test is performed up to the highest test concentration (C_{max}) and this value is used for calculation of the > PIF:

$$> PIF = \frac{C_{max}(-UV)}{ED_{50}(+UV)}$$

Since the > PIF is not an exact numerical value, no bio-statistical procedure can be applied to determine the optimum cut-off. Consequently, the classification rule has to be:

If only a > PIF can be obtained, then any value > 1 predicts a phototoxic potential.

The Mean Phototoxic Effect (MPE) is based on comparison of the complete concentration response curves. It is defined as the weighted average across a representative set of photo effect values.

$$MPE = \frac{\sum_{i=1}^{n} w_i PEc_i}{\sum_{i=1}^{n} w_i}$$

The photo effect (PEc) at any concentration (C) is defined as the product of the response effect (REc) and the dose effect (DEc) i.e. PEc = REc x DEc. The response effect (REc) is the difference between the responses observed in the absence and presence of light, i.e. REc = Rc (-UV) – Rc (+UV). The dose-effect is given by:

$$DEc = \left| \frac{C/C^* - 1}{C/C^* + 1} \right|$$

where C* represents the equivalence concentration, i.e. the concentration at which the +UV response equals the –UV response at concentration C. If C* cannot be determined because the response values of the +UV curve are systematically higher or lower than Rc (-UV) the dose effect is set to 1. The weighting factors w_i are given by the highest response value, i.e. w_i = MAX {Ri (+UV), Ri (-UV)}. The concentration grid Ci is chosen such that the same number of points falls into each of the concentration intervals defined by the concentration values used in the experiment. The calculation of MPE is restricted to the maximum concentration value at which at least one of the two curves still exhibits a response value of at least 10%. If this maximum concentration is higher than the highest

concentration used in the +UV experiment the residual part of the +UV curve is set to the response value "0". Depending on whether the MPE value is larger than a properly chosen cut-off value (MPE = 0.15) or not, the chemical is classified as phototoxic.

B5. Evaluation of Results

Based on the results obtained, the test item is evaluated as follows:

If **PIF < 2 or MPE < 0.1**: no phototoxic potential 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 predicted

B6. Acceptability of the Assay

The assay meets the acceptance criteria:

- if after irradiation with a UVA dose of 5 J/cm² the cell viability of the solvent control is > 80% of non-irradiated cells.
- if for the positive control CPZ the factor (PIF) between the two ED50 values is > 6
- if the mean OD540 of solvent controls is > 0.4.

II. RESULTS AND DISCUSSION

Table 5.2.7-1: Treatment of BALB/c 3T3 with Foramsulfuron Technical (AE F130360) in the RFE

With artificial sunlight				Without artificial sunlight			
Conc. [µg/mL]	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**	**Conc. [µg/mL]**	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**
Solvent Control	0.5438*	0.1085	100.00	**Solvent Control**	0.6463*	0.0517	100.00
7.81	0.5867	0.0794	107.88	**7.81**	0.6897	0.0481	106.71
15.63	0.5931	0.0601	109.06	**15.63**	0.6623	0.0669	102.47
31.25	0.5914	0.0340	108.75	**31.25**	0.6814	0.0995	105.43
62.5	0.5939	0.0459	109.21	**62.5**	0.6814	0.0618	105.43
125	0.5852	0.0469	107.60	**125**	0.6940	0.0317	107.37
250	0.5766	0.0633	106.02	**250**	0.7080	0.0740	109.54
500	0.5406	0.0364	99.39	**500**	0.6955	0.0464	107.60
1000	0.5512	0.0347	101.34	**1000**	0.7076	0.0362	109.48

* mean O.D.$_{540\ nm}$ out of 12 wells

ED_{50} values = could not be determined, since the viability of the cells was not reduced with and without irradiation
PIF = could not be determined, since no ED50 values could be calculated
MPE = 0.001

Table 5.2.7-2: Treatment of BALB/c 3T3 with the Positive Control (chlorpromazine) in the RFE

With artificial sunlight				Without artificial sunlight			
Conc. [µg/mL]	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**	**Conc. [µg/mL]**	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**
Solvent Control	0.6249*	0.0680	100.00	**Solvent Control**	0.6267*	0.0800	100.00
0.125	0.4350	0.0468	69.60	**6.25**	0.4498	0.0452	71.77
0.250	0.1368	0.0214	21.89	**12.50**	0.0640	0.0127	10.20
0.500	0.0729	0.0239	11.66	**25.00**	0.0504	0.0031	8.03
0.750	0.0530	0.0049	8.47	**37.50**	0.0512	0.0029	8.16
1.000	0.0530	0.0043	8.48	**50.00**	0.0489	0.0019	7.81
1.500	0.0537	0.0065	8.59	**75.00**	0.0502	0.0040	8.01
2.000	0.0532	0.0054	8.51	**100.00**	0.0559	0.0099	8.91
4.000	0.0534	0.0041	8.54	**200.00**	0.0546	0.0067	8.71

* mean O.D.$_{540\ nm}$ out of 12 wells

ED_{50} value (with artificial sunlight) = 0.16 µg/mL
ED_{50} value (without artificial sunlight) = 7.45 µg/mL
PIF = 47.11
MPE = 0.734

Table 5.2.7-3: Treatment of BALB/c 3T3 with Foramsulfuron Technical (AE F130360) in the ME

With artificial sunlight				Without artificial sunlight			
Conc. [µg/mL]	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**	**Conc. [µg/mL]**	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**
Solvent Control	0.7010*	0.0613	100.00	**Solvent Control**	0.7180*	0.0473	100.00
7.81	0.6977	0.0574	99.53	**7.81**	0.7012	0.0543	97.67
15.63	0.7130	0.0649	101.70	**15.63**	0.6892	0.0313	96.00
31.25	0.6917	0.0232	98.68	**31.25**	0.7056	0.0321	98.27
62.5	0.6634	0.0342	94.63	**62.5**	0.7063	0.0468	98.38
125	0.6868	0.0281	97.97	**125**	0.7162	0.0385	99.75
250	0.6891	0.0218	98.30	**250**	0.7054	0.0420	98.25
500	0.6945	0.0590	99.07	**500**	0.7081	0.0334	98.63
1000	0.7015	0.0437	100.07	**1000**	0.7107	0.0384	98.98

* mean O.D.$_{540\ nm}$ out of 12 wells

ED_{50} values = could not be determined, since the viability of the cells was not reduced with and without irradiation
PIF = could not be determined, since no ED50 values could be calculated
MPE = 0.002

Table 5.2.7-4: Treatment of BALB/c 3T3 with the Positive Control (chlorpromazine) in the ME

With artificial sunlight				Without artificial sunlight			
Conc. [µg/mL]	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**	**Conc. [µg/mL]**	**O.D.$_{540\ nm}$ Mean Value**	**Standard Deviation**	**% of Solv. Control**
Solvent Control	0.6548*	0.0684	100.00	**Solvent Control**	0.7420*	0.0390	100.00
0.125	0.5502	0.0685	84.02	**6.25**	0.7176	0.0536	96.71
0.250	0.1367	0.0945	20.87	**12.50**	0.2227	0.0555	30.01
0.500	0.0705	0.0242	10.77	**25.00**	0.0576	0.0014	7.76
0.750	0.1368	0.0982	20.89	**37.50**	0.0571	0.0038	7.70
1.000	0.0780	0.0317	11.90	**50.00**	0.0567	0.0032	7.64
1.500	0.0653	0.0060	9.97	**75.00**	0.0570	0.0031	7.68
2.000	0.0820	0.0489	12.53	**100.00**	0.0570	0.0031	7.69
4.000	0.0793	0.0255	12.11	**200.00**	0.0564	0.0026	7.60

* mean O.D.$_{540\ nm}$ out of 12 wells

ED_{50} value (with artificial sunlight) = 0.18 µg/mL
ED_{50} value (without artificial sunlight) = 11.29 µg/mL
PIF = 64.69
MPE = 0.771

The study was performed to assess the phototoxic potential of Foramsulfuron Technical (AE F130360). The test was performed using BALB/c 3T3 cells clone 31. Two experiments were performed. The first experiment served as range finder (RFE), the second experiment (ME) was the confirming experiment. 1000 µg/ml of the test item, dissolved in EBSS were applied as the highest concentration in both experiments.

Cytotoxic effects were not observed after treatment of cells with Foramsulfuron Technical (AE F130360), neither in the presence nor in the absence of irradiation with artificial sunlight in both experiments. Due to the missing cytotoxic effects, neither ED50-values nor a PIF could be calculated. The resulting MPE were 0.004 or -0.002, respectively, and therefore, the test item is classified as not phototoxic.

III. CONCLUSIONS

In conclusion, it can be stated that in this study and under the experimental conditions reported, the test item Foramsulfuron Technical (AE F130360) does not possess any phototoxic potential.

CA 5.3 Short-term toxicity

The short-term toxicity studies were performed and reported in accordance with OECD and EU testing guidelines and were fully compliant with GLP. A summary of these results is presented in Table 5.3-1. All necessary studies were presented and evaluated during the EU process for Annex I listing. Please refer to the monograph and the baseline dossier of foramsulfuron. No additional studies are presented for the re-approval of foramsulfuron.

Table 5.3-1: Summary of short-term toxicity studies

Study and dose levels	NOEL/NOAEL		LOAEL		Effects
	ppm	mg/kg bw/d	ppm	mg/kg bw/d	
Rat 28-d oral diet 0-1000-5000-20000 ppm	5000	m: 434 f: 490	20000	m: 1789 f: 1884	females only: ↓ bw gain. ↑water intake
Rat 90-d oral diet 0-20-200-5000-20000 ppm	20000	m: 1568 f: 1786	–	–	No effects observed
Mouse 28-d oral diet 0-400-1600-6400 ppm	6400	m: 1164 f: 1695	–	–	No effects observed
Mouse 90-d oral diet 0-64-3200-6400 ppm	6400	m: 1002 f: 1178	–	–	No effects observed
Dog 28-d oral gavage 0-40-200-1000 mg/kg bw/d	–	1000	–	–	No effects observed
Dog 90-d oral gavage 0-10-250-1000 mg/kg bw/d	–	1000	–	–	No effects observed
Dog 1-yr oral gavage 0-5-100-1000 mg/kg bw/d	–	1000	–	–	No effects observed
Rat 28-d dermal 0-10-100-1000 mg/kg bw/d	–	1000	–	–	No effects observed

In a recent 28-day dietary neurotoxicity study in Wistar rats with exposure to nominal concentrations of 0, 3750, and 15000 ppm foramsulfuron no treatment-related effects were seen at any dose level in either sex so that there was no evidence of a neurotoxic potential of foramsulfuron (see details under CA 5.7).

In summary, the short-term toxicity studies revealed a low toxicity of foramsulfuron after repeated administration in all tested species, and no target organs. Furthermore, the NOAELs are very high. The studies from the baseline dossier are listed under points CA 5.3.1 to 5.3.3.

CA 5.3.1 Oral 28-day study

Report:	K[redacted]7;[redacted];;1998;M-147543-01
Title:	Rat 28 day dietary repeat dose study Code: Hoe 130360 00 ZC90 0001
Report No:	A67148
Document No(s):	Report includes Trial Nos.: TOX95405 M-147543-01-1
Guidelines:	**EU (=EEC): 92/69 B7; JMAF: (1985); OECD: 407; USEPA (=EPA): F 82-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]$;[redacted];;1998;M-147445-01
Title:	Code: Hoe 130360 00 ZC90 0001 - Mouse 28-day dietary toxicity
Report No:	A67045
Document No(s):	Report includes Trial Nos.: TOX95385 M-147445-01-1
Guidelines:	**EU (=EEC): 79/831 B.7; JMAF: 4200; OECD: 405;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]l;[redacted];;1998;M-182949-01
Title:	Dog 28-day oral toxicity study Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC98 0001
Report No:	C001562
Document No(s):	Report includes Trial Nos.: TOX95386 M-182949-01-1
Guidelines:	**EU (=EEC): 92/96 Annex V part B; JMAF: 4200; OECD: 409; USEPA (=EPA): F 82-1;Deviation not specified**
GLP/GEP:	**yes**

CA 5.3.2 Oral 90-day study

Report:	K[redacted]9;[redacted];;1998;M-147446-01
Title:	Code: Hoe 130360 00 ZC97 0001 (AE F130360 00 ZC97 0001) - Rat 90-day dietary toxicity study with 3 week off dose period
Report No:	A67046
Document No:	M-147446-01-1
Guidelines:	**EU (=EEC): 78/831 B; JMAF: 4200; OECD: 408 Sect. 4; USEPA (=EPA): F 82-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]·;[redacted];;1998;M-147727-01
Title:	Mouse 90-day dietary toxicity Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC98 0001
Report No:	A67340
Document No(s):	Report includes Trial Nos.: TOX95388 M-147727-01-1
Guidelines:	**EU (=EEC): 78/834 B; JMAF: 4200; OECD: 408; USEPA (=EPA): F82-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]b;[redacted];;1998;M-181801-01
Title:	Dog 90-day oral toxicity study Hoe 130360 (AE F130360) Code: AE F130360 00 1C93 0001
Report No:	C001488
Document No(s):	Report includes Trial Nos.: TOX95406 M-181801-01-1
Guidelines:	**EU (=EEC): A11A.5.3.2.2; JMAF: 4200; USEPA (=EPA): 82-1;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]2;[redacted];;1999;M-186725-01
Title:	Dog 12 month oral toxicity study AE F130360 (Hoe 130360) code: AE F130360 00 1C96 0001
Report No:	C003751
Document No(s):	Report includes Trial Nos.: TOX96121 M-186725-01-1
Guidelines:	**EU (=EEC): 88/302B/EEC; JMAF: 4200; OECD: 452; USEPA (=EPA): 83-1;Deviation not specified**
GLP/GEP:	**yes**

CA 5.3.3 Other routes

Report:	K[redacted]p;[redacted];;1999;M-191434-01
Title:	Rat 28-day dermal toxicity study Hoe 130360 (AE F130360) AE F130360 00 1C94 0001
Report No:	C005128
Document No(s):	Report includes Trial Nos.: Tox9613 M-191434-01-1
Guidelines:	**EU (=EEC): 92/69 EEC; USEPA (=EPA): 82-2;Deviation not specified**
GLP/GEP:	**yes**

CA 5.4 Genotoxicity testing

All the required genotoxicity studies were presented and evaluated during the EU process for Annex I listing. Please refer to the Monograph and the baseline dossier for foramsulfuron. Foramsulfuron was tested on its genotoxic potential in a complete battery of genotoxicity tests on gene mutation in bacteria and mammalian cells, chromosome damage in *vitro* and in *vivo* and DNA damage in mammalian cells in *vivo*. Overall, it was concluded that the weight of evidence suggested that foramsulfuron is of no genotoxic concern. An overview on the tests performed is given in table 5.4-1.

Table 5.4-1: Summary of genotoxicity studies with foramsulfuron (Purity: 98.4 % in all studies)

Study/strains/species	Dose range	S-9 mix	Results
	***In vitro* studies**		
Bacterial reverse mutation test (Ames test) • S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 • E. coli WP2 uvrA	0-5000 µg/plate	with and without	Negative (bacterial toxicity at ≥ 20 µ/g plate)
Chromosome aberrations Human lymphocytes 0-2400 µg/ml	0-2400 µg/ml	with	Negative
		without	Slightly positive at 2400 µg/ml
HPRT mutation test Chinese hamster lung V79 cells	0-2000 µg/ml	with and without	Negative

Study/strains/species	Dose range	S-9 mix	Results
***In-vivo* studies**			
Mouse micronucleus test NMRI mouse	200-1000-2000 mg/kg bw	–	Negative
UDS-Test (DNA repair), Sprague-Dawley rat hepatocytes	600 and 2000 mg/kg bw	–	Negative

Photomutagenicity study:

Report:	[redacted]4;[redacted];2013;M-465939-01
Title:	Foramsulfuron - Overview on photosafety and waiver for conduct of a photomutagenicity study
Report No:	M-465939-01-1
Document No:	M-465939-01-1
Guidelines:	**not applicable;not applicable**
GLP/GEP:	**no**

According to the new data requirements the conduct of a photomutagenicity study may be required under certain circumstances. Since for foramsulfuron no circumstances exist which could provide evidence of a potential to cause photochemical effects, and since the quantum yield for foramsulfuron was very low, a photomutagenicity study was not deemed to be required. This was confirmed by the negative result of the phototoxicity study conducted with foramsulfuron. Since the mechanisms underlying the photochemical effects, like phototoxicity and photomutagenicity are the same, a photomutagenic reaction is not expected. Therefore, the conduct of a photomutagenicity study was not deemed necessary (for more detailed please refer to the attached statement KCA 5.4/01).

The studies from the baseline dossier are listed under the sub-headers below (5.4.1-5.4.3).

CA 5.4.1 *In vitro* studies

Report:	[redacted]7;[redacted];1996;M-141320-01
Title:	Hoe 130360 Code: Hoe 130360 00 ZC98 0001 - Bacterial reverse mutation test
Report No:	A57619
Document No(s):	Report includes Trial Nos.: TOX96105 M-141320-01-1
Guidelines:	**EU (=EEC): 92/69,L,Ann.B; OECD: 471;472; USEPA (=EPA): Subd.F;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted];[redacted];1997;M-141958-01
Title:	Hoe 130360 (AE F130360); Code: Hoe 130360 00 ZC98 0001 - In vitro human lymphocyte chromosome aberrations
Report No:	A58266
Document No(s):	Report includes Trial Nos.: TOX96106 M-141958-01-1
Guidelines:	**EU (=EEC): 92/69 B.10; MAFF: 35 (1989); OECD: 473;Deviation not specified**
GLP/GEP:	**yes**

Report:	[redacted] §; [redacted] ;1996;M-141837-01
Title:	Hoe 130360; Code: Hoe 130360 00 ZC98 0001 - In vitro chinese hamster lung V79 cell HPRT mutation
Report No:	A58125
Document No(s):	Report includes Trial Nos.: TOX96109 M-141837-01-1
Guidelines:	**EU (=EEC): 87/302 L133 p. 61-63; OECD: 476; USEPA (=EPA): 798.500, 40 pt.700-;Deviation not specified**
GLP/GEP:	**yes**

CA 5.4.2 *In vivo* studies in somatic cells

Report:	K[redacted]5; [redacted] ;;1997;M-142032-01
Title:	Hoe 130360 Code: Hoe 130360 00 ZC98 0001 - Mouse micronucleus test
Report No:	A58340
Document No(s):	Report includes Trial Nos.: TOX96108 M-142032-01-1
Guidelines:	**EU (=EEC): 92/69,L383A,Ann.B12; OECD: 474; USEPA (=EPA): 798.5395;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted] ; [redacted] ;;1996;M-141156-01
Title:	Hoe 130360 Code: Hoe 130360 00 ZC98 0001 - In vivo rat hepatocyte unscheduled DNA synthesis
Report No:	A57435
Document No(s):	Report includes Trial Nos.: TOX96107 M-141156-01-1
Guidelines:	**OECD: 482;Deviation not specified**
GLP/GEP:	**yes**

CA 5.4.3 *In vivo* studies in germ cells

Since all of the aforementioned genotoxicity studies produced essentially negative results, and since no evidence of an effect on germ cells was seen in other studies, an *in vivo* study in germ cells was not regarded as necessary.

CA 5.5 Long-term toxicity and carcinogenicity

All necessary studies were presented and evaluated during the EU process for Annex I listing. Please refer to the Monograph and the baseline dossier. The long-term toxicity and carcinogenicity studies in rats and mice did not give evidence of a carcinogenic potential of foramsulfuron. The following table gives an overview of these studies. No additional studies are required for the re-approval of foramsulfuron.

Table 5.5-1: Summary of long-term toxicity studies with foramsulfuron

Study and dose levels	NOAEL		LOAEL	Effects
	ppm	mg/kg/bw/d		
Rat combined chronic toxicity/ carcinogenicity 0-100-600-1000-20000 ppm	20000	m: 849 f: 1135		No effects
Mouse oncogenicity 0-40-800-8000 ppm	8000	m: 1115 f: 1358		No effects

The studies submitted in the baseline dossier are listed below.

Report:	K[redacted]g; [redacted];2000;M-193439-01
Title:	Rat dietary combined chronic toxicity and oncogenicity study AE F130360 (Hoe 130360) Code: AE F130360 00 1C95 0001
Report No:	C006180
Document No(s):	Report includes Trial Nos.: Tox06119 M-193439-01-1
Guidelines:	**EU (=EEC): 88/302/EEC B; JMAF: 4200; OECD: 453; USEPA (=EPA): 83-5;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]x; [redacted];2000;M-190282-01
Title:	1st Addendum to Report Number TOX/99/262-42 Rat dietary combined chronic toxicity and oncogenicity study: Provision of historical control histopathology data as requested by the EU Code: AE F130360 00 1C95 0001
Report No:	C010585
Document No:	M-199282-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

Report:	K[redacted]v; [redacted];1999;M-193893-01
Title:	Mouse dietary oncogenicity study AE F130360 Code: AE F130360 00 1C96 0001
Report No:	C006433
Document No(s):	Report includes Trial Nos.: 12/176 TOX96020 M-193893-01-1
Guidelines:	**EU: EEC: 88/302; JMAF: 4200; OECD: 451; USEPA (=EPA): OPPTS 870.4200;Deviation not specified**
GLP/GEP:	**yes**

CA 5.6 Reproductive toxicity

All the necessary studies were presented and evaluated during the EU process for Annex I listing. Please refer to the Monograph and the baseline dossier of foramsulfuron. The 2-generation study in rats did not indicate any reproduction toxic potential of foramsulfuron. Also the developmental toxicity studies in rats and rabbits did not reveal a developmental toxic potential. Therefore, no further studies were required or are needed for the re-approval of foramsulfuron. Table 5.6-1 gives an overview of the studies.

Table 5.6-1: Summary of reproduction and developmental toxicity studies with foramsulfuron

Studies and dose levels	Target	NOEL/NOAEL	LOAEL	Effects
Rat 2-generation study 0-100-1225-15000 ppm	Parental & reproductive toxicity	15000 ppm m: 1038 mg/kg/ bw/d f: 1430 mg/kg/ bw/d		No effects observed
Rat teratogenicity 0-5-71-1000 mg/kg bw/d	Maternal & developmental toxicity	1000 mg/kg bw/d	–	No effects observed
Rabbit teratogenicity 0-5-50-500 mg/kg bw/d	Maternal toxicity	50 mg/kg bw/d	500 mg/kg bw/d	↓body weight gain. ↓food intake, reddish urine
	Developmental toxicity	500 mg/kg bw/d	–	No effects observed

All studies submitted in the baseline dossier are listed under points CA 5.6.1 and CA 5.6.2.

CA 5.6.1 Generational studies

Report:	K[redacted]o; [redacted];;1999;M-187748-01
Title:	Rat dietary two-generation reproductive toxicity study AE F130360 Code: AE F130360 00 1999 0002
Report No:	C004338
Document No(s):	Report includes Trial Nos.: FOX96123 M-187748-01-1
Guidelines:	**EU (=EEC): 88/302/EEC; JMAF: 4200; OECD: 416; USEPA (=EPA): OPPTS 870.3800; Deviation not specified**
GLP/GEP:	**yes**

CA 5.6.2 Developmental toxicity studies

Report:	K[redacted]2; [redacted];;1997;M-143157-01
Title:	Hoe 130360 (AE F130360) Code: Hoe 130360 00 ZC98 0001 - Rabbit oral developmental toxicity (teratogenicity) range finding study
Report No:	ZC9486
Document No(s):	Report includes Trial Nos.: 96-1564 FOX95391 M-143157-01-1
Guidelines:	**EU (=EEC): 88/302; JMAF: 4200; OECD: 414; USEPA (=EPA): F 83-3; Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]p;[redacted];;1997;M-147435-01
Title:	Rat oral development toxicity (teratogenicity) study Code: Hoe 130360 00 ZC98 0001
Report No:	A67035
Document No(s):	Report includes Trial Nos.: 96.0760 TOX95390 M-147435-01-1
Guidelines:	**EU (=EEC): 88/302; JMAF: 4200; OECD: 414; USEPA (=EPA): 83-3;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]ü;[redacted];;1997;M-147441-01
Title:	Code: Hoe 130360 00 ZC98 0001 - Rabbit oral developmental toxicity (teratogenicity) study
Report No:	A67041
Document No(s):	Report includes Trial Nos.: 96.0761 TOX95392 M-147441-01-1
Guidelines:	**EU (=EEC): 88/302; JMAF: 4200; OECD: 414; USEPA (=EPA): 83-3;Deviation not specified**
GLP/GEP:	**yes**

Report:	K[redacted]ü;[redacted];;2000;M-199311-01
Title:	1st Addendum to Report number TOX/98/262-25 Rabbit oral developmental toxicity (teratogenicity) study: Provision of historical control body weight data as requested by the EU Code: Hoe 130360 00 ZC98 0001
Report No:	C010603
Document No:	M-199311-01-1
Guidelines:	**Deviation not specified**
GLP/GEP:	**no**

CA 5.7 Neurotoxicity studies

Foramsulfuron, a sulfonylurea herbicide, has no structural relationship to neurotoxic substances and furthermore, there was no evidence of a neurotoxic potential in the conducted apical studies. Consequently, no neurotoxicity studies were required, and no special studies have been conducted for this endpoint.

CA 5.7.1 Neurotoxicity studies in rodents

Since the approval of foramsulfuron at European level Bayer CropScience has performed a 28-day neurotoxicity study following a request from the Japanese authorities. This study is not required for European approval however following discussions with the RMS, Finland, it was agreed that the study would be included in the dossier for completeness. No neurotoxic effects were observed in the study.

Report:	K[redacted]4;[redacted];;2009;M-352628-01
Title:	A 28-day dietary neurotoxicity study with technical grade foramsulfuron in wistar rats
Report No:	09-N72-QZ
Document No:	M-352628-01-1
Guidelines:	**OECD Test Guideline No. 424 (1997);not specified**
GLP/GEP:	**yes**

Executive Summary
In this 28-day neurotoxicity study the neurotoxic potential of Foramsulfuron was investigated in rats. Technical grade Foramsulfuron was mixed in the diet and given for 28 days to young-adult male and female Wistar rats (12/sex/dietary level), using nominal concentrations of 0, 3750 and 15000 ppm. Twelve rats/sex/dietary level were used for neurobehavioral evaluation, with micropathology performed on selected tissues from six rats/sex from control and high-dose groups. Body weight and food consumption determinations, as well as detailed clinical observations were conducted weekly throughout the study. Observations for moribundity and mortality were performed at least once daily. Automated measurements of activity (figure-eight maze) and a functional observational battery (FOB) were conducted the week prior to treatment and again during week 4. Ophthalmologic examinations were conducted on all animals prior to shipment release and then again on all study animals during week 4. All animals placed on study were subjected to a gross necropsy during week 5. For selected animals, the brain was weighed in order to calculate the brain/body weight ratio and skeletal muscle, peripheral nerves, eyes (with optic nerves) and tissues from the central nervous system were also examined microscopically for lesions.

The mean daily intake of the test substance (mg Foramsulfuron/kg bw/day) over approximately 4 weeks at nominal dietary concentrations of 3750 and 15000 ppm, respectively, was 307.0 and 1208 mg/kg/day for males and 362.4 and 1415 mg/kg/day for females. There were no treatment-related effects attributed to exposure to Foramsulfuron at any dose level. Based on neurotoxicology endpoints, a NOAEL of 15000 ppm was established for males and females (equivalent to 1208 and 1415 mg Foramsulfuron/kg bw/day for male and female rats, respectively).

I. MATERIALS AND METHODS

A. MATERIALS:

A1.

Test Material:	Foramsulfuron Technical (AE F130360)
Description:	White powder
Lot/Batch #:	A1.F130360-01-01 (Origin Batch No. ELIR004130)
Purity:	97.6 % w/w
CAS #:	173159-57-4
Stability of test compound:	The test material was found to be stable over a 2-year storage period.

A2. Vehicle and/or positive control: None

A3. Test animals

Species:	Rat
Strain:	Wistar Han Crl:WI (HAN) rat
Age:	7 weeks old eight weeks of age / s and 146.6 – 193.7 g
Weight at dosing:	185.6 - 295.9 g for males; 146.6- 193.7 g for females
Source:	XXXXXXXXXXXX
Acclimation period:	6 days
Diet:	Purina Mills Certified Rodent Diet Meal 5002M (Lot Code JAN 10 09 2A) provided for *ad libitum* consumption during the acclimation period and throughout the study except during neurobehavioral testing
Water:	Tap water (XXXXXXXXXXXX Municipal Water) *ad libitum*, except during neurobehavioral testing
Housing:	Individually housed in suspended stainless steel wire-mesh cages, each containing a feeder, a source of

	water (pressure-activated water lixits), and deotized cage board in the bedding tray
Husbandry:	Husbandry conditions were in accordance with the USPHS-NIH publication Guide to the Care and Use of Laboratory Animals.
Environmental conditions -	
Temperature:	The daily average of 18-26°C was maintained.
Humidity:	The daily average of 30-70% relative humidity was maintained.
Air changes:	Minimum daily average of 10.15 (room 317) and 10.63 (room 318) air changes per hour
Photoperiod:	12 hours of light alternating with 12 hours of darkness; lights toggled off during ophthalmic examinations

B. STUDY DESIGN:

B1. In-life dates:	Start: April 6th, 2009 End: May 6th, 2009

B2. Animal assignment and treatment

Two dose groups (12 rats/sex/dietary level) were administered the test substance mixed in the diet at nominal concentrations of 0, 3750 and 15000 ppm for males (307.0 and 1208 mg/kg/day) and females (362.4 and 1415 mg/kg/day). All 12 rats/sex/dietary level were used for neurobehavioral testing, with six/sex/level used for micropathology.

B3. Diet preparation and analysis

The diet was prepared every other week with the test substance mixed directly with the feed. A sample of each batch of feed mixed was taken and retained in the freezer (~ -23°C) until the study was complete and the analytical data deemed satisfactory. The concentration of Foramsulfuron in the ration was measured by LC-MS/MS analysis. The stability [following both room temperature (~ 22°C) and freezer (~ -23°C) exposure] and homogeneity of the test substance in the feed were established by analysis of samples at nominal concentrations of 2000 and 17500 ppm. The concentration of the test substance in the ration was measured for the ration that was used during all weeks of the study.

Homogeneity Analysis: Homogeneity of the test substance in the ration was within the acceptable range for concentrations that bracket those used in this study. These concentrations of 2000 and 17500 ppm had percent relative standard deviations (%RSD) of 1.78% and 2.37%, respectively.

Stability Analysis: The stability of Foramsulfuron in the ration was established at room temperature at dietary concentrations of 2000 and 17500 ppm, with no appreciable decrease in concentration with seven days of storage. Foramsulfuron was stable at freezer conditions for 35 days, with no appreciable decrease in concentration at 2000 and 17500 ppm.

Concentration Analysis: Actual (analytically-determined) concentrations of the active ingredient in the 3750 and 15000 ppm dietary levels used in this study averaged 105% and 104%, respectively. Based on these results, the mean analytically-confirmed dietary levels for this study were 3927 and 15668 ppm.

B4. Statistics

Statistical evaluations were performed using software from either INSTEM Computer Systems or SAS. The level used to establish statistical significance was p≤0.05, with the exception of Bartlett's test, which was tested at p≤0.001, Continuous data were analysed using an Analysis of Variance (ANOVA), followed by a Dunnett's test if a significant F-value was determined in the ANOVA. For

the FOB, continuous data were first analysed using a Repeated-Measures ANOVA, followed by a one-way ANOVA if there was a significant interaction between dose group and test week. Categorical data collected in the FOB were analysed in a similar manner, using General Linear Modeling (GLM) and Categorical Modeling (CATMOD) Procedures, with post-hoc comparisons using Dunnett's test and an Analysis of Contrasts, respectively.

Motor and locomotor activity (activity for the entire session and activity for each 10-minute interval) were analysed using ANOVA procedures. Session activity data were first analysed using a Repeated-Measures ANOVA, followed by a one-way ANOVA. For pathology, continuous data were evaluated initially using Bartlett's Test to analyze for homogeneity of variances among groups. Homogeneous data were further analysed using an Analysis of Variance (ANOVA) followed by Dunnett's Test for pair-wise comparisons. In the event of non-homogeneous data, statistical analysis was performed using the non-parametric Kruskal-Wallis Test followed by a Mann-Whitney U Test for pair-wise comparisons.

Micropathology frequency data were analysed using a Chi-Square Test followed by a one-tailed Fisher's Exact Test in cases of significant variation by the Chi-Square analysis. A probability value of $p \leq 0.05$ was accepted as significant for all statistical tests with the exception of Bartlett's Test in which a probability value of $p \leq 0.001$ was used.

C. METHODS:

C1.Observations

Cage-side observations were conducted twice daily (once daily on holidays and weekends) for mortality or clinical signs of moribundity. Detailed physical examinations for clinical signs of toxicity were carried out and recorded once each week.

C2. Body Weight

Individual body weight determinations were made weekly. Additionally, all animals were weighed on the day of sacrifice for terminal body weight measurement.

C3. Food Consumption

Feed was available for *ad libitum* consumption for a period of one week prior to changing, at which time any uneaten feed was collected and disposed of. Individual food consumption was measured weekly. Daily food consumption was averaged over the duration of the study, based on per kg body weight. The average daily intake of the active ingredient (A.I.) (mg a.i./kg body weight/day) was calculated using weekly body weight (from the beginning of the week) and food consumption data. The general relationship used for this calculation was: [a.i.in feed (ppm)/1,000] x [feed consumed (g/kg body wt/day)] = mg AI/kg body wt/day. Using this formula, the average consumption of a.i. for males and females that received diets containing analytically-determined nominal concentrations of 0, 3750 and 15000 ppm Foramsulfuron was 0, 307.0 and 1208 mg/kg/day, for males and 0, 362.4 and 1415 mg/kg/day, for females.

C4. Neurobehavioral Assessment

All animals that were assigned to the study were tested using the FOB and motor activity on two occasions - once during the week prior to initiating the exposure and again during week 4. The order of testing and assignment of animals to mazes were done in a semi-random manner, such that groups were balanced across test times and test devices, and no animal would be tested more than once in the same maze. On the day prior to each test day, the appropriate animals were placed in the correct sequence that had been established for testing on that day and allowed to acclimate with minimal disturbance until testing on the following day. The dose group identification was concealed prior to testing to ensure that testing would be conducted without knowledge of the group assignment. Sets of eight animals (maximum) were evaluated individually using the FOB and then, approximately 30

minutes after the last animal in the set had finished being tested in the FOB, all eight rats were placed individually into the mazes to measure activity.

Each week, testing was staggered over three days to accommodate the schedule for behavioral testing. The open field and mazes were cleaned prior to testing the opposite sex to reduce the residual scent from the other sex.

a. Functional Observational Battery (FOB)
The FOB closely follows the battery of tests described by [redacted], with each animal tested individually. Scoring criteria and explicitly-defined scales were used to rank the severity of observations which are not readily quantified. The procedures used to determine landing foot splay and grip strength are based on established methods. The technicians who conducted the FOB were blinded with respect to the animal's group assignment. Inter-observer reliability has been established in order to allow multiple persons to perform either the observations and/or measurements, ensuring the consistency of the results of each technician.

When applicable, observations were scored on intensity as follows: 1) slight (barely perceptible or infrequent) or 2) moderate to severe. Data were collected while the rats were in their home cage, during handling, and in an open field for 2 minutes (in the center of a flat surface with a perimeter barrier, such as a cart). In addition, reflex and physiologic observations and measurements were made while the animals were sitting on the cart surface following open field observations. Home cage observations included: posture, piloerection, involuntary motor movements (such as repetitive "chewing" movements of mouth and jaw, tremors, and convulsions), gait abnormalities, vocalizations, decreased activity, repetitive head bobbing, and increased reactivity.

Observations during handling included: ease of removal from cage, reaction to being handled, muscle tone, palpebral closure, lacrimation, salivation, nasal discharge, stains (lacrimal, nasal, perianal, urine, oral), alopecia, emaciation, bite marks, exophthalmia, broken teeth/malocclusion, missing toe nail(s), dehydration, and temperature upon touching (cool to touch).

Open field (2 min.) observations included: number of rears, piloerection, respiratory abnormalities, posture, involuntary motor movements, stereotypy (excessive or repetitive behavior), bizarre behavior, gait abnormalities, vocalizations, arousal level, and amount of excretion.

Reflex and physiologic observations/measurements included approach response, touch response, auditory response, tail pinch, pupil size at normal lighting, pupil response, righting reflex, grip strength, body weight, body temperature, and landing foot splay.

b. Motor and Locomotor Activity
Motor and locomotor activity was evaluated approximately 30 minutes after the last animal in the set (8 rats maximum) had finished the FOB. All eight rats in each set were placed individually into figure-eight mazes and activity was measured for a total of 60 minutes. The figure-eight maze was selected as an established and widely-used automated activity-measuring device that can be used to detect both increases and decreases in activity. Each maze consisted of a series of inter-connected alleys, converging on a central arena and was covered by transparent plastic. Eight infrared emitter / detector pairs (three in each of the figure-eight alleys and one in each of the blind alleys) measured activity; each time a beam was interrupted, an activity count was registered. The floor of each maze rested above absorbent paper which was changed at the end of each day. A Columbus Instruments (Columbus, OH) Universal Maze Monitoring System and a personal computer were used for automated data collection. Broad-spectrum background noise (74±2 dB(A)) was provided throughout the test to minimize acoustical variations during testing. The uniformity of light intensity (100±70 lux) over each of the mazes was verified daily.

Motor and locomotor activity was examined during each of the six, ten-minute intervals. Motor activity was measured as the number of beam interruptions that occurred during the test session. Locomotor activity was measured by eliminating consecutive counts for a given beam. Thus, for locomotor activity, only one interruption of a given beam was counted until the rat relocated in the maze and interrupted one of the other beams. Habituation was evaluated as a decrement in activity during the test session.

C5. Ophthalmology

Pre-exposure and pre-terminal (week 4) ophthalmic exams were conducted on study animals in a semi-darkened room. The pre-exposure examination was used to select animals which did not have ophthalmological defects that could interfere with the interpretation of study results. Animals with such defects were sacrificed without necropsy. The pupillary reflex was tested using a penlight or transilluminator with Finnoff ([redacted], NY) and then a mydriatic agent was applied to each eye to dilate the pupil. After mydriasis, the conjunctiva, cornea and lens were examined with a slit lamp microscope, and the vitreous humor, retina, choroid, and optic disc were examined using an indirect ophthalmoscope and a condensing lens (40 diopters).

C6. Sacrifice and Pathology

All animals placed on study were subjected to a complete gross necropsy. The necropsy involved an examination of all organs, body cavities, cut surfaces, external orifices and surfaces. The first six males and six females at each dietary level were selected for perfusion and collection of tissues, with replacement, as necessary (e.g., if the perfusion was considered inadequate or animals replaced due to early termination from study). These animals were deeply anesthetized using an intraperitoneal dose (50 mg/kg) of sodium pentobarbital and then perfused via the left ventricle with a sodium nitrite (in phosphate buffer) flush followed by universal fixative (4% (w/v) EM-grade formalin) in phosphate buffer. The entire brain and spinal cord, both eyes (with optic nerves) and selected (bilateral) peripheral nerves (sciatic, tibial and sural), the gasserian ganglion, gastrocnemius muscle, both forelimbs, gross lesions in neural tissues or skeletal muscle and physical identifier were dissected from each animal and post-fixed in 10% phosphate buffered formalin. The brain was weighed upon removal from the skull, prior to placement into formalin, and the brain body weight ratio was calculated. The remaining animals, including ones that were sacrificed prior to study termination, were sacrificed by carbon dioxide asphyxiation and necropsied. Terminal body weights were performed immediately prior to necropsy to allow for calculation of organ to body weight ratios. Micropathology examinations were conducted on a comprehensive selection of neural tissues from perfusion-fixed control and high-dose rats of both sexes. Eight coronal sections of the brain and sections from three levels of the spinal cord (cervical, thoracic, lumbar) and the cauda equina were embedded in paraffin and stained with hematoxylin and eosin (H&E). Dorsal root ganglia (including dorsal and ventral root fibers) from the cervical and lumbar swellings and gasserian ganglion were embedded in glycol methacrylate (GMA). Eyes, optic nerves and gastrocnemius muscle tissues were embedded in paraffin and stained using H&E. Peripheral nerves (sciatic, tibial and sural) were embedded in GMA and cut in cross/transverse-section, as well as longitudinal section. GMA-embedded tissues were sectioned at 2-3 µm and stained using a modified Lee's stain. The sciatic nerve was also cut in cross-section at approximately 2-3 µm and stained with a modified Lee's stain. In addition, histopathology was performed on any gross lesion collected at necropsy. Tissues from perfusion-fixed animals at the low- and mid-dose levels were not subjected to micropathology unless a compound-related lesion was present in the high-dose group.

C7. Positive Controls

This study did not include concurrent positive controls, but references are made to previous studies conducted at this laboratory to serve that purpose. For the Functional Observational Battery (FOB), studies were conducted with acrylamide, carbaryl and untreated rats to establish the sensitivity, reliability, and validity of these test procedures, the adequacy of training of technical personnel and to serve as a historical control. To assess motor activity, studies with untreated animals and with rats

treated with reference substances that increase (triadimefon) and decrease (chlorpromazine) motor activity have established the sensitivity, reliability and validity of the test procedures used. Studies performed at this laboratory with trimethyltin and acrylamide have established the sensitivity and reliability of the micropathology procedures for detecting lesions in peripheral nerves and the central nervous system.

II. RESULTS AND DISCUSSION
A. OBSERVATIONS:
A1. Clinical signs of toxicity
There were no treatment-related clinical observations seen at any dietary level in either sex. Findings that were considered incidental and unrelated to treatment were a scab on right shoulder in one high-dose male, areas of hair loss described as alopecia in two control and two low-dose females and one low-dose female described as a spiller on one occasion. .

A2. Mortality
There were no deaths at any dietary level.

B. BODY WEIGHT AND BODY WEIGHT GAIN
Body weight was not affected by treatment in either sex at any dietary level (Table 5.7.1-1).

Table 5.7.1-1: Body weights (means (g) ± s.d.)

Day No.	**Dose Level (ppm)**		
	Control	**3750** (307.0 mg/kg bw (m), 362.4 mg/kg bw (f))	**15000** (1208 mg/kg bw (m), 1415 mg/kg bw (f))
	Males (n=12)		
Day 0	237.9±14.2	238.3±19.9	248.4±25.8
Day 7	271.7±20.4	269.0± 25.5	284.7±33.8
Day 14	294.8±26.6	289.3±25.8	307.0± 40.5
Day 21	311.4±32.5	303.4±28.6	322.0±46.0
Day 28	329.7±35.8	322.8±30.6	344.0±48.3
	Females (n=12)		
Day 0	167.1±10.4	165.9±12.2	163.6±7.8
Day 7	182.5±11.5	181.7±12.6	177.1±7.3
Day 14	189.9±10.1	192.6±11.7	189.3±7.8
Day 21	199.5±10.7	200.8±14.2	200.0±9.7
Day 28	212.0±12.5	212.5±13.2	208.9±10.1

Values represent mean ± s.d

Body weights were not statistically different from controls (p≤0.05; ANOVA + Dunnet's test)

C. FOOD CONSUMPTION

Food consumption was not affected by treatment in males or females at any dietary level (Table 5.7.1-2).

Table 5.7.1-2: Food consumption (g/animal/day ± s.d.)

Day No.	Dose Level (ppm)		
	Control	**3750** (307.0 mg/kg bw (m), 362.4 mg/kg bw (f))	**15000** (1208 mg/kg bw (m), 1415 mg/kg bw (f))
		Males (n=12)	
Day 7	21.28±1.75	21.22±2.56	21.57±3.31
Day 14	22.23±2.54	21.75±2.38	23.02±3.62
Day 21	22.38±2.41	21.90±2.35	22.90±3.76
Day 28	20.71±1.89	20.42±1.97	21.39±2.80
		Females (n=12)	
Day 7	16.05±2.78	16.95±3.67	15.73±2.04
Day 14	16.15±1.78	16.95±2.09	16.95±1.38
Day 21	16.73±2.55	17.38±2.65	17.22±1.53
Day 28	15.40±1.67	16.75±2.21	15.65±1.38

Values represent mean ± s.d.

Food consumption was not statistically different from controls (p ≤ 0.05; ANOVA + Dunnet's test)

D. NEUROBEHAVIORAL RESULTS

D1. FOB Findings

There were no findings related to treatment at any dietary level in either sex. Observations considered incidental and unrelated to treatment included a dermal lesion described as a scab in one high-dose male (week 4), urine stain in one female assigned to the low-dose group (pretreatment week) and hair loss (described as alopecia) in two low-dose females (week 4). None of these findings are associated with treatment since most are commonly seen in control animals (e.g., hair loss and dermal lesions) and the urine stain was seen prior to treatment initiation.

D2. Motor activity

In order to measure the magnitude of the difference that should be considered biologically significant the average pretreatment values among the three groups of males and females were taken as basis for comparison.

For motor activity, the pretreatment values for groups that later received the test substance averaged from 1% lower to 3% higher than animals assigned to the control group for males and from 6% to 10% lower than controls for females (Table 5.7.1-3). For locomotor activity, the pretreatment values for groups that later received the test substance averaged from 3% lower to 6% higher than controls for males and from 2% to 8% lower than controls for females (Table 5.7.1-4). As a general guide, these results confirm that differences of approximately ± 20% are within the range of normal variability in this laboratory for groups of 10-12 rats/sex/dietary level and, therefore, are not biologically significant. For the overall 60-minute test session, motor and locomotor activity was not affected by treatment at any dietary level in either sex. For males and females, interval motor and locomotor activity were not affected by treatment at any dietary level. Habituation was also not affected by treatment with Foramsulfuron in males or females at any dietary level.

Table 5.7.1-3: Summary session motor activity results (% difference from controls)

Test week	Dose Level (ppm)	
	3750 (307.0 mg/kg bw (m), 362.4 mg/kg bw (f))	**15000** (1208 mg/kg bw (m), 1415 mg/kg bw (f))
Males (n=12)		
Pretreatment	-1	+3
Week 4	-6	-7
Females (n=12)		
Pretreatment	-10	-6
Week 4	-3	-2

Values are percent greater (+) or less (-) than concurrent control
Summary session motor activity was not statistically different from control (($p \leq 0.05$; ANOVA)

Table 5.7.1-4: Summary session locomotor activity results (% difference from controls)

Test week	Dose Level (ppm)	
	3750 (307.0 mg/kg bw (m), 362.4 mg/kg bw (f))	**15000** (1208 mg/kg bw (m), 1415 mg/kg bw (f))
Males (n=12)		
Pretreatment	-3	+6
Week 4	-8	-8
Females (n=12)		
Pretreatment	-2	-8
Week 4	-3	-13

Values are percent greater (+) or less (-) than concurrent control
Summary session locomotor activity was not statistically different from control (($p \leq 0.05$; ANOVA)

E. OPHTHALMOLOGY

All ophthalmologic findings were considered incidental and unrelated to exposure to foramsulfuron. The incidental ocular abnormalities were recorded at study termination included corneal opacity and retinal degeneration. Corneal opacity and retinal degeneration noted at the terminal ophthalmologic examination were considered to be background and/or incidental observations because the changes were not statistically significant; the changes in the perfused animals were not correlated to the results of the microscopic examination of the eyes from perfused control and 15000 ppm dose level animals; and/or there were no treatment-related findings at any dietary level in either sex in a 90-day toxicity study conducted with this compound in Sprague Dawley rats at nominal concentrations of 20, 200, 5000, or 20000 ppm (see CA 5.3.2).

F. SACRIFICE AND PATHOLOGY

F1. Gross Pathology

No compound-related gross lesions or gross observations were evident at terminal sacrifice in males or females at any dietary level.

F2. Terminal Body and Brain Weights

There were no treatment-related differences in absolute and relative brain weights between control and treated perfused rats.

F3. Micropathology
There were no treatment-related findings in neural and/or non-neural tissues from perfusion-fixed high-dose males or females. Tissues from animals at lower dose levels were, therefore, not examined.

III. CONCLUSIONS
Technical grade Foramsulfuron was administered in the diet for 28 days to young-adult Wistar rats (12/sex/dietary level), using nominal concentrations of 0, 3750 and 15,000 ppm for males and females. Twelve rats/sex/dietary level were used for neurobehavioral evaluation, with selected tissues from six perfused rats/sex from control and high-dose groups used for neuropathology. Through 28 days of continuous dietary exposure to the test substance, there were no neurotoxic effects or treatment-related findings at any dietary level in either sex. Based on these results a NOAEL for neurotoxicology endpoints was established at 15,000 ppm which is equivalent to 1208 mg/kg bw/day in males and to 1415 mg/kg bw/day in females.

CA 5.7.2 Delayed polyneuropathy studies

Since foramsulfuron does not belong to the class of organophosphates or carbamates from which some candidates have the potential to cause polyneuropathy, and since in the other toxicology studies no evidence of any nerve effects was seen it was not necessary to conduct such testing with foramsulfuron.

CA 5.8 Other toxicological studies

No other toxicology studies were deemed necessary.

CA 5.8.1 Toxicity studies of metabolites

Since no plant- or soil-specific metabolites have been identified no specific studies with metabolites have been conducted.

CA 5.8.2. Supplementary studies on the active substance

No supplementary toxicology studies were performed.

CA 5.8.3 Endocrine disrupting properties

In the apical studies no evidence of an endocrine effect of foramsulfuron was obvious. No clinical signs, organ weight effects or morphological finding in endocrine organs or organ systems were seen in any sub chronic or chronic/carcinogenicity study which would indicate such an effect. Furthermore, the reproduction toxicity study in rats and the developmental toxicity studies in rats and rabbits did not indicate any impact of foramsulfuron on reproduction or developmental parameters indicating an endocrine effect. Furthermore, foramsulfuron does not fall under the interim definition for Endocrine Disruption.

CA 5.9 Medical data

The following information (CA 5.9.1) was provided by the global medical director of Bayer CropScience, XXXXXXXXXXXX and gives the most current facts (January 2012).

CA 5.9.1 Medical surveillance on manufacturing plant personnel and monitoring studies

Number of employees handling product: 30
Production period: 2002 to 2013

Personal safety measures: Work clothing, safety shoes, rubber gloves, goggles, dust protection suit, dust mask or face mask with ABED/P2 filter
In-company experience: No unusual occurrences or complaints

CA 5.9.2 Data collected on humans

No data were collected on humans.

CA 5.9.3 Direct observations

Please refer to point 5.9.7.

CA 5.9.4 Epidemiological studies

No epidemiological studies were performed, also the literature search according to the new data requirements for the required period of the last 10 years did not reveal any published epidemiology work.

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

Please refer to point 5.9.7.

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

Please refer to point 5.9.7.

CA 5.9.7 Expected effects of poisoning

There are no reports on poisoning in humans. Animal experiments with high doses of other sulfonyl urea herbicides showed unspecific symptoms with decreased activity, irregular breathing and labored breathing. Though it is a sulfonyl urea compound, foramsulfuron does not influence glucose metabolism.

First Aid:

- Remove patient from exposure/terminate exposure
- Thorough skin decontamination with copious amounts water and soap, if available with polyethylenglycol 300 followed by water.

Note: Most formulations with this active ingredient can be decontaminated with water (and soap), so for formulations polyethyleneglycol 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 carthartic) might be considered in significant ingestions.
- As there is no antidote, treatment has to be symptomatic and supportive.