

Draft Renewal Assessment Report
under Regulation (EC) 1107/2009



FORAMSULFURON

Volume 3 – B.6 (AS)

Rapporteur Member State: Finland
Co-Rapporteur Member State: Slovakia

March 2015

Volume 1

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Annex C: Confidential information and, where relevant, details of any task force formed for the purpose of generating tests and studies submitted

List of Endpoints

Version History

When	What
2015/March	First draft RAR

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B.6. TOXICOLOGY AND METABOLISM DATA

In this renewal submission, a previous evaluation/comments box has been inserted above each study to indicate studies already evaluated in the original RAR. Additional studies/information have been submitted and evaluated in this revised RAR. New evaluations and changes to the text are highlighted in yellow.

B.6.1. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION IN MAMMALS

The absorption, distribution, metabolism and excretion, including plasma and blood pharmacokinetics of foramsulfuron has been investigated in the Sprague-Dawley rat following a nominal single oral gavage dose of 10 or 1000 mg/kg bw and following 14 daily oral doses of 10 mg/kg bw. There were no significant differences in the excretion profile of the phenyl- or pyrimidyl-labelled foramsulfuron and a very low level of metabolism of the compound. In view of these results [¹⁴C-phenyl]-foramsulfuron was used for the majority of the studies, although [¹⁴C-pyrimidyl]-foramsulfuron was also dosed as part of the determination of the metabolism.

Absorption

Following oral administration of foramsulfuron at a single dose of 10 mg/kg bw in bile-duct cannulated rats, 12.7% of the radiolabel was recovered in urine, 4.2% in bile and 2.3% in the cage wash within 48 h. Furthermore, 1.5% of the administered radiolabelled dose (AD) was detected in the residual carcass, which included the gastrointestinal tract and tissues. On this basis, the fraction of the administered radiolabel (10 mg/kg bw) absorbed within 48 h from the gastrointestinal tract is approximately 20%.

Distribution

Radioactivity was distributed into almost all tissues within 30 min after administration of a single dose of radiolabelled foramsulfuron. At 30 hours after administration of the low dose (10 mg/kg bw), highest residue levels were detected in liver and kidney; by 72 h, levels of all tissues were near or below the limit of detection. At the high-dose level (1000 mg/kg bw) comparably high concentrations were determined at the 30-h timepoint in the thyroid (69–79 µg eq./g), adrenals (36–61 µg eq./g), female gonads (13 µg eq./g), eyes (~7.4 µg eq./g) and liver (3.8–6.8 µg eq./g), while the residue levels in the other tissues were below the limit of detection. All tissue residue levels were below 0.5 µg eq./g tissue at the 72-h timepoint with the exception of the spleen, heart and renal fat in males (0.7–1.6 µg eq./g) and liver and spleen of females (0.5 µg eq./g).

Potential for accumulation

Upon repeated administration of radiolabelled foramsulfuron at 10 mg/kg bw/d, increases of residue concentration levels resulted in most tissues over the 14-d treatment period. These increases did not exceed 3-fold with the exception of the following male tissues: brain (20x increase), testes (15x), thyroid (10x), and heart (6.5x). The level of the radioactive residues in the tissues throughout the study was generally below 0.1 µg equivalent/g. The liver was the only tissue exhibiting clearly increased radiolabel concentrations compared to plasma at both timepoints of investigation (24 and 48 h). This finding is considered to reflect redistribution of the radiolabel prior to biliary/renal excretion and should not be interpreted as an indication of an accumulation potential of foramsulfuron. This view is further supported by the fact that the extent of elimination from the body was independent of dose and frequency of administration.

Elimination

Foramsulfuron was rapidly eliminated from the body following absorption. The elimination half-life in the plasma was 5.4–18.5 h at the low dose and 2.4–2.8 h at the high dose level. A mean of 96% of the dose was present in the 0-48 hour excreta at both dose levels. Faecal excretion predominated with only 5.6% of the low dose and 1.4% of the high dose being found in the urine. There was no significant sex

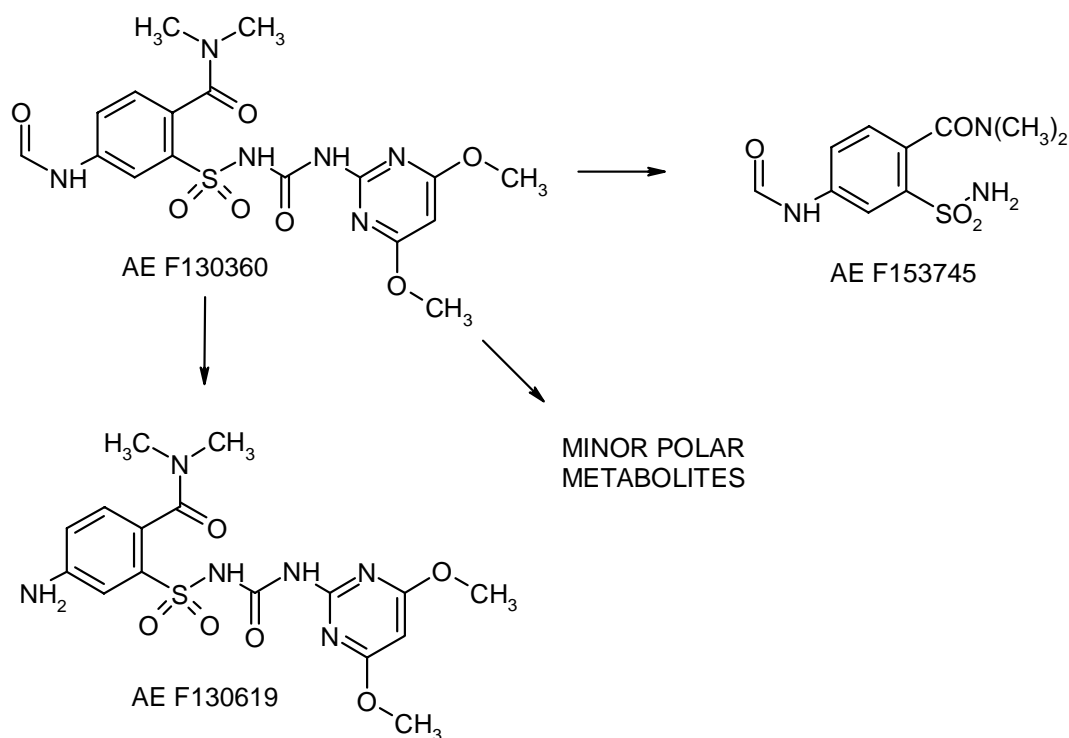
difference in the route of excretion and no excretion of radiolabelled carbon dioxide, demonstrating the stability of the position of the radiolabel. Repeat dosing at 10 mg/kg bw/day for 14 days had no significant effect on the excretion profile.

Metabolism

The metabolism of foramsulfuron has been determined in the rat following dosing at 10 or 1000 mg/kg bw. The main excretion product was unchanged foramsulfuron excreted mainly in the faeces. There were two metabolic pathways identified, deformylation to give the amine AE F130619 (= N,N-dimethyl-2-[3-(4,6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-4-aminobenzamide), and cleavage of the sulfonylurea bridge to produce AE F153745 (= N,N-dimethyl-2-sulfamoyl-4-formylamino-benzamide), both of which were excreted as minor metabolites. In addition a number of minor (< 4% of dose) polar metabolites from both the phenyl- and pyrimidyl-labelled compound were also excreted but not identified. These results support the decision to use only phenyl-labelled foramsulfuron for the majority of the studies as the minor metabolites associated only with the pyrimidine ring were found to be polar and would therefore be readily excreted.

The metabolic profile of foramsulfuron in the rat is shown in Figure B.6.1-1.

Figure B.6.1-1: Metabolic profile of foramsulfuron in rats



B.6.1.1. Absorption, distribution, metabolism and excretion by oral route

B.6.1.1.1 Single oral dose

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. The study
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	is acceptable as supplementary information.
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Report: [REDACTED], 1999 (TOX2000-1035)
Code: AE F130360 ZE – Preliminary toxicokinetic studies in the rat
Report-No. TOX/98/262-28, Doc.No. (Aventis): C004339, unpublished
Testing facility: [REDACTED]
(Experimental work: 29 July 1996 to 20 September 1996)

Test Material: [¹⁴C-phenyl]-foramsulfuron or [¹⁴C-pyrimidyl]-foramsulfuron
98.4% (w/w) purity of the non-radiolabelled test material (batch H 2037)

Test Animals: Sprague Dawley CRL:CD(SD)BR rats, 139-178 g bw at dosing
Supplied by: [REDACTED]

GLP: Yes

Test Method: OECD TG 417 (adopted 4 April 1984)

Deviations: Animal group sizes were smaller than required in OECD TG 417

Acceptability: The study is considered to be acceptable as supplementary information.

Material and Methods:

Two rats of each sex were dosed orally by gavage with a suspension of either [¹⁴C-phenyl]- or [¹⁴C-pyrimidyl]-radiolabelled foramsulfuron in aqueous gum tragacanth (1% w/v) at 10 mg/kg bw. A further animal of each sex was dosed with a suspension of phenyl-labelled foramsulfuron at 1000 mg/kg bw. All animals were deprived of food for 16 h prior to dosing.

Following dosing the rats were placed in all-glass metabolism cages and urine and faeces were collected for 7 days (3 days for rats dosed with pyrimidyl-labelled foramsulfuron) in cooled containers to prevent bacterial degradation of the metabolic products. Expired air was monitored for excreted radioactivity and at the end of the collection period (7 or 3 days after dosing) the rats were sacrificed and the concentration of radioactive residues in the tissues was determined. Radioactivity in the urine and cage wash was measured by direct addition to scintillation cocktail. Blood and bone were combusted and all other samples were solubilised, either following homogenisation or as whole tissue pieces, before being added to scintillation cocktail.

The profile of metabolites in the urine and faeces was compared between sexes and between dose levels using radio-HPLC.

An additional animal of each sex was dosed with either 10 or 1000 mg phenyl-labelled foramsulfuron/kg bw and the blood pharmacokinetic parameters at each dose level were examined. Tail bleeds were taken at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24, 30, 48, and 72 hours after dosing to collect blood samples. After examining the results of this study, further animals were dosed at 10 or 1000 mg/kg bw and sacrificed at 1 hour after dosing, when the blood levels of radioactivity were expected to be at a maximum. The nature of the radioactivity present in the plasma was determined by radio-hplc.

Findings:

Foramsulfuron was rapidly absorbed and eliminated following the administration of either 10 or 1000 mg/kg bw with no significant differences in the rate of absorption and route of elimination being seen between the sexes. At both dose levels the maximum blood concentration (C_{max}) occurred at approx. 1

hour after dosing. Based on radiolabel recovered in urine, carcass, and tissues, at least 10% of the administered radioactivity was absorbed.

The majority of the dosed radioactivity was excreted within 24 hours following oral dosing at 10 mg/kg bw (94.6% and 70.1% for rats dosed with pyrimidyl- or phenyl-labelled foramsulfuron, respectively). At the higher dose of 1000 mg/kg bw, excretion of the majority of the dose (92.7%) was found in the 0-48 hour excreta. The major route of excretion was via the faeces (see Table B.6.1-1, which contained about 87% of the dose from rats dosed with 10 mg/kg bw (approx. 10% in urine), and approx. 92% from rats dosed at 1000 mg/kg bw (4% in urine).

Table B.6.1-1: Excretion data of preliminary toxicokinetic study

	Mean percentage of recovered administered dose (%)								
Label	Pyrimidyl			Phenyl					
Dose	10 mg/kg bw			10 mg/kg bw			1000 mg/kg bw		
N (m/f)	2/2			2/2			1/1		
	urine	faeces	Total	urine	faeces	Total	urine	faeces	Total
0–24h	9.0	85.6	94.6	9.1	65.7	74.8	3.2	28.2	31.4
0–48h	9.2	86.8	96.0	10.0	80.0	90.0	4.0	88.7	92.7
0–72h	9.3	87.0	96.3	10.1	80.9	91.0	4.2	92.3	96.5
0–168h	N.A.	N.A.	N.A.	10.2	85.7	95.9	4.4	92.4	96.8
TOTAL*	96.5 (0–72 h)			96.0 (0–168 h)			97.3 (0–168 h)		

*including cage wash and CO₂-trap (range 0.00–0.02% AD); carcass levels were below limit of quantification

N.A. not applicable

The mean total recovery of radioactivity was 96.6% for all animals. There was no significant excretion of radiolabelled carbon dioxide and this demonstrated the stability of the positions of the radiolabel.

As would be expected for such a rapidly excreted compound, the concentration of radioactive residues in the tissues at necropsy was low. The only tissue to contain radioactive residues above the limit of detection was the liver of rats dosed with pyrimidyl-labelled foramsulfuron (mean of 0.038 µg eq./g tissue).

Foramsulfuron was found to undergo only limited metabolism regardless of the position of the radiolabel or dose level. In rats administered the pyrimidyl-radiolabel, faecal radioactivity was found to consist almost entirely of parent compound. Urinary radioactivity consisted of an unidentified polar metabolite (~ 5% AD), together with parent compound (~ 2.5% AD) and the free amine AE F130619 (= N,N-dimethyl-2-[3-(4, 6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-4-aminobenzamide, ~ 2.5% AD). Similarly, for the phenyl radiolabel, it was shown that foramsulfuron was the major compound in both faeces and urine (~ 72% and 4.5% AD, respectively). The cleavage product AE F153745 (= N,N-dimethyl-2-sulfamoyl-4-formylaminobenzamide) was seen in the urine (~3.5% AD) and faeces (~6% AD), while AE F130619 was detected in the urine, only. Thus, metabolic profiles showed some qualitative differences between radiolabels, with more polar metabolites seen in the urine of rats dosed with pyrimidyl-labelled foramsulfuron. Foramsulfuron was the only component seen in the plasma.

Conclusion:

This study provides preliminary information that foramsulfuron was rapidly excreted following the administration of a single gavage dose of 10 or 1000 mg/kg bw, and the concentration of residues in the tissues at necropsy was low. There was no significant radioactivity excreted in the expired air, showing that the positions of the radiolabel were stable and expired air would therefore not need to be

There were no significant differences in the excretion profile of the phenyl- or pyrimidyl-labelled foramsulfuron and the parent compound was excreted mainly unchanged with very little metabolism of the compound occurring. The only identified metabolites were AE F130619 and AE F153745. On the basis of these results, the majority of the succeeding balance studies were conducted with the phenyl-labelled foramsulfuron only.

Report:	[REDACTED], 1999 (TOX2000-1036) (C)-AE F130360: Rat – Absorption, distribution, elimination following oral dosing at 10 and 1000 mg/kg body weight Report-No. TOX/98/262-29, Doc.No. (Aventis): C004532, unpublished Testing facility: [REDACTED] (Experimental work:8–11 April 1997)
Test Material:	[¹⁴ C-phenyl]-radiolabelled foramsulfuron in aqueous gum tragacanth (1% w/v); purity: >99% (radiolabel) and 98.4% (w/w, non-radiolabel, batch H 2037)
Test Animals:	Sprague Dawley CRL:CD(SD)BR rats, 148-171 g bw at dosing Source: [REDACTED]
GLP:	Yes
Test Method:	OECD TG 417 (adopted 4 April 1984)
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Five male and five female rats were dosed orally by gavage with a suspension of [^{14}C -phenyl]-radiolabelled foramsulfuron in aqueous gum tragacanth (1% w/v) as a single oral gavage dose of nominally 10 or 1000 mg/kg bw. All animals were deprived of food for 16 h prior to foramsulfuron administration. After dosing, animals were maintained in all-glass metabolism cages for 3 days, during which time the urine and faeces were collected in cooled containers to monitor the excretion of the radiolabelled dose. The animals were sacrificed 72 h after dosing and levels of radiolabelled residues in the tissues were determined. Radioactivity in the urine and cagewash was measured by direct addition to scintillation cocktail. Blood and bone were combusted and all other samples were solubilised, either following homogenisation or as whole tissue pieces, before being added to scintillation cocktail.

Findings:

Foramsulfuron appeared to be poorly absorbed with mean values of 5.7% of the dose being excreted in the urine of male and female rats at the low dose within 72 h, and 1.5% at the high dose. In the faeces, approx. 90% and 96% of the radiolabel was recovered 72 h after administration of the low and high dose, respectively. Elimination was rapid, with a mean of 91.5% of the dose being found in the 0 to 24-hour excreta at both dose levels (see Table B.6.1-2).

Table B.6.1-2: Excretion data of main toxicokinetic study

	Mean percentage of recovered administered dose (%)								
	Urine + cage wash			Faeces			Total eliminated		
	male	female	combined	male	female	combined	male	female	combined
1x 10 mg/kg bw									
0-24 h	5.0	5.7	5.4	85.7	87.9	86.8	90.7	93.6	92.2
0-48 h	5.2	5.9	5.6	89.8	89.4	89.6	95.0	95.3	95.2
0-72 h	5.3	6.1	5.7	90.0	89.5	89.7	95.3	95.6	95.5
1x 1000 mg/kg bw									
0-24 h	1.1	1.3	1.2	87.5	91.8	89.7	88.6	93.1	90.9
0-48 h	1.3	1.5	1.4	94.3	96.9	95.6	95.6	98.4	97.0
0-72 h	1.4	1.5	1.5	94.4	97.1	95.8	95.8	98.6	97.2

The concentrations of radioactive residues in the tissues are shown in Table B.6.1-3. At necropsy (72 hours after dosing) the concentration of radioactive residues in all tissues was below 0.05 µg eq./g for the rats dosed at 10 mg/kg bw. At the higher dose level mean concentrations of radioactive residues were generally below 0.5 µg eq./g with the exception of the spleen, heart and renal fat in males (0.653-1.608 µg eq./g) and liver and spleen of females (0.510-0.551 µg eq./g).

Table B.6.1-3: Concentrations of radioactive residues in rat tissues 72 h following single oral administration

Tissue	Concentration of radioactive residues (as µg eq./g tissue)							
	Dose of 10 mg/kg bw				Dose of 1000 mg/kg bw			
	Males		Females		Males		Females	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Adrenal	0.001	0.001	0.001	0.000	0.309	0.112	0.196	0.047
Blood	0.001	0.000	BLQ		0.101	0.020	0.097	0.030
Bone	BLQ		BLQ	-	0.130	0.027	0.146	0.070
Brain	BLQ		BLQ		0.152	0.048	0.131	0.025
Carcass	BLQ		BLQ		0.032	0.038	0.094	0.110
Eyes	0.001	0.000	0.001	0.001	0.005	0.010	BLQ	
Heart	BLQ		BLQ		0.813	0.406	0.459	0.058
Kidney	BLQ		BLQ		0.006	0.013	0.007	0.014
Liver	0.002	0.000	0.002	0.000	0.480	0.117	0.510	0.161
Lung	BLQ		BLQ		0.004	0.008	0.005	0.010
Muscle	0.003	0.001	0.002	0.000	0.182	0.016	0.180	0.037
Ovaries			0.001	0.000			0.264	0.185
Plasma	BLQ		BLQ		0.036	0.029	0.018	0.028
Renal fat	0.001	0.001	0.001	0.000	0.653	0.237	0.485	0.218
Skin	0.001	0.000	BLQ		0.104	0.114	0.116	0.064
Spleen	BLQ		BLQ		1.608	0.859	0.551	0.258
Testes	BLQ				0.293	0.110		
Thyroid	BLQ		BLQ		BLQ		BLQ	

BLQ = Below the Limit of Quantification.

SD = Standard Deviation

Conclusion:

Overall the results show that following a single oral dose of 10 or 1000 mg/kg bw, foramsulfuron was absorbed to a limited degree and rapidly eliminated with 96% of the dose being found in the 0 to 48-hour excreta at both dose levels. Faecal excretion was the predominant route with less than 6% of the dose appearing in the urine.

Report:

██████████, 1998 (TOX2000-1037)
 (¹⁴C)-AE F130360 : A study of excretion following oral administration to bile duct cannulated rats
 – Amended Final Report –
 Report No. TOX/98/262-33, Doc.No. (Aventis): A67666; unpublished
 Testing facility: ██████████
 (Experimental work: 7 February to 4 September 1997)

Thornley K.F., 2000
 1st Amendment to Report No. TOX/98/262-33
 (¹⁴C)-AE F130360 : A study of excretion following oral administration to bile duct cannulated rats
 Report No. TOX/98/262-33, Doc.No. (Aventis): C007333; unpublished

Test Material:	[¹⁴ C-phenyl]-foramsulfuron in aqueous gum tragacanth (1% w/v); radiolabel purity 94%, purity of non-radiolabelled substance (batch H 2037): 98.4% (w/w)
Test Animals:	Male Sprague Dawley CRL:CD(SD)BR rats, 272–311 g bw at dosing Supplied by: [REDACTED]
GLP:	Yes
Test Method:	OECD TG 417, adopted 4 April 1984
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:

Four male rats were dosed orally by gavage with a suspension of [U-¹⁴C-phenyl]-foramsulfuron in aqueous gum tragacanth (1% w/v) at a nominal dose rate of 10 mg/kg bw. All animals were starved overnight prior to dosing. Bile, urine, faeces, cage washings and debris were sampled over a 48-hour time course. Urine, diluted bile and cage wash plus debris were measured by direct addition to scintillation cocktail, faeces were homogenised and combusted to carbon dioxide, and the carcass (including tissues and the intact gastrointestinal tract) was solubilised prior to analysis by scintillation counting.

Findings:

The results showed that foramsulfuron was poorly absorbed following oral administration with a mean of 75.6% of the dose being detected in the faeces. The mean absorption of foramsulfuron, as measured by the amount of dose found present in the urine, bile, cage washes and debris, was 19.2%; radioactivity present in the carcass could not be included in the absorbed total, because the gastrointestinal tract remained intact during solubilisation prior to analysis. Biliary excretion was not a major route of elimination accounting for about 25% of the absorbed dose, while the largest portion of the absorbed dose was excreted via the urine.

The overall recovery of the experiment was $96.2 \pm 2.0\%$. The results are given in the following Table B.6.1-4.

Table B.6.1-4: Recovery of radioactivity orally administered to bile-cannulated rats (single dose)

	Mean percentage of recovered administered dose (%)						
	Urine	Bile	Cage-Wash / Cage Debris	Faeces	Carcass (incl. tissues+ GIT)	Total absorbed	Total eliminated
0–24 h	10.5	3.6	N.D.	62.9	N.D.	14.1	77.0
0–48 h	12.7	4.2	2.3	75.6	1.5	19.2	94.8

N.D. Not determined GIT: Gastrointestinal tract

Conclusion:

Following the administration of a single oral dose of foramsulfuron to bile duct cannulated rats only 19.2% of the dose was found to be absorbed within 48 h. The majority of the dose was excreted unabsorbed in the faeces.

Previous evaluation	Deviation from the current OECD Test Guideline 417 (adopted 22nd July, 2010): Only three animals/sex/dose were tested but both sexes were tested.
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Report: [REDACTED], 1999 (TOX2000-1038)
 (¹⁴C)-AE F130360 : Tissue distribution and clearance in the rat
 Report No. TOX/99/262-43, Doc.No. (Aventis): C005630; unpublished
 Testing facility: [REDACTED]
 (Experimental work: 5 May to 6 July 1999)

Test Material: [¹⁴C-phenyl]-foramsulfuron in aqueous gum tragacanth (1% w/v)
 radiolabel purity 98.6%, purity of non-radiolabelled substance (batch no. 28777–11): 99%

Test Animals: Sprague Dawley CRL:CD(SD)BR rats, 158–202 g bw upon arrival
 Supplied by: [REDACTED]

GLP: Yes

Test Method: OECD 417, adopted 4 April 1984

Deviations: Deviation from protocol:
 Low-dose animals were not starved overnight prior to dosing.

Acceptability: The study is considered to be acceptable.

Material and Methods:

Male and female rats were dosed orally with a suspension of [¹⁴C-phenyl]-foramsulfuron in aqueous gum tragacanth (1% w/v) at a nominal dose level of either 10 or 1000 mg/kg bw. For each dose group, three animals of each sex were sacrificed at 0.5, 1, 4, 12 and 30 hours after dose administration. At necropsy, whole blood, the major organs and samples of selected tissues were taken and analysed for radioactivity. The concentration and recovery of radioactivity of each tissue and the residual carcass were then determined. Blood and bone were combusted and all other samples were solubilised, either following homogenisation or as whole tissue pieces, before being added to scintillation cocktail.

Findings:

Following the administration of 10 mg/kg bw to male and female rats, radioactivity was distributed into almost all tissues within 30 minutes of a single dose. Maximum concentrations of radioactivity in whole blood and plasma were observed at 0.5 and 1 hour after dosing for males and females respectively in the 10 mg/kg dose group, and 4 hours after dosing for the 1000 mg/kg dose group. The maximum concentrations of radioactivity for all tissues occurred within 1–4 and 4–12 hours after dosing for the low and high dose level groups, respectively. Clearance of radioactivity from the systemic circulation and tissues was rapid and extensive. 30 h after low-dose administration, the highest concentrations were detected in liver and kidney tissue. After single dose treatment with 1000 mg/kg bw, maximum concentrations levels were achieved in the eyes, adrenals, thyroids and female gonads. A summary of the pharmacokinetic parameters for plasma, of the mean tissue concentrations, and the % dose present in the tissues at the terminal time point are shown in Table B.6.1-5 and Table B.6.1-6, respectively.

Table B.6.1-5: Pharmacological parameters of foramsulfuron after single oral administration to rats

Pharmacokinetic parameters	10 mg/kg bw		1000 mg/kg bw	
	Male	Female	Male	Female
Plasma C _{max} (µg/g)	0.903	0.691	11.57	14.81
Plasma T _{max} (h)	0.5	1.0	4.0	4.0
t _{1/2} elim (h)	18.46	5.437	2.407	2.865
Range (h)	12–30	4–30	4–12	4–12
AUC _{0-t} (µg.h/g)	5.028	4.305	84.66	101.6
AUC _{0-∞} (µg.h/g)	5.800	4.384	88.68	110.4

Table B.6.1-6: Radioactivity in tissues of rats 30 h after single oral administration of foramsulfuron

Tissue	10 mg/kg bw				1000 mg/kg bw			
	Male		Female		Male		Female	
	Conc. (µg/g)	% Dose	Conc. (µg/g)	% Dose	Conc. (µg/g)	% Dose	Conc. (µg/g)	% Dose
Adrenals	N.D.	N.D.	0.018	<0.001	61.19	0.001	35.64	0.001
Blood	0.011	<0.001	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Bone	0.004	0.004	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Brain	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Carcass*	0.075	0.613	0.106	0.835	2.532	0.241	7.891	0.733
Eyes	0.007	<0.001	0.002	<0.001	7.691	0.001	7.188	0.001
Fat	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
GIT	–	4.993	–	3.022	–	0.526	–	1.591
Gonads	0.009	0.001	0.017	<0.001	N. D.	N. D.	12.78	0.001
Heart	0.043	0.002	0.016	<0.001	N. D.	N. D.	N. D.	N. D.
Kidney	0.113	0.008	0.038	0.003	N.D.	N.D.	N.D.	N.D.
Liver	0.228	0.126	0.078	0.039	6.790	0.038	3.842	0.017
Lung	0.061	0.003	0.016	<0.001	N. D.	N. D.	N. D.	N. D.
Muscle	0.010	0.041	0.005	0.024	N.D.	N.D.	N.D.	N.D.
Plasma	0.029	0.023	0.010	<0.001	N.D.	N.D.	N.D.	N.D.
Spleen	0.015	<0.001	0.008	<0.001	N.D.	N.D.	N.D.	N.D.
Thyroid	N.D.	N.D.	N.D.	N.D.	78.66	<0.001	68.80	<0.001

N.D. = Not Detected

* Concentration of radioactivity may be increased by contamination of the skin by urine.

Conclusion:

The results show that foramsulfuron was well distributed throughout the tissues following a single oral dose of 10 or 1000 mg/kg bw. However, the compound was rapidly and extensively cleared from the tissues at both dose levels with an elimination half-life in the plasma of 5.4–18.5 hours at the low dose and 2.4–2.9 hours at the high dose level. The maximum tissue concentrations were observed at 1–4 hours at the low dose and 4–12 hours at the high dose. At the high-dose level, relatively high tissue concentrations of radioactivity were determined in the eyes, adrenals, thyroid and female gonads.

Report:

[REDACTED], 1999 (TOX2000-1039)

(C)-AE F130360 : Metabolism in the rat following a single oral administration of 10 or 1000 mg/kg body weight

Report-No. TOX/99/262-38, Doc.No. (Aventis): C004971, unpublished
Testing facility: [REDACTED]
(Experimental work: 17 September 1996 to 11 April 1997)

Test Material: [¹⁴C-phenyl]- foramsulfuron: purity 99.3% (low dose) or 96.8% (high dose);
[2-¹⁴C-pyrimidyl]-foramsulfuron: > 98.7%; unlabelled foramsulfuron (batch
no. H 2037): 98.4%; in aqueous gum tragacanth (1% w/v)

Test Animals: Sprague Dawley CRL:CD(SD)BR rats, 7 wk old at dosing
Source: [REDACTED]

GLP: Yes

Test Method: OECD 417, adopted 4 April 1984

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Rats (4/sex) were given a single oral dose of 10 or 1000 mg/kg bw [¹⁴C-phenyl]-foramsulfuron in aqueous gum tragacanth (1% w/v). A second group of 2 rats/sex received 10 mg/kg bw of [¹⁴C-pyrimidyl]-radiolabelled foramsulfuron. All animals were deprived of food for 16 h prior to dosing. Urine and faeces were collected in cooled containers to prevent bacterial degradation of the excretion products, for 72 or 24 hours after the final dose for the rats dosed with phenyl- of pyrimidyl-labelled foramsulfuron respectively. The metabolites present in the urine were isolated by radio-hplc; the metabolites in the faeces were extracted by solvent and solid-phase extraction prior to isolation by radio-hplc. The structures of the metabolites present were determined using mass-spectroscopy and co-chromatography with synthetic standards.

The excreta from the rats, pooled by sex and time of collection, were then analysed by radio-hplc to quantify the amount of each metabolite excreted.

Findings:

Foramsulfuron underwent limited metabolism in both labels and at both doses, with the majority of the dose (72–80%) being excreted as unchanged parent compound in the faeces. The metabolic profile was qualitatively and quantitatively similar between males and females, and between dose levels. However, there were minor qualitative differences seen in the metabolism of foramsulfuron depending on the position of the radiolabel. In rats administered the phenyl-label at the 10 mg/kg dose level, the principal metabolite besides parent to be recovered in the faeces with 8.4-8.7% AD was N,N-dimethyl-2-sulfamoyl-4-formylaminobenzamide (= AE F153745), formed by the cleavage of foramsulfuron's sulfonylurea bridge. The remainder of the metabolites for both labels were polar compounds, no single component of which exceeded 0.2%. The major metabolites in urine were AE F153745 (2.3% AD; phenyl-label only) and N,N-dimethyl-2-[3-(4,6-dimethoxypyrimidin-2-yl)-ureidosulfonyl]-4-amino-benzamide (= AE F130619, 0.8-2.6% AD) formed by cleavage of the formyl group. The remainder of the metabolites (approx. 9% in the case of pyrimidyl-labelled foramsulfuron) was comprised of unidentified polar components, each of which was present at less than 4% of the dose.

A similar metabolic profile was seen after dosing at 1000 mg/kg bw, though AE F130619 was found in small amount in the faeces at the higher dose rate.

The amount of each of the major metabolites excreted in the urine and faeces are given in Table B.6.1-7 and the metabolic profile is shown in Figure B.6.1-1.

Table B.6.1-7: Metabolites in excreta of rats after single oral administration of foramsulfuron (as % of dose)

Dose mg/kg bw	Label	Sex	Excreta	Amount of metabolite (as % of dose)				
				Parent	AE F153745	AE F130619	Polar unknown	Total
10	Pyrimidyl	Male	24-h urine	2.1	n.a.	2.6	3.9	81.8
			24-h faeces	73.2	n.a.	n.d.	n.d.	
		Female	24-h urine	3.0	n.a.	2.5	3.6	82.5
			24-h faeces	73.3	n.a.	n.d.	n.d.	
10	Phenyl	Male	72-h urine	1.7	2.3	0.8	0.023	87.4
			72-h faeces	74.0	8.4	n.d.	0.176	
		Female	72-h urine	2.1	2.3	0.8	0.023	86.3
			72-h faeces	72.3	8.7	n.d.	0.095	
1000	Phenyl	Male	72-h urine	0.4	0.2	0.3	0.0	91.1
			72-h faeces	80.4	3.4	0.5	5.856	
		Female	72-h urine	0.4	0.3	0.3	n.d.	88.5
			72-h faeces	77.7	1.3	2.8	5.637	

n.a. = not applicable

n.d. = not detected

Note:

The excreta of rats treated with pyrimidyl-radiolabelled substance were sampled over a 24-h period for HPLC analysis, while the time-window of investigation was 72 h for excreta of rats administered phenyl-radiolabelled substance. However, only a total mean of 1.7% of the administered pyrimidyl-radiolabel (0.3% AD via urine and 1.3% AD via faeces) was additionally eliminated during the remaining 48-h period (see Table B.6.1-1). The metabolite levels in urine and faeces would only have marginally increased if the excreta had been pooled over 72-h instead of a 24-h period. Therefore, the amounts of the pyrimidine-labelled metabolites determined over 24-h can be used for comparison with the 72-h data obtained for the phenyl-labelled metabolites.

Conclusion:

Foramsulfuron has been shown to undergo only limited metabolism in the rat with the unchanged sulfonylurea being the main excretion product. The free amine AE F130619 was present as a minor metabolite with cleavage of the sulfonylurea bridge forming AE F153745 (phenyl label only). A number of minor (< 4%) polar metabolites from both the phenyl- and pyrimidyl-labelled compound were also excreted but were not identified.

B.6.1.1.2 Repeated oral dose

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed.
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	After the study was performed, a new version of the OECD Test Guideline 417 has been adopted 22nd July, 2010. Only three animals/sex were tested but several timepoints were measured. No sex differences were observed. Hence, the study is considered to be acceptable.
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Report:	[REDACTED], 1999 (TOX2000-1040) (¹⁴ C)-AE F130360 Rat : Absorption, distribution and elimination – repeat oral dose (10 mg/kg/day), Report-No. TOX/99/262-41, Doc.No. (Aventis): C005527, unpublished [REDACTED] (Experimental work: 15–30 June 1999)
Test Material:	[¹⁴ C-phenyl]-foramsulfuron in aqueous gum tragacanth (1% w/v); purity radiolabel (batch no.: Z 29036-0 and Z 29026-1): >98% purity non-radiolabelled foramsulfuron (batch no. H 2037): 98.2%
Test Animals:	Sprague Dawley CRL:(IGS) CD BR rats; bw at dosing: 151–210 g Source: [REDACTED]
GLP:	Yes
Test Method:	OECD 417, adopted 4 April 1984
Deviations:	None.
Acceptability:	The study is considered to be acceptable.

Material and Methods:

Groups of three male and three female rats were given a single daily oral dose of 10 mg [¹⁴C-phenyl]-radiolabelled foramsulfuron/kg bw as a suspension in aqueous gum tragacanth (1% w/v) for up to 14 days. Groups were killed 24 hours after having received 1, 9 or 14 daily doses. These animals had free access to food and water throughout the treatment period. At necropsy whole tissues or representative samples of adrenals, blood, bone, brain, eyes, heart, kidneys, liver, lungs, muscle, ovaries, plasma, renal fat, skin, spleen, testes, thyroid and carcass (inclusive of the gastrointestinal tract) were removed and analysed to determine the level of radioactive residues. A further group of 3 males and 3 females were fasted overnight before receiving the final 14th dose (the other groups were not fasted) and transferred to individual all-glass metabolism cages after final dosing. Urine and faeces of these animals were collected over the next 48 hours in cooled containers to prevent bacterial degradation of metabolites.

Radioactivity in the urine and cage wash was measured by direct addition to scintillation cocktail. Blood and bone were combusted and all other samples were solubilised, either following homogenisation or as whole tissue pieces, before being added to scintillation cocktail. The profile of metabolites in the excreta was determined by radio-HPLC.

Findings:

When the 0–48 h excretion data was based on recovered radioactivity, the route and rate of excretion after 14 daily doses of foramsulfuron was found to be similar to that seen following a single oral dose (see Table B.6.1-8). The mean low recovery rate in faeces in combination with a high recovery rate in the carcass/GIT was found in males, indicating a delay of faecal excretion, which however was mainly

attributed to one animal. 48 h after administration of the final dose, a maximum of 1.7% of the recovered radiolabel was found in the tissues investigated (excluding the gastrointestinal tract).

Table B.6.1-8: Excretion mean of radiolabel within 48 h after administration of the final dose

Sample	Excretion mean of radioactivity (as % recovered radioactivity)	
	Males (n=3)	Females (n=3)
Urine [0–48 h]	11.5 (range: 10.5–12.6)	7.4 (range: 5.8–8.9)
Cage wash [48 h]	2.3 (range: 1.6–2.6)	0.5 (range: 0.2–0.9)
Faeces [0–48 h]	61.0 (range: 36.1–78.7)	88.8 (range: 83.1–93.3)
Carcass / GIT [48 h]	24.5 (range: 6.9–48.2)	3.1 (range: 0.6–7.5)
Tissues [48 h]	0.7 (range: 0.2–1.7)	0.1 (range: 0.08–0.21)
Total excretion	74.8 (range: 50.2–92.9)	96.7 (range: 92.3–99.3)
Overall total	100.0	100.0

The concentrations of radioactive residues in the tissues of rats killed either 24 h after administration of 1, 9, or 14 doses, or 48 h after administration of 14 doses, are shown in Table B.6.1-9.

Table B.6.1-9: Concentration of radioactivity in tissues and body fluids of rats after repeated oral administration of foramsulfuron

Tissue	Concentration in male rats (µg eq./g tissue)				Concentration in female rats (µg eq./g tissue)			
	24 h after receiving			48 h after receiving	24 h after receiving			48 h after receiving
	1 dose	9 doses	14 doses	14 doses	1 dose	9 doses	14 doses	14 doses
Adrenal	0.001	0.001	0.003	0.010	0.002	0.004	0.003	0.002
Blood	0.012	0.009	0.012	0.087	0.012	0.011	0.014	0.010
Bone	0.009	0.013	0.012	0.031	0.009	0.033	0.019	0.014
Brain	0.001	0.000	0.020	0.003	0.003	0.001	0.008	0.001
Eyes	0.002	0.002	0.003	0.007	0.002	0.003	0.005	0.001
Heart	0.002	0.000	0.013	0.035	0.004	0.002	0.019	0.008
Kidney	0.021	0.017	0.027	0.120	0.048	0.022	0.026	0.020
Liver	0.079	0.182	0.222	1.232	0.114	0.184	0.280	0.187
Lung	0.008	0.004	0.019	0.046	0.006	0.006	0.022	0.051
Muscle	0.018	0.006	0.008	0.026	0.011	0.015	0.014	0.004
Ovaries	-		-	-	0.003	0.005	0.003	0.003
Plasma	0.017	0.014	0.019	0.147	0.015	0.016	0.021	0.015
Renal fat	0.004	0.003	0.012	0.020	0.019	0.008	0.013	0.006
Skin*	0.022	0.014	0.042	0.046	0.026	0.043	0.166	0.025
Spleen	0.004	0.008	0.009	0.025	0.005	0.006	0.016	0.013
Testes	0.005	0.005	0.073	0.021	-		-	-
Thyroid	0.002	0.004	0.020	0.033	0.001	0.005	0.002	0.022

* These results may be affected by contamination from urine during housing.

Tissue levels recorded 24h after a single dose were generally very low, with the liver (both sexes) and the kidney (females only) to show clearly higher concentrations than in plasma.

For most of the tissues investigated, repeated-dose treatment over 14 days resulted in increased residue levels. In the tissues of rats killed 24 h after administration of the last dose, these increases did not exceed 3-fold with the exception of the following male tissues: brain (20x increase), testes (15x), thyroid (10x), and heart (6.5x). Only residue concentrations in liver (both sexes) and testes were clearly higher than in plasma at this timepoint of investigation.

At 48 h after administration of the 14th dose, the only tissue to show clearly higher levels than those determined in plasma was the liver (the increased mean residue level in female lung tissue was due to an outlier produced by a single animal).

Compared to the group of rats killed 24 h after the final dose, the residue levels were higher in most tissues of the group of male rats that was killed after 48 hours, with the exception of brain and testes, where decreased concentrations were found, possibly indicating redistribution of foramsulfuron residues to other compartments.

The profile of metabolites of foramsulfuron seen in the urine and faeces of rats following 14 daily oral doses of foramsulfuron was similar to that previously found after a single oral dose. The major excretion product was foramsulfuron, which was the only substance to be identified in the faeces, while parent and the metabolites AE F153745 and AE F130619 were found in the urine.

Table B.6.1-10: Metabolic profile

	Percentage of dose present in						Total
	urine			faeces			
	parent	AE F153745	AE F130619	parent	AE F153745	AE F130619	
male	4.00	4.08	3.50	64.30	—	—	75.88
female	5.27	2.41	1.65	98.06	—	—	107.39

Conclusion:

Following repeated daily dosing with 10 mg/kg bw for up to 14 days, the compound was rapidly eliminated in the excreta with little effect on rate or route of excretion when compared to the findings following a single oral dose. The magnitude of the radioactive residues in the tissues increased only slightly (3-fold in most tissues) with repeated dosing. The level of the radioactive residues in the tissues throughout the study was generally below 0.1 µg equivalent/g. The liver was the only tissue exhibiting clearly increased radiolabel concentrations compared to plasma at both timepoints of investigation (24 and 48 h). This finding is considered to reflect redistribution of the radiolabel prior to biliary/renal excretion rather than to be an indication of an accumulation potential of foramsulfuron. Overall the concentration of residues in the tissues was similar in male and in female rats. The metabolic profile of foramsulfuron was not significantly affected by repeated administration of foramsulfuron.

B.6.1.2. Absorption, distribution, metabolism and excretion by other routes

Report:

2013

[Pyrimidine-2-¹⁴C]Foramsulfuron: Metabolic Stability and Profiling in Liver Microsomes from Rats and Humans for Inter-Species Comparison,
Report No.: EnSa-13-0827, unpublished

(Completion date: 15 November 2013)

Test Material: [Pyrimidine-2-¹⁴C]Foramsulfuron; purity radiolabel > 99%;
purity non-radiolabelled foramsulfuron (batch no. AE F130360 00 1B99
0003): 98.3%

1-

Test System: Pooled liver microsomes from male Wistar rats (RLM, batch 1010126) and
humans (HLM, batch 1210153)
Source: [REDACTED]

GLP: Yes

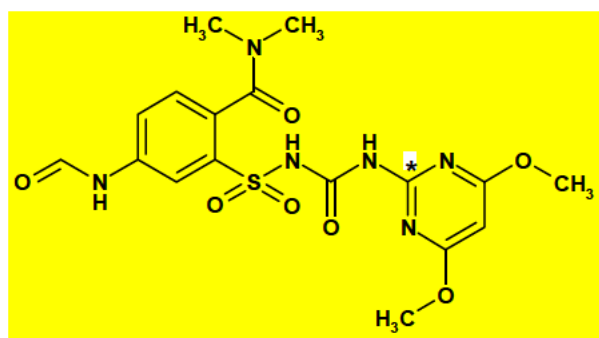
Test Method: The study was not performed according to any official test guideline. *In vitro*
metabolism study is a data requirement according to the Commission
Regulation (EU) No. 283/2013.

Acceptability: The study is considered to be acceptable.

Material and methods

The comparative metabolism of [pyrimidine-2-¹⁴C]-foramsulfuron was investigated in animal *in-vitro* systems by incubating the test item separately with 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) in the presence of NADPH cofactor at 37 ± 1 °C.

Figure B.6.1-2: Chemical structure of the test item



* denotes the ¹⁴C-label position

The potential biotransformation of ¹⁴C-foramsulfuron over time together with the qualitative comparison of the metabolite profiles in each of the species was evaluated by HPLC with radiochemical detection.

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. Samples were analysed by HPLC-RAD for the unchanged test item and metabolites. Liquid scintillation counting (LSC) analyses were performed for the determination of the recovery of radioactivity.

The metabolic activity of the microsomes for a positive control sample was determined by measurement of 6 β -hydroxytestosterone that was formed from testosterone by testosterone 6 β -hydroxylase, the biochemical reaction known for the CYP3A microsomal enzyme. The test duration of 1 hour for the test item was considered as reasonable because positive results were obtained from the enzymatic reaction of the positive metabolism control incubations from testosterone to 6 β -hydroxytestosterone already after 10 minutes.

Results

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.

¹⁴C-Foramsulfuron was found to be stable after incubation with rat and human liver microsomes (RLM and HLM) at 37 \pm 1 °C for 1 hour, in the presence of NADPH cofactor. No detectable metabolites were found after the 1 hour incubation period.

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

Table B.6.1-11: Recovery of radioactivity after sample preparation

SAMPLE	Incubation time (min)	Replicate	LSC Vial Empty tube (g)	LSC Vial Filled tube	LSC Aliquot (g)	Incubate Aliquot (dpm)	Incubate Aliquot dpm/g
RLM INCUBATES	0	1	12.3074	12.3487	0.0413	40106.0	971089.1
		2	12.2252	12.2667	0.0415	41829.0	1007926.7
		3	12.3526	12.3932	0.0406	41283.8	1016842.9
	60	1	12.3622	12.4043	0.0421	40238.2	955777.0
		2	12.3369	12.3785	0.0416	40732.7	979150.5
		3	12.3245	12.3660	0.0415	40412.0	973781.9
HLM INCUBATES	0	1	12.2705	12.3121	0.0416	41868.2	1006447.4
		2	12.2971	12.3377	0.0406	41617.0	1025049.5
		3	12.3561	12.3970	0.0409	40835.3	998419.1
	60	1	12.3163	12.3581	0.0418	40472.0	968228.7
		2	12.2789	12.3207	0.0418	41157.8	984635.6
		3	12.3610	12.4024	0.0414	40725.1	983699.0
BUFFER CONTROL	60	1	12.3746	12.4180	0.0434	40613.4	935791.9

SAMPLE	Incubation time (min)	Replicate	LSC Vial Empty tube (g)	LSC Vial Filled tube	LSC Aliquot (g)	Supernatant Aliquot (dpm)	Supernatant Aliquot dpm/g
RLM SUPER-NATANT	0	1	12.3739	12.4158	0.0419	39644.9	946179.2
		2	12.3352	12.3764	0.0412	40328.8	978853.9
		3	12.2683	12.3096	0.0413	40240.3	974340.9
	60	1	12.3498	12.3927	0.0429	41794.8	974238.5
		2	12.3193	12.3607	0.0414	36846.3	890007.2
		3	12.3547	12.4025	0.0478	42554.5	890261.9
HLM SUPER-NATANT	0	1	12.3359	12.3772	0.0413	41284.7	999628.6
		2	12.2579	12.2993	0.0414	40858.4	986918.1
		3	12.3655	12.4082	0.0427	40815.2	955860.2

	60	1	12.3270	12.3733	0.0463	38419.2	829788.8
		2	12.3532	12.3977	0.0445	38650.9	868558.9
		3	12.2975	12.3439	0.0464	40969.1	882955.2
BUFFER CONTROL	60	1	12.2919	12.3352	0.0433	40424.0	933578.5

SAMPLE	Incubation time (min)	Replicate	Recovery (%)	Recovery Mean (%)
RLM SUPER-NATANT	0	1	97.4	96.8
		2	97.1	
		3	95.8	
	60	1	101.9	94.8
		2	90.9	
		3	91.4	
HLM SUPER-NATANT	0	1	99.3	97.1
		2	96.3	
		3	95.7	
	60	1	85.7	87.9
		2	88.2	
		3	89.8	
BUFFER CONTROL	60	1	99.8	99.8

RLM: Rat Liver Microsomes; HLM: Human Liver Microsomes; LSC: Liquid Scintillation Counting

Table B.6.1-12: Metabolite profile of ¹⁴C-Foramsulfuron in rat and human liver microsomes

SAMPLE	Incubation time (min)	Replicate	Unchanged ¹⁴ C-Foramsulfuron (Ret. Time: 18.8) Peak area (HPLC-RAD)		
			Individual Values	MEAN	cv (%)
RLM INCUBATES	0	1	162641	161807	0.5
		2	161801		
		3	160980		
	60	1	156640	157985	0.7
		2	158822		
		3	158494		
HLM INCUBATES	0	1	171241	168909	3.2
		2	172674		
		3	162811		
	60	1	141965	153134	9.8
		2	147304		
		3	170133		
BUFFER CONTROL	60	1	157212	—	—

RLM: Rat liver microsomes

HLM: Human liver microsomes

cv (%): Coefficient of variation in percentage

The retention time for unchanged ^{14}C -Foramsulfuron is approximate

Table B.6.1-13: Testosterone-6 β -hydroxylase activity in rat liver microsomes (positive control)

Sample	6 β -hydroxytestosterone (pmol/mL)		Testosterone-6 β -hydroxylase (pmol/mg/min)
Replicate 1	1774.86		1183.2
Replicate 2	1616.84		1077.9
Replicate 3	1956.56		1304.4
		Mean	1188.5
		cv (%)	9.5

Male Wistar rat liver microsomes (batch 1010126)

10 min. incubation with 100 μM Testosterone

0.15 mg protein/mL

LC-MS/MS detection

Table B.6.1-14: Testosterone-6 β -hydroxylase activity in human liver microsomes (positive control)

Sample	6 β -hydroxytestosterone (pmol/mL)		Testosterone-6 β -hydroxylase (pmol/mg/min)
Replicate 1	Ns		-
Replicate 2	3763.26		2508.8
Replicate 3	3192.62		2128.4
		Mean	2318.6
		cv (%)	-

Human liver microsomes (pool of both sexes, batch 1210153)

10 min. incubation with 100 μM Testosterone

0.15 mg protein/mL

LC-MS/MS detection

Ns: sample lost during LC-MS/MS acquisition

Conclusion

^{14}C -Foramsulfuron was found to be stable after incubation with rat and human liver microsomes (RLM and HLM) at 37 ± 1 °C for 1 hour, in the presence of NADPH cofactor. No detectable metabolites were found after the 1 hour incubation period.

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

B.6.2. ACUTE TOXICITY

The acute toxicity of technical foramsulfuron (purity 93.7–98.4%) was low for all routes evaluated (oral, dermal and inhalational). The oral LD₅₀ for rats of both sexes was greater than 5000 mg/kg bw and only non-specific clinical signs of piloerection, hunched posture and white, soft to liquid faeces were seen. The rat acute dermal LD₅₀ was >2000 mg/kg bw and caused only transient slight irritation in a couple of animals. The rat acute inhalation LC₅₀ (4-h) was >5.04 mg/l air, which was the highest achievable concentration and did not cause mortality. The principal clinical signs observed were again non-specific and included wet fur, hunched posture and piloerection. Other signs were increased (in one case, decreased) respiratory rate and red/brown staining around the head and snout, and in one instance, of the eyes. Therefore there was no indication of any sex-specific susceptibility in any of the acute studies.

Foramsulfuron was not irritant to rabbit skin. Exposure to eyes caused reversible slight to moderate reddening, slight chemosis and a slight to moderate discharge of the conjunctivae, which fully resolved within 48 hours post instillation. Based on EU criteria, classification and labelling of foramsulfuron as an skin or eye irritant is not required.

No evidence of skin sensitisation (delayed contact hypersensitivity) was seen in a guinea pig Magnusson and Kligman maximisation test.

Due to the data requirements (EU) No 283/2013 a phototoxicity 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 and a phototoxicity study was conducted and this showed that foramsulfuron does not possess any phototoxic potential.

Table B.6.2-1: Summary of acute toxicity data for foramsulfuron

Type of study	Species	Sex	Results
Oral LD ₅₀	Rat	Male and female	LD ₅₀ > 5000 mg/kg
Dermal LD ₅₀	Rat	Male and female	LD ₅₀ > 2000 mg/kg
Inhalation LC ₅₀ (4-h, nose-only)	Rat	Male and female	LC ₅₀ > 5.04 mg/l air
Skin irritation	Rabbit	Male	Not irritating
Eye irritation	Rabbit	Male	Not irritating
Sensitisation (M & K test)	Guinea pig	Male	Not a skin sensitizer
Phototoxicity	<i>In vitro</i> assay with BALB/c 3T3 cells		No phototoxic potential

Classification:

With respect to the prevailing EU classification schemes, a classification of foramsulfuron is not required.

Classification is not required according to CLP Regulation (EC) No 1272/2008.

B.6.2.1. Oral

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. Classification is not required according to CLP Regulation (EC) No 1272/2008.
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Report:	[REDACTED], 1997 (TOX2000-1041) Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001: Rat acute oral toxicity. Study No.: TOX 96110, Doc.No. (Aventis): A58267, unpublished Testing facility: [REDACTED] (Experimental work from 2 to 16 September 1996)
Test Material:	Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w); formulated at a concentration of 50% w/v in 1% w/v aqueous methylcellulose and administered at a dose volume of 10 ml/kg bw
Test Animals:	Hsd/Ola: Sprague-Dawley (CD) rats, bw (Day 1): 228–278 g Source: [REDACTED]
GLP:	Yes
Test Method:	OECD TG 401, adopted 24 February 1987 (Limit Test)
Deviations:	None that were considered to have affected the integrity or validity of the study.
Acceptability:	The study is considered to be acceptable.

Material and Methods:

A group of five male and five female Sprague-Dawley rats was given foramsulfuron as a single oral dose by gavage of 5000 mg/kg bw following overnight fasting.

Animals were observed soon after dosing and at frequent intervals for the remainder of Day 1 (day of dosing). Thereafter they were observed twice daily for 15 days. Individual body weights were recorded just prior to dosing and once weekly thereafter. All animals were sacrificed and examined externally and internally (abdominal and thoracic cavities) for macroscopic abnormalities on Day 15, the end of the observation period.

Findings:

There were no deaths during the study. Treatment-related clinical signs seen in all the animals included piloerection (seen within 5 minutes of dosing), hunched posture and white, soft to liquid faeces. Recovery was complete in all cases by Day 4. A slightly low body weight gain was recorded on Day 15 for all males and 3/5 females. No abnormalities were detected in any animal at the necropsy on Day 15.

Conclusion:

The acute lethal oral dose (LD₅₀) of foramsulfuron to rats was > 5000 mg/kg bw.

B.6.2.2. Dermal

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. Classification is not required according to CLP Regulation (EC) No 1272/2008.
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Report:	<p>██████████, 1997 (TOX2000-1042) Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001: Rat acute dermal toxicity Study No.: TOX 96111, Doc.No. (Aventis): A58268, unpublished Testing facility: ██████████ (Experimental work from 27 August to 10 September 1996)</p>
Test Material:	Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w); formulated at a concentration of 75% w/v in 1% w/v aqueous methylcellulose
Test Animals:	Hsd/Ola: Sprague-Dawley (CD) rats, bw (Day 1): 201–242 g Source: ██████████
GLP:	Yes
Test Method:	OECD TG 402, adopted 24 February, 1987 (Limit Test)
Deviations:	None that were considered to have affected the integrity or validity of the study.
Acceptability:	The study is considered to be acceptable.

Material and Methods:

A group of five male and five female Sprague-Dawley rats was given a single occlusive 24-h dermal application of 2000 mg/kg bw at the maximum practical concentration of 75% w/v in 1% w/v aqueous methylcellulose. At the end of the exposure period, the dressing was removed and the treated area of skin washed with warm water to remove any remaining test substance, then blotted dry.

Animals were observed soon after dosing and at frequent intervals on the remainder of Day 1 (day of dosing). On subsequent days they were observed twice. Any mortalities and local or systemic symptoms of toxicity were recorded during a 14-day observation period. Body weights were recorded immediately prior to dosing and at weekly intervals thereafter. All animals were sacrificed on Day 15 and examined externally and internally (abdominal and thoracic cavities) for macroscopic abnormalities.

Findings:

No deaths occurred during the study and no signs of systemic reaction to the treatment were seen. Transient slight irritation (grade 1 for erythema and oedema) was seen on Day 2 alone in 2/10 animals at the application site following the removal of the dressings. These reactions had disappeared by the following day. No other dermal reactions were observed in any other animals throughout the study.

Conclusion:

The acute dermal LD₅₀ of foramsulfuron to rats was > 2000 mg/kg bw.

B.6.2.3. Inhalation

Previous evaluation	<p>This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 403 has been adopted 7th September, 2009. The study practically fulfils the current data requirements. Classification is not required according to CLP Regulation (EC) No 1272/2008.</p>
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Report: [REDACTED], 1998 (TOX2000-1043)
AE F130360, Code: AE F130360 00 1C94 0002:
Rat acute inhalation toxicity
Study No.: TOX 96115, Doc.No. (Aventis): A67640, unpublished
Testing facility: [REDACTED]
(Experimental work from 30 October 1997 to 11 February 1998)

Test Material: Foramsulfuron, batch no. 1/97M, purity: 93.7% (w/w) after milling

Test Animals: Sprague-Dawley CD strain rats;
bw (Day 1), males: 281–314 g; females: 222–255 g;
Source: [REDACTED]

GLP: Yes

Test Method: OECD TG 403, adopted 12 May, 1981 (Limit Test)

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

A group of five male and five female Sprague-Dawley rats were exposed by inhalation for 4 h using a nose-only system to an achieved dust aerosol atmosphere of 5.04 mg/l. The dust atmosphere was generated by a Wright's dust feed mechanism and the chamber atmosphere was equilibrated prior to exposure of the animals. Before the start of the study, test material atmospheres were generated within the exposure chamber by varying the amount of input in order to achieve the optimum atmospheric conditions.

The mean achieved chemically analysed atmospheric concentration of foramsulfuron was 5.04 mg/l. The nominal (gravimetric) atmosphere concentration was 9.7 mg/l. By particle size analysis of the atmosphere drawn from the animals' breathing zone, the mass median aerodynamic diameter of the particles (MMAD) was 2.0 µm (79.9% particles <4 µm) and the geometric standard deviation was 0.44 µm.

Animals were observed for mortality and clinical signs at hourly intervals during exposure, immediately on removal from the restraining tubes at the end of exposure, one hour after termination of exposure and once daily thereafter for 14 days post exposure, then sacrificed and necropsied. Individual body weights were recorded prior to treatment on the day of exposure and at weekly intervals thereafter.

Findings:

There was no mortality.

During the exposure all animals exhibited wet fur. Increased or decreased respiratory rate was also seen occasionally. On removal from the chamber, wet fur, hunched posture, piloerection and increased respiration were commonly observed and several animals had red/brown staining around the eyes, snout or head. Wet fur was no longer seen 1 hour after completion of the exposure period and signs of increased respiratory rate and red/brown staining had diminished. On Day 1 after exposure, all animals appeared normal and no further clinical signs were observed during the study.

Body weight gain was unaffected by treatment and no abnormalities were detected at necropsy.

Conclusion:

The 4-hour acute inhalation median lethal concentration (LC₅₀) of foramsulfuron to the rat was >5.04 mg/l, which did not cause mortality and was the highest achievable concentration.

B.6.2.4. Skin irritation

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. After the study was performed, a new version of the OECD Test Guideline 404 has been adopted 24th April, 2002. The study fulfils the current data requirements. Conclusion has not been changed. Classification is not required according to CLP Regulation (EC) No 1272/2008.
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Report:

[REDACTED], 1997 (TOX2000-1044)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001:
Rabbit skin irritancy
Study No.: TOX 96112, Doc.No. (Aventis): A59370, unpublished
Testing facility: [REDACTED]
(Experimental work: 28–31 August 1996)

Test Material:

Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w)

Test Animals:

New Zealand White rabbits, bw (Day 1): 2.9–3.5 kg
Source: [REDACTED]

GLP:

Yes

Test Method:

OECD TG 404, adopted 17 July, 1992

Deviations:

None

Acceptability:

The study is considered to be acceptable.

Material and Methods:

A 500 mg quantity of foramsulfuron, moistened with 0.5 ml distilled water, was administered for 4 hours to an area (2.5 cm x 2.5 cm) of intact, clipped, dorsal-lumbar skin of 6 adult male New Zealand White rabbits under a semi-occlusive dressing. At the end of exposure the dressing was removed and the treatment site washed with warm water to remove any residual test substance, then blotted dry.

The rabbits were observed daily for clinical signs and mortality. Skin responses were evaluated 60 minutes and 24, 48 and 72 hours after the end of the exposure period and graded according to OECD Guideline 404.

Findings:

There were no clinical signs of toxicity and no mortality.

No dermal reactions were observed in any of the animals throughout the observation period (grade 0 erythema and oedema).

Conclusion:

Foramsulfuron was not irritant to rabbit skin. Classification and labelling as skin irritant is not required according to EU criteria.

B.6.2.5. Eye irritation

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. At the moment of the AIR-3 dossier submission, a new version of the OECD Test Guideline 405 (adopted 24th April, 2002) should have been followed. The study fulfils these data requirements. Conclusion has not been changed. Classification is not required according to CLP Regulation (EC) No 1272/2008.
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Report:

[REDACTED], 1997 (TOX2000-1045)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001:
Rabbit eye irritancy
Study No.: TOX 96113, Doc.No. (Aventis): A59371, unpublished
Testing facility: [REDACTED]
(Experimental work: 2–12 September 1996)

Test Material:

Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w)

Test Animals:

New Zealand White rabbits bw (Day 1): 2.8–3.6 kg
Source: [REDACTED]

GLP:

Yes

Test Method:

OECD TG 405, adopted 24 February 1987

Deviations:

None

Acceptability:

The study is considered to be acceptable.

Material and Methods:

Seven healthy adult male New Zealand White rabbits, were used, one of which served as a screen animal, and another as a pilot animal for initial assessments for eye irritancy in accordance with animal welfare regulations.

0.1 ml (57 mg) of foramsulfuron was instilled into one eye of the screen rabbit whilst the other eye served as a control. The treated eye was then rinsed for 30 seconds with distilled water 30 seconds after instillation. The rationale for this was to prevent further animals being treated if the reaction was severe.

The pilot animal was treated in exactly the same way, except that the eye was not rinsed. The next day the remaining five rabbits were treated in a similar fashion to the pilot animal. These six animals comprised the main study.

All animals were observed daily for clinical signs of toxicity and mortality. Examination of the eyes of all animals was conducted 1, 24, 48 and 72 hours after instillation.

Findings:

There was no mortality and no clinical signs of systemic toxicity. Ocular lesions were graded according to OECD guideline 405, the corresponding scores are summarised in Table B.6.2-2.

Table B.6.2-2: Ocular reactions in eye irritation study

Eye effect	Corneal Opacity				Iris				Conjunctival Redness				Conjunctival Swelling			
Reading (h)	1	24	48	72	1	24	48	72	1	24	48	72	1	24	48	72
Rabbit No.																
494 ¹	0	0	0	0	0	0	0	0	2*	1	0	0	0	0	0	0
495 ²	0	0	0	0	0	0	0	0	2*	1	0	0	1	0	0	0
377	0	0	0	0	0	0	0	0	1*	1	0	0	1	0	0	0
378	0	0	0	0	0	0	0	0	1*	1	0	0	1	0	0	0
379	0	0	0	0	0	0	0	0	1	1	0	0	1	1	0	0
380	0	0	0	0	0	0	0	0	2* *	1	0	0	1	0	0	0
381	0	0	0	0	0	0	0	0	1*	1	0	0	0	0	0	0
Mean Score		0.0				0.0				0.33				0.06		

¹ Screen animal, eyes rinsed 30 s after application; ² Pilot animal (eyes unrinsed, treated prior to other rabbits)

*Discharge (slight) **Discharge (moderate)

The screen animal exhibited well-defined conjunctival irritation and a slight discharge one hour post instillation. These reactions had resolved 48 hours post instillation.

No corneal or iridial effects were observed at any time point of investigation. All 6 main study rabbits exhibited slight to moderate conjunctival redness, which was accompanied by slight chemosis and slight to moderate conjunctival discharge in 5 of 6 rabbits at 1 h after exposure. By 24 h after treatment, slight conjunctival redness without any discharge was observed in all rabbits; only one rabbit remained to have slight chemosis. Responses had completely resolved in all rabbits 48 hours post instillation.

Conclusion:

The test substance is not considered to have produced eye irritation according to EU criteria. Thus, classification and labelling is not required.

B.6.2.6. Skin sensitization

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. Classification is not required according to CLP Regulation (EC) No 1272/2008.
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Report: [REDACTED], 1997 (TOX2000-1046)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001:
Guinea-pig skin sensitisation (Magnusson and Kligman test)
Study No.: TOX 96114, Doc.No. (Aventis): A58182; unpublished
Testing facility: [REDACTED]
(Experimental work: 3 September to 11 October 1996)

Test Material: Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w)

Test Animals: Dunkin /Hartley guinea pigs; bw (Day 1): 365–422 g
Source: [REDACTED]

GLP: Yes

Test Method: OECD TG 406, adopted 17 July 1992

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Fifteen male albino Dunkin /Hartley guinea pigs consisting of 5 control and 10 test animals were used for the main study. Six animals were used for the preliminary dose ranging investigations. Positive control data of the test facility demonstrated the sensitivity of the guinea pig strain used.

Preliminary study

The intradermal and topical irritancy of a range of dilutions of the test substance was evaluated to identify where possible, a) a concentration that would produce irritation suitable for the induction phase of the main study and b) a maximum non-irritant concentration by topical application for the challenge phase.

Main Study

Based on the results of the preliminary study the following concentrations were used:

Induction phase intradermal injections: 2.5% w/v in Alembicol D¹
Induction phase topical applications: 60% w/v in Alembicol D
Challenge phase topical applications: 60% w/v in Alembicol D

Induction phase:

- i) Intradermal injections: On study Day 1, three pairs of intradermal injections (0.1 ml each) were made into a 20 x 40 mm area within a clipped and shaved dorso-lumbar area of skin on each guinea-pig:
 - a) Freund's Complete Adjuvant diluted with an equal volume of water
 - b) Foramsulfuron, 2.5% in Alembicol D
 - c) Foramsulfuron, 2.5% w/v in a 50:50 mixture of Freund's Complete Adjuvant and water
- ii) Topical applications: Six days after the injections, the same interscapular site of each guinea pig was clipped and shaved. Because topical treatment with the maximum concentration of foramsulfuron had not induced any irritancy, the site was pre-treated by gentle rubbing with 0.5 ml of 10% w/w sodium lauryl sulphate in petrolatum. 24 h later a piece of filter paper saturated with about 0.4 ml of foramsulfuron (60% in Alembicol D) was placed on the skin,

¹ A product of coconut oil (Alembic Products, Saltney, Chester, UK)

secured with impermeable plastic adhesive tape and then covered with an elastic adhesive bandage. This remained in place for 48 h.

Challenge phase:

The test and control animals were challenged topically two weeks after the topical induction application (study Day 22) with concentrations of 30 and 60% w/v foramsulfuron in Alembicol D. Filter papers saturated with about 0.2 ml of these concentrations were applied to the shaved posterior and anterior left flank, respectively and secured as for the topical induction application and left for 24 hours.

Skin responses at the challenge sites were evaluated 24 and 48 hours after removal of the dressing. A test animal was considered to show positive evidence of skin sensitisation if the reactions at challenge were definitely more marked and/or more persistent than the maximum reaction in the controls. If the reactions were slightly more marked and/or persistent but not clearly distinguishable from controls, the animal was classified as inconclusive. If the reactions were similar to or less marked than the maximum response in controls, the test animal was considered to show no evidence of skin sensitisation.

All animals were observed daily for signs of ill health or toxicity. Body weights were recorded on Day 1 and Day 25.

Findings:

Preliminary study

- a) 2.5% w/v of foramsulfuron in Alembicol D (maximum concentration that could be dosed intradermally) caused well-defined erythema and oedema after 24 and 72 hours, but did not adversely affect the animals.
- b) 60% w/v of the test compound in Alembicol D (maximum practical concentration) applied topically did not cause any irritation.

Main study

Induction phase:

- i) Intradermal injections
Necrosis was seen at sites receiving Freund's Complete Adjuvant in all test and control animals. Slight erythema was seen in test animals at sites receiving 2.5% w/v test compound in Alembicol D and in control animals receiving Alembicol D alone.
- ii) Topical applications
Slight erythema was observed in test animals following application with 60% w/v foramsulfuron in Alembicol D and in the control guinea pigs receiving Alembicol D alone.

Challenge phase:

No dermal reactions in any test or control animal were observed following administration of either 30% or 60% w/v foramsulfuron.

Conclusion:

Foramsulfuron was not a skin sensitiser in this guinea pig Magnusson and Kligman test.

B.6.2.7. Phototoxicity

Due to the data requirements (EU) No 283/2013 a phototoxicity study is required if the molar extinction coefficient is higher than $10 \text{ L} \times \text{mol}^{-1} \times \text{cm}^{-1}$. For foramsulfuron this is the case and a phototoxicity study was conducted.

Report: [REDACTED]; 2013

Foramsulfuron TC: Cytotoxicity assay *in vitro* with BALB/c3T3 cells: Neutral red (NR) test during simultaneous irritation with artificial sunlight

Report No.: 1561300; unpublished

Testing facility: [REDACTED]

Bayer CropScience

(Study completion date: 16 September 2013)

Test Material: Foramsulfuron TC, batch no. ELIR004294, purity: 97.3% (w/w)

Test System: BALB/c 3T3 cell line

GLP: Yes

Test Method: OECD TG 432, adopted 13 April 2004

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and methods

As the molar extinction coefficient of foramsulfuron is higher than $10 \text{ L} \times \text{mol}^{-1} \times \text{cm}^{-1}$, a phototoxicity study is required according to the data requirements (EU) No 283/2013.

For the determination of a phototoxic potential of foramsulfuron, the Balb/c 3T3 cells (clone 31) were used. The experiment was performed twice. The first experiment served as a range finding experiment (RFE), the second one was the main experiment (ME). The cells were treated with the concentrations of 7.81, 15.63, 31.25, 62.5, 125, 250, 500 and 1000 $\mu\text{g/mL}$ foramsulfuron TC (batch: ELIR004294, purity: 97.3 % w/w) in the absence and presence of irradiation with artificial sunlight (wave length > 320 nm) in both experiments.

For the performance of the test, foramsulfuron TC was dissolved in EBSS at above-mentioned concentrations. EBSS was used as the solvent control. Chlorpromazine dissolved in EBSS was used as the positive control at concentrations of 6.25, 12.5, 25, 37.5, 50, 75, 100 and 200 $\mu\text{g/mL}$ in the absence of irradiation and 0.125, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0 and 4.0 $\mu\text{g/mL}$ in the presence of irradiation.

2×10^4 cells per well were seeded in 100 μL culture medium. Two 96-well plates were used. 24 hours after seeding the cultures were treated with foramsulfuron. Both plates were pre-incubated for 1 hour in the dark. After 1 hour one 96-well plate was irradiated through the lid at $2.4 - 2.55 \text{ mW/cm}^2$ ($7.2 - 7.65 \text{ J/cm}^2$), for $50 \pm 2 \text{ min}$ at $20 - 30^\circ\text{C}$, the other plate was stored for $50 \pm 2 \text{ min}$ at $20 - 30^\circ\text{C}$ 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 $37 \pm 1.5^\circ\text{C}$ and $7.5 \pm 0.5\% \text{ CO}_2$.

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. The neutral red test is based on the uptake of neutral red, a vital dye, and its accumulation in the lysosomes of viable uninjured 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 equipped with a 540 nm filter to determine the absorbance of the extracted dye.

The ED₅₀ values, the Photo-Irritancy-Factor (PIF) and Mean Phototoxic Effect (MPE) were calculated using the software Phototox (Version 2.0). The ED₅₀ 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:

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

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.

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

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.

Results

Table B.6.2-3: 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

ED₅₀ 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 B.6.2-4: 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

ED₅₀ value (with artificial sunlight) = 0.16 µg/mL

ED₅₀ value (without artificial sunlight) = 7.45 µg/mL

PIF = 47.11

MPE = 0.734

Table B.6.2-5: 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

ED₅₀ 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 B.6.2-6: 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	11.91	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 wellsED₅₀ value (with artificial sunlight) = 0.18 µg/mLED₅₀ value (without artificial sunlight) = 11.29 µg/mL

PIF = 64.69

MPE = 0.771

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 0.001 or -0.002, respectively, and therefore, the test item is classified as not phototoxic.

Conclusion

In this study, under the experimental conditions reported, Foramsulfuron Technical (AE F130360) did not show any phototoxic potential.

B.6.3. SHORT-TERM TOXICITY

The short-term toxicity studies were conducted in 1996 and 1997. All 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 B.6.3-1.

In rats, continuous dietary administration for 28 days at the high dose of 20000 ppm caused a decrease in female body weight gain and food conversion rates, and a slight reduction in food consumption. Water consumption was increased. Based on body weight effects the NOEL was 5000 ppm, equivalent to a daily intake of 434 mg/kg bw/d.

Results of the dog and mouse 28-day oral studies and the rat, mouse and dog 90-day oral studies showed that foramsulfuron (purity 90.0% – 98.4% w/w) was well tolerated up to the international limit dose, 1000 mg/kg bw/d. In all of these studies the NOEL was the highest dose level given (Table B.6.3-1), with the exception of the dog 90-day, which gave a NOAEL of 1000 mg/kg bw /d, based on occasional beige faeces, particularly in females.

The only findings in dogs given a daily oral dose by gavage of 1000 mg/kg bw /d for 1 year were an increased incidence of beige faeces (beige being the colour of the test material) and isolated incidents of beige vomit.

Table B.6.3-1: Summary of short term toxicity of foramsulfuron

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 Acceptable as a range-finding study	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 Acceptable as a range-finding study	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 Acceptable as a range-finding study	–	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

B.6.3.1. Rat oral toxicity studies

B.6.3.1.1 Oral 28-day study

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. The study is acceptable as a range-finding study.
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Report:

1998 (TOX2000-1047)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC90 0001:
Rat 28 day dietary repeat dose study
Report-No. TOX/96/262-1, Doc.No. (Aventis): A67148; unpublished
Testing facility:
(Experimental work: 15 January to 14 February 1996)

Test Material:	Foramsulfuron, batch no. H 2022/1, purity: 90.0% (w/w)
Test Animals:	Sprague Dawley CRL:CD (SD) BR rats; bw (Day 1): males 192-232 g; females 144–185 g Source: [REDACTED]
GLP:	Yes
Test Method:	OECD TG 407, adopted 12 May 1981
Deviations:	(1) Functional tests required in the current TG 407 (adopted 27.07.95) were not performed. (2) Sampling of Peyer's patches as required in current TG 407 was not mentioned in the report
Acceptability:	The study is considered to be acceptable as a range-finding study.

Material and Methods:

Groups of 5 male and 5 female Sprague Dawley rats, housed in groups of 5 by sex and dose level, were given dietary concentrations of either 0, 1000, 5000 or 20000 ppm foramsulfuron for 29 or 30 consecutive days. The conduct of the study generally followed the current OECD TG 407, with the exceptions listed above. Water intake was measured for each cage over a 4-day period during week 3 of treatment.

Findings:

The mean achieved intakes were 0, 95, 462 and 1837 mg foramsulfuron /kg bw/d for the combined sexes at 0, 1000, 5000 and 20000 ppm, respectively. The corresponding values for the two sexes were 92, 434 and 1789 mg/kg bw/d for males and 97, 490 and 1884 mg/kg bw/d for females at 1000, 5000 and 20000 ppm, respectively.

There were no mortalities and no clinical signs of toxicity.

At 20000 ppm, female body weight gain was decreased by 26% compared to control animals over the treatment period, whilst water intake was increased by 16% (Table B.6.3-2).

Table B.6.3-2: Mean body weight, food and water consumption and food conversion

Parameter	Dose Level (ppm)							
	Males				Females			
	0	1000	5000	20000	0	1000	5000	20000
Body weight gain (g) Weeks 1-4 (% control)	173 –	191 (110)	174 (101)	178 (103)	78 –	74 (95)	69 (88)	58 (74)
Food consumption (g/rat/d) Weeks 1-4 (% control)	29.3 –	30.6 (105)	28.7 (98)	29.3 (100)	21.2 –	21.1 (100)	20.4 (96)	19.5 (92)
Water consumption (g/rat/d) Week 3 (% control)	33.9 –	33.7 (99)	31.9 (94)	33.7 (99)	25.5 –	26.1 (102)	23.4 (92)	29.7 (116)
Food conversion ratios (%) Weeks 1-4 (% control)	21.2 –	22.3 (105)	21.7 (102)	21.8 (103)	13.2 –	12.5 (95)	12.3 (93)	10.6 (80)

Food consumption in these females was also reduced over this period by an average of 8% compared with controls. Their mean food conversion ratio was also decreased by 20% from weeks 2 to 4. The only possible treatment-related change at 5000 ppm was a marginally reduced body weight gain in females (-12%), which on its own was not considered to represent an adverse effect. Thus, no adverse effects were seen in females at 5000 or 1000 ppm or in males at any dose level.

No toxicologically significant treatment-related effect was observed in haematology or blood chemistry indices. Similarly there were no macroscopic abnormalities at necropsy that were ascribed to treatment and no histopathological findings.

Conclusion:

The no observed adverse effect level (NOAEL) was 5000 ppm foramsulfuron, equivalent to a daily intake of 434 mg/kg bw/d (males), 490 mg/kg bw/d (females) and 462 mg/kg bw/d (combined sexes), primarily based on body weight effects in females at the high dose level, 20000 ppm.

B.6.3.1.2 Oral 90-day study

Previous evaluation	<p>This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed.</p> <p>After the study was performed, a new version of the OECD Test Guideline 408 has been adopted 21st September, 1998. The study does not fulfil the data requirements in the sense that no neurotoxic effects were studied.</p> <p>28-day neurotoxicity study was submitted in the AIR-3 dossier. No neurotoxic effects were observed in that study. Hence, despite the lack of neurotoxicity data, this rat 90-day dietary toxicity study is considered to be acceptable.</p>
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Report:

1998 (TOX2000-1050)
 HOE 130360 (AE F130360), Code: Hoe 130360 00 ZC97 0001: Rat 90-day dietary toxicity study with 4 week off dose period.
 Report-No. TOX/96/262-3/TOX 95387; unpublished
 Testing facility:
 (Experimental work: 29 February to 6 July 1996)

Test Material:

Foramsulfuron batch number H 2027/1, containing 97.4% w/w of active substance

Test Animals:

Sprague Dawley CRL:CD (SD) BR rats,
 Source:

GLP:

Yes

Test Method:

OECD 408, adopted 12 May 1981

Deviations:

None

Acceptability:

The study is considered to be acceptable.

Material and Methods:

Groups of 10 male and 10 female Sprague Dawley rats were fed diet containing either 0, 20, 200, 5000 or 20000 ppm of foramsulfuron for 13 consecutive weeks. Two further groups (off-dose animals), each consisting of 10 males and 10 females were fed either 0 or 20000 ppm for 13 weeks and then maintained on untreated (control) diet for a further 4 weeks to examine the reversibility of any effects seen. At the start of treatment the animals were just over 5 weeks of age and weighed 121 to 170 g (males) and 110 to 170 g (females). They were housed by sex and dose level in groups of 5 and had been acclimatised for 7 days.

Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Individual body weights were recorded weekly throughout the treatment period and at necropsy. Cage group food consumption was also measured weekly. Water intake was recorded for each cage group over 4-day periods (monday to friday) during weeks 4, 8 and 12. Ophthalmoscopy was performed on all animals prior to the start of treatment and on all control and high dose level rats in week 13. Biochemistry, haematology and urinalysis were carried out in week 13 of treatment. At necropsy, all animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs recorded and a comprehensive range of tissues preserved. All organs and tissues from the control and high dose level groups and both kidneys, livers and lungs from animals of the remaining dose levels sacrificed in week 13 and all organs and tissues from any animal sacrificed during the study were examined histopathologically.

Test diets were prepared at weekly intervals throughout the study. In order to minimise degradation of foramsulfuron in the diet, half of the mix was stored deep frozen and fed to the animals over the last 3 days of the week; the unfrozen portion being fed during the first 4 days. Achieved concentration was measured at all dose levels in diet samples from weeks 5, 6, 10 and 13. Mean values were within the range 101.2% to 109.3% of nominal (i.e., within the range of – 10% to + 10% of nominal) except for week 10, where results of all dose levels above 200 ppm were in the range of 117.8% to 142.8%. Homogeneity, measured in the week 1 mix, was acceptable since for all dose levels, the mean values for the top, middle and bottom of the mix were between 104.9% and 109.2% of nominal and the standard deviations were between 0.6 and 3.7. Stability at 20 ppm, the lowest dose level, was acceptable since nominal values declined by a maximum of 5% over the time of use of the test diets (8 days). After 35 days storage at room temperature, the maximum decline was 6% at this dose level.

Findings:

The mean achieved daily intakes for the combined sexes were 0, 1.68, 17.4, 432 and 1677 mg foramsulfuron/kg bw/d at 0, 20, 200, 5000 and 20000 ppm, respectively. The corresponding values for the two sexes were 1.54, 15.4, 388 and 1568 mg/kg bw/d for males and 1.81, 19.4, 475 and 1786 mg/kg bw/d for females at 20, 200, 5000 and 20000 ppm, respectively.

There were no treatment-related mortalities. At 20 ppm, one male was sacrificed *in extremis* on Study Day 58. In view of its isolated occurrence, this death was considered to be fortuitous. One female given 20 ppm died during blood sampling on Study Day 92.

No treatment-related effects were seen at any dose level.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for the combined sexes was 20000 ppm, equivalent to a daily intake of 1677 mg/kg bw/d, which is in excess of the 1000 mg/kg bw/d international limit dose.

B.6.3.2 Mouse oral toxicity studies**B.6.3.2.1 28-day oral toxicity**

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. The study is acceptable as a range-finding study.
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Report:

[REDACTED] 1998 (TOX2000-1048)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC90 0001: Mouse 28-day dietary toxicity
Report-No. TOX/96/262-2/TOX 95385, unpublished
Testing facility: [REDACTED]
(Experimental work: 12 February to 12 March 1996)

Test Material:

Foramsulfuron batch number H 2022/1, containing 90.0% w/w of the active substance

Test Animals:

CRL:CD-1 (ICR) BR mice
Source: [REDACTED]

GLP:

Yes

Test Method:

OECD 407, adopted 12 May 1981

Deviations:

Due to a technical error the diet preparation in the low dose group (400 ppm) contained only 32.6 and 32.4% of the nominal concentration.

Acceptability:

The study is considered to be acceptable as a range finding study

Material and Methods:

Groups of 5 male and 5 female CD-1 mice, 34 days old and weighing between 23 to 27.1 g (males) and 21.7 to 24.5 g (females) on the first day of treatment, were given diet containing either 0, 400, 1600 or 6400 ppm of foramsulfuron for 28 or 29 consecutive days. They were housed in groups of 5 by sex and dose level.

Animals were observed daily (once on weekends and on public holidays) for clinical signs and mortality. Individual body weights and cage group food consumption were measured weekly. Haematology and clinical chemistry investigations on all animals were conducted at termination. At necropsy, animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs recorded and a range of tissues preserved. Tissues from all control and high dose animals and gross lesions from all other mice were subsequently examined histopathologically.

Prior to the start of treatment a procedure was developed to prepare homogeneous and suitably stable mixtures of foramsulfuron in the laboratory rodent diet at the required nominal concentrations. During the study, test diets were prepared on a weekly basis for weeks 1 to 3 but diets for week 4 were prepared at the same time as those for week 3. The achieved concentration of all dietary concentrations of foramsulfuron was measured in diet samples from weeks 1 and 4. Mean results were within the range of 98.1% –102.6% of nominal (i.e., within the range of –10% to +10% of nominal) except for the weeks 3 and 4 mixes at 400 ppm where values were 32.6% and 32.4% of nominal respectively. In view of the overall no observed effect level in this study, these low values were considered to have no impact on the study.

Homogeneity and stability of foramsulfuron in the laboratory diet had been established in the rat 28-day toxicity study (see B.6.3.1.2).

Findings:

The mean achieved daily intakes of foramsulfuron were 0, 57 (adjusted according to the achieved concentration which was 32% of nominal for weeks 3 and 4), 357 and 1430 mg/kg bw/d for the combined sexes at 0, 400, 1600 and 6400 ppm, respectively. The corresponding values for the two sexes were 0, 51.5, 312 and 1164 mg/kg bw/d for males and 62.5, 401 and 1695 mg/kg bw/d for females at 0, 400, 1600 and 6400 ppm, respectively.

No treatment-related mortalities or clinical signs of toxicity occurred during the study.

Dietary administration of foramsulfuron to mice at dose levels up to 6400 ppm caused no treatment-related effects.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for both sexes was 6400 ppm of foramsulfuron, the highest dose level and equivalent to a daily intake of 1164 mg/kg bw/d for males, 1695 mg/kg bw/d for females and 1430 mg/kg bw/d for both sexes.

B.6.3.2.2. 90-day oral toxicity

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 408 has been adopted 21st September, 1998. The study does not fulfil the data requirements in the sense that no neurotoxic effects were studied.
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Report:

1998 (TOX2000-1051)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001: Mouse 90-day dietary toxicity
Report-No. TOX/96/262-5/TOX 95388, unpublished
Testing facility:
(Experimental work: 13 May to 15 August 1996)

Test Material:

Foramsulfuron batch number H 2037/ H2027, containing 98.4% w/w of active substance

Test Animals:

CRL:CD-1 (ICR) BR mice
Source:

GLP:

Yes

Test Method:

OECD 408, adopted 12 May 1981

Deviations:

None

Acceptability:

The study is considered to be acceptable.

Material and Methods:

Groups of 10 male and 10 female CD-1 mice were fed diet containing either 0, 64, 3200 or 6400 ppm of foramsulfuron for 13 consecutive weeks. At the start of treatment, the animals were approximately 6 weeks of age and weighed 23.9 to 34.4 g (males) and 23.8 to 30.1 g (females). They were housed in groups of 5 by sex and dose level and had been acclimatised for 12 days.

Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Detailed observations were conducted prior to weighing once weekly until day 71 and daily thereafter. During these observations swellings/lumps were noted in several males in the urinogenital region. Therefore mass tracking was implemented from day 85 to termination. Individual body weights were recorded weekly throughout the treatment period and at necropsy. Food consumption was also measured weekly. Biochemistry and haematology were carried out in week 14. At necropsy, all animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs recorded and a comprehensive range of tissues preserved. Subsequently all tissues from the control and high dose level animals sacrificed in week 13 and any mice sacrificed during the study were examined histopathologically.

Prior to the start of treatment, a procedure was developed to prepare homogeneous and suitably stable mixtures of the test material in the diet. Test diets were prepared at weekly intervals and stored at room temperature for 5 days prior to usage. The achieved concentration at all dose levels was measured in diet samples from weeks 1, 5, 10 and 14. The week 4 sample at 64 ppm was also analysed. For all concentrations, the mean results were between 95.1% and 100.4% of nominal. Homogeneity, measured in the week 1 mix, was also shown to be satisfactory at all dose levels since the mean values at the top, middle and bottom of the mixes were 95.8% to 100.4% of nominal. Data from previous studies had demonstrated acceptable stability over the time of use of the diet (8 days) at concentrations between 100 and 20000 ppm.

Findings:

The achieved mean daily intakes of foramsulfuron were 0, 12.6, 660 and 1090 mg/kg bw/d for the combined sexes at 0, 64, 3200 and 6400 ppm, respectively. The corresponding values for the separate sexes were 10.5, 498 and 1002 mg/kg bw/d for males and 14.6, 822 and 1178 mg/kg bw/d for females at 64, 3200 and 6400 ppm, respectively.

There were no treatment-related deaths.

No treatment-related effects were found in mice at any dose level, including no effects on the incidence of swelling in the urinogenital region.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) were 6400 ppm (equivalent to 1002 mg/kg bw/d for males, 1178 mg/kg bw/d for females and 1090 mg/kg bw/d for the combined sexes, which is approximately the international limit dose of 1000 mg/kg bw/d).

B.6.3.3 Dog oral toxicity studies**B.6.3.3.1 28-day oral toxicity**

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 409 has been adopted 21st September, 1998. Because of the low number of test animals (only two males and two females per dose), the study is only acceptable as a range-finding study.
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Report:

1998 (TOX2000-1049)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001:
Dog 28-day oral toxicity study
Report-No. TOX/96/262-4/TOX 95386, unpublished

	Testing facility: [REDACTED] (Experimental work: 15 May to 13 June 1996)
Test Material:	Foramsulfuron, batch number A 2037, containing 98.4% w/w of active substance
Test Animals:	Beagle dogs Source: [REDACTED]
GLP:	Yes
Test Method:	OECD 409, adopted 12 May 1981
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:

Groups of 2 male and 2 female beagle dogs, 4 months old and weighing between 5.9 to 8.0 kg (males) and 5.3 to 7.6 kg (females) at the start of dosing, were used. Each was given a single daily oral dose, by gavage, of either 0, 40, 200 or 1000 mg/kg bw/d for 28 or 29 consecutive days. The test material was administered as a suspension in 0.5% w/v methylcellulose in distilled water at a constant volume of 5 ml/kg bw/d. Controls received the vehicle alone.

Animals were examined thoroughly prior to the start of and at the end of treatment. They were observed for clinical signs twice daily (once on weekends and on public holidays). Individual body weights were recorded weekly throughout the treatment period and at necropsy. Food consumption was measured daily and water intake determined over four days in the third/fourth week of treatment. Ophthalmoscopy was conducted on all animals prior to the start of treatment and on the control and highest dose group animals prior to termination. An electrocardiogram was recorded for each dog one week prior to the start of treatment and on Study Day 28, pre-dose and post-dose (approximately 2 hours after dosing). Haematology and blood biochemistry investigations were conducted before the start of the treatment period (on Study Days –8 and –1) and on Days 14 and 27 of dosing. Urinalysis parameters were measured at termination from a urinary bladder sample. At necropsy, all animals were examined thoroughly for gross abnormalities, the weights of selected organs recorded and an extensive range of tissues was preserved. Subsequently, the range of tissues required by the testing guidelines was examined histopathologically.

Dosing suspensions were prepared on a daily basis. A trial mix at the 40 mg/kg bw/d, prepared before the start of the study, was analysed for stability after storage for 4 days at 4 °C and found to be satisfactory, i.e., within the acceptable range of 80% – 120% of nominal. During the study, samples of all dose levels from Study Days 1, 7, 8, 16, 23 and 29 were analysed to establish the achieved concentration of foramsulfuron. The mean results were within the range 94.5% – 120.2% of nominal except for the Day 1 and 7 samples at 40 mg/kg bw/d and 200 mg/kg bw/d where results in the range 46.4% to 75.2% of nominal were obtained. Since no treatment-related effects were seen at the highest dose level, 1000 mg/kg bw/d, and the actual achieved concentrations at this dose level were within the acceptable range, it was considered that the lower achieved levels at 40 and 200 mg/kg bw/d had no impact on the study.

Findings:

There were no mortalities and no treatment-related effects at any dose level.

Conclusion:

The no observed effect level (NOEL) and no observed adverse effect level (NOAEL) for both sexes was 1000 mg foramsulfuron /kg bw/d.

B.6.3.3.2 90-day oral toxicity

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 409 has been adopted 21st September, 1998. The study fulfils these data requirements.
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Report:

1998 (TOX2000-1052)
Hoe 130360 (AE F130360), Code: AE F130360 00 1C93 0001: Dog 90-day oral toxicity study
Report-No. TOX/97/262-18/TOX 95406, unpublished
Testing facility:
(Experimental work: 18 December 1996 to 24 March 1997)

Test Material:

Foramsulfuron batch number 2/96, containing 94.1% w/w of active substance

Test Animals:

Beagle dogs
Source:

GLP:

Yes

Test Method:

OECD 409, adopted 12 May 1981

Deviations:

None

Acceptability:

The study is considered to be acceptable.

Material and Methods:

Groups of 4 male and 4 female beagle dogs were given a single daily oral dose, by gavage, of either 0, 10, 250 or 1000 mg/kg bw/d for 13 consecutive weeks. The test material was administered as an aqueous suspension in 0.5% w/v methylcellulose at a constant volume of 5 ml/kg bw. Controls received the vehicle alone. At the start of treatment the dogs were approximately 7 to 8 months old and weighed 8.4 to 11.8 kg (males) and 8.0 to 9.5 kg (females). They had been acclimatised for 42 days prior to treatment and were housed in pens of 2 by sex and dose group, except during dosing and feeding when they were housed individually.

Each animal was given a thorough clinical examination prior to and at the end of the treatment period. Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Veterinarian visits/advice was obtained as necessary. Ophthalmoscopy was conducted on each dog prior to the first dose and on all control and high dose animals during the last week of treatment. Individual body weights were recorded at the start of treatment, at weekly intervals thereafter and at necropsy. Individual food consumption was also measured weekly. Biochemistry and haematology were carried out on Days 41 and 92. Urinalysis was performed on a bladder sample at necropsy (Days 93 and 94 for males and on Days 97 and 98 for females). At necropsy, all animals were examined thoroughly for macroscopic abnormalities, the weights of selected organs recorded and a

comprehensive range of tissues preserved. Subsequently, tissues from all animals were examined histopathologically.

The dosing suspensions were prepared on a daily basis. Samples of all dose levels from Days 1, 3, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85 and 92 of dosing were analysed to determine achieved concentration of foramsulfuron. The mean results were within the 80.0% and 104.8% of nominal, except for Day 15 at the 250 mg/kg bw/d and Days 22 and 29 at 1000 mg/kg bw/d which were 68.8%, 78.0% and 76.1% of nominal, respectively. However these isolated low values were considered to have no effect on the overall study results. Because the test material tended not to remain in suspension for any length of time, as shown in a trial mix (conducted before the study commenced which examined stability at all dose levels), the dosing preparations were prepared freshly each day and were stirred (mixed) continuously. Homogeneity results of Day 1 gave standard deviations up to 29% and therefore homogeneity was assessed weekly. It was acceptable in general at all dose levels from Day 22 since the standard deviation was <10%.

Findings:

There were no mortalities and no clinical signs directly related to treatment. Occasional beige faeces (beige being the colour of the test material) were noted at 1000 mg/kg bw/d from week 3 of treatment, particularly in females. Isolated incidences of this finding were also observed in one male in each of the 10 mg/kg bw/d and 250 mg/kg bw/d groups.

No treatment-related adverse effects were observed at any dose level.

Conclusion:

The no observed adverse effect level (NOAEL) for both sexes was 1000 mg/kg bw/d, the international limit dose.

B.6.3.3.3 1-year oral toxicity

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 452 has been adopted 7th September, 2009. The study fulfils these data requirements.
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Report:

1999 (TOX2000-1053)
AE F130360 (Hoe 130360), Code AE F130360 00 1C96 0001: Dog 12 month oral toxicity study
Report No. TOX/99/262-37/TOX 96121, unpublished
Testing facility:
(Experimental work: 24 June 1997 to 26 June 1998)

Test Material:

Foramsulfuron, code number AE F130360 00 1C96 0001, containing 96.4% w/w of active substance

Test Animals:

Beagle dogs
Source:

GLP:

Yes

Test Method:

OECD 452, adopted 12 May 1981

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Groups of 4 male and 4 female Beagle dogs were given a single daily oral dose, by gavage, of either 0, 5, 100 or 1000 mg/kg bw/d, suspended in 0.5 or 1.0% w/v methylcellulose in distilled water for 52 consecutive weeks. The control group received the vehicle alone. A constant volume of 5 ml/kg bw was used. The dogs were approximately 8 months old and weighed 8.1 to 12.6 kg (males) and 7.6 to 11.6 kg (females) at the start of treatment. They were housed in pairs by sex and dose group, except during feeding and dosing when they were housed individually.

Each animal was given a thorough clinical examination prior to the treatment period. Animals were observed for clinical signs twice daily (once on weekends and on public holidays). Veterinarian visits/advice was obtained as necessary. Ophthalmoscopy was conducted on each dog prior to the first dose and on all control and high dose animals during the last week of treatment. Individual body weights were recorded at the start of treatment, at weekly intervals thereafter and at necropsy. Individual food consumption was measured daily throughout the treatment period. Biochemistry and haematology were carried out at 3, 6, and 12 months of treatment. Urinalysis was performed on a bladder sample taken by catheterisation at 3 and 6 months and directly from the bladder at necropsy. Animals were sacrificed by exsanguination under deep anaesthesia induced by sodium pentobarbitone. Each animal was examined thoroughly for macroscopic abnormalities, the weights of the discrete organs recorded and a comprehensive range of tissues preserved. A bone marrow smear was also taken. Subsequently, all prepared tissues from all animals were examined histopathologically.

Dose suspensions were prepared freshly each day. Samples from all dose levels in weeks 1, 4, 5, 6, 7, 12, 14 to 28 inclusive, 33, 37 and 50 were analysed for achieved concentrations of foramsulfuron. In addition a trial mix in week 19 was analysed. The mean achieved values were between 81.4% and 111.7% of nominal (range -20% to +20% of nominal), except during week 15 at 1000 mg/kg bw/d when a value of 76.0% was recorded and for weeks 4, 5, 6, 21, 23 and 28 at 5 mg/kg bw/d where results of 79.7, 133.3, 71.6, 124.6, 124.0 and 122.8 % were found, respectively. However, the 5 mg/kg bw/d dose level represents the lowest dose level and the below range values were considered to have no impact on the overall result of this study since the NOAEL was 1000 mg/kg bw/d. Homogeneity was shown to be satisfactory since mean values from a trial mix prepared prior to the start of the study were within the acceptable range of 80% to 120% of nominal and the standard deviations differed by <10%. Since homogeneity results of dose suspensions from the Day 1 gave standard deviations of up to 22%, samples from weeks 4 to 7 and 14 to 28 were also assessed for homogeneity. Reanalysis of all concentrations of the trial mix following storage at 4 °C for 1, 2 and 4 days showed no decline in the content of foramsulfuron, i.e. this material was stable in the vehicle.

Findings:

There were no mortalities. A slight increase in the incidence of beige faeces (beige was the colour of foramsulfuron) of females given 1000 mg/kg bw/d was seen, particularly during the first week of treatment. In addition, isolated incidents of beige vomit were seen throughout the study in both sexes at this dose level.

No treatment-related ophthalmic changes or effects on body weight, food intake, haematology, biochemistry, urinalysis, organ weights, macroscopic pathology and histopathology were observed.

Conclusion:

The no observed adverse effect level (NOAEL) for both sexes was 1000 mg/kg bw/d, the international regulatory limit dose.

B.6.3.4 Other routes

B.6.3.4.1 28-day inhalation toxicity in rats

Hazards of inhaled substances are influenced by the inherent toxicity and by physical factors such as volatility and particulate size.

In the case of foramsulfuron, the inherent toxicity of the molecule is extremely low with no effects seen in rats, mice and dogs at 849, 1115 and 1000 mg/kg bw/d respectively after chronic oral exposure. Similarly, no signs of systemic toxicity were observed in rats given a single oral dose of 5000 mg/kg bw/d and there were no effects following 90-days dietary exposure to concentrations of up to 20000 ppm (corresponding to 1568 and 1786 mg/kg bw/d in males and in females, respectively). The only findings after 28-days of dietary treatment with 20000 ppm (corresponding to 1884 mg/kg bw/d in females) were decreases in body weight gain and food consumption in females. Foramsulfuron has also been shown to be of low volatility (4.2×10^{-11} Pa (20°C)).

The rat acute (4-hour) inhalation LC_{50} was >5.04 mg/l, the highest technically achievable concentration, which did not cause any mortality (see B.6.2.3). The only clinical signs observed were those commonly seen following nose-only exposure in a confined exposure cylinder and had resolved 1 day after exposure. The achieved concentration, corresponded to a theoretical maximum oral dose of approximately 775 mg/kg bw/d, as calculated below and assuming 100% of the particles are respired. This would increase to 1163 mg/kg bw/d for a 28-day inhalation study (6-hour exposure).

$$\text{Dose (mg / kg bw)} = \frac{\text{Concentration (}\mu\text{g / l)} \times \text{RMV} \times \text{D} \times \text{F}}{\text{W} \times 100}$$

Concentration = chamber concentration		RMV = Respiratory Minute Volume ($4.19 \times W(g)^{0.66}$)
D = duration of exposure (minutes)		W = body weight (g)
F = proportion by weight of respirable particles ($<7 \mu\text{m}$) and assumed to be 100% for the above calculations		
McMahon et al, 1977 ⁽²⁾		

Toxicokinetic studies in rats showed approximately 20% absorption after oral dosing with 10 mg/kg bw (see B.6.1.1). Absorption at the higher doses used in the 90-day oral toxicity studies would likely correspond to 10%. Thus, dietary exposure of 1786 mg/kg bw/d (actual absorbed dose = 179 mg/kg bw/d assuming 10% absorption) would correspond to an air concentration of approximately 0.78 mg/l (assuming 100% of the compound reaches the lungs). In reality, however, only 20% of the administered dose is likely to reach the lungs. Therefore, this pulmonary burden would be equivalent to an air concentration of 3.88 mg/l, which was close to the maximum dose achieved in the acute inhalation study.

Experience has shown that, in practice, the maximum concentration that would be used in a rat 28-day inhalation toxicity study with a low toxicity powder would be 1-2 mg/l which is comparable to the above estimated pulmonary burden of 0.78 mg/l. (Higher atmosphere concentrations would result in death by suffocation rather than the inherent toxicity of the compound). Thus, the maximum exposure in a 28-day inhalation study is within the range of dietary concentrations tolerated over a 90-day period and is considered unlikely to cause any significant toxicity.

For these reasons, it is concluded that a 28-day inhalation toxicity study in rats will not result in significant new toxicological information and thus is not scientifically justified.

² McMahon, T.A., Brain, J.D., and Lemott, S.: Species Difference in Aerosol Deposition, Inhaled particles IV (edited by Walton, W.H.), Part 1, 23-32, 1977

B.6.3.4.2 90-day inhalation toxicity in rats

No 90-day inhalation toxicity study has been conducted for the same reasons as stated above in B.6.3.4.1.

B.6.3.4.3 Percutaneous 28-day toxicity in rats

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed.
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Report:	[REDACTED] 1999 (TOX2000-1054) AE F130360, Code: AE F130360 00 1C94 0001: Rat 28-day dermal toxicity study Report number: TOX/98/262-34/TOX 96128, unpublished Testing facility: [REDACTED] (Experimental work: 2 September 1997 to 1 October 1997)
Test Material:	Foramsulfuron batch number 1/97, containing 94.2% w/w of active substance
Test Animals:	Sprague-Dawley CRL:CD (IGS)BR rats Source: [REDACTED]
GLP:	Yes
Test Method:	OECD 410, adopted 12 May 1981
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:

Groups of five male and five female Sprague-Dawley rats were given a daily, topical 6-hour application of either 0, 10, 100 or 1000 mg/kg bw/d for a total of 28 or 29 consecutive days for males and females respectively, excluding weekends. The test material was suspended in the vehicle, 1% w/v methylcellulose in distilled water. Control animals received the vehicle alone over the same period. On the first day of treatment, the animals were approximately 8 weeks of age (54 days old) and weighed between 247 g and 276 g (males) and between 208 g and 249 g (females).

Animals were observed for clinical signs twice daily (once on weekends and on public holidays). The treated skin site was examined macroscopically for local irritation prior to the first topical application and between about 30 and 60 minutes at the end of each exposure period. Individual body weights were recorded at the start of treatment, twice weekly thereafter and at necropsy. Cage group food consumption was measured weekly throughout the treatment period. Biochemistry and haematology were carried out on Day 29. At necropsy, all animals were examined thoroughly for macroscopic abnormalities. Particular attention was paid to the site of application. The weights of selected organs were recorded and a limited range of tissues preserved. The liver, kidneys, treated and untreated skin sites from the control and high dose level groups were examined histopathologically.

Suspensions of dose preparations were made freshly each day. Those from all dose levels prepared on Days 1, 8, 22 and 29 were analysed to establish the achieved concentration of foramsulfuron. The mean achieved test material concentrations were within the range 85.3% to 103.8% of nominal at the time of preparation, except for the 100 and 1000 mg/kg bw/d dose levels from Day 29, when results were 69.2% and 67.9% of nominal, respectively. In addition, samples from all dose levels from a trial mix prepared prior to the start of the study were analysed to determine homogeneity and stability over 24 hours. Homogeneity was satisfactory since the standard deviations were <10%. Stability was acceptable since there was no evidence of a decline of the test material concentration after 24 hours storage at 4 °C.

Findings:

There were no treatment-related mortalities or systemic clinical signs of toxicity.

At 1000 mg/kg bw/d, the highest dose level, yellow staining was observed at the treatment site in both sexes from Day 1 until termination, whilst slight redness was noted in 1/5 females in week 4. The yellow staining was due to the colour and concentration of the material.

At 100 mg/kg bw/d slight yellow staining was seen in 1/5 males during week 4.

There were no other findings at these dose levels and no findings at 10 mg/kg bw/d.

Conclusion:

The no observed effect level (NOEL) and the no observed adverse effect level (NOAEL) of foramsulfuron for systemic effects in both sexes was 1000 mg/kg bw/d, the regulatory limit dose.

B.6.3.4.4. Percutaneous 90-day toxicity in rats

In the rat 28-day dermal toxicity study, no evidence of systemic toxicity was observed at the regulatory limit dose of 1000 mg/kg bw/d. Furthermore, dermal absorption in rats has been shown to be very low (<2% of the applied dose of an undiluted formulation containing 22.5 mg/ml, or its spray dilution, respectively). Therefore not only is this compound of very low repeat-dose dermal toxicity, it also has a very low potential for absorption via the percutaneous route. Consequently, a 90-day percutaneous toxicity study is not triggered.

B.6.4. GENOTOXICITY

All genotoxicity tests were carried out in 1996 according to prevailing EEC, USEPA and/or OECD testing guidelines and were fully compliant with GLP requirements. A summary of the results is presented in Table B.6.4-1.

Table B.6.4-1: Summary of the genotoxicity studies with foramsulfuron (purity: 98.4% in all studies)

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

The genotoxic potential of foramsulfuron was evaluated in a battery of tests which examined gene mutation in bacteria and mammalian cells, chromosome damage *in vitro* and *in vivo* and DNA damage in mammalian cells *in vivo*. The only indication of genotoxicity was a slightly increased incidence of chromosomal aberrations observed in an *in vitro* assay with human lymphocytes. The increased incidences occurred only at the highest dose level tested, 2400 µg/ml, and only in the absence of exogenous metabolic activation. However, since there was no evidence of chromosomal damage *in vivo*, and in view of the negative test result obtained the *in vivo* assay for unscheduled DNA synthesis, this isolated positive test result is considered to be an *in vitro* specific effect. Overall, the weight of evidence suggests that foramsulfuron is of no genotoxic concern.

According to the data requirements (EU) No 283/2013 testing 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 $1000 \text{ L} \times \text{mol}^{-1} \times \text{cm}^{-1}$, photomutagenicity testing is not required.

Report: Bomann W., 2013
Foramsulfuron - Overview on photosafety and waiver for conduct of a photomutagenicity study
Bayer CropScience
Report No.: M-465939-01-1, unpublished
(18 September 2013)

GLP: No

The applicant has submitted a waiver for conducting a photomutagenicity study. According to the applicant a photomutagenic potential of foramsulfuron is not expected because of the following facts:

-Based on the structure of foramsulfuron no structural peculiarities exist, like presence of chromophors, conjugated double or triple bonds etc. which could provide evidence of a potential to cause photochemical effects.

-The quantum yield determined for foramsulfuron was very low, demonstrating a very low probability of generation of radicals by absorbed photons which minimizes the potential of phototoxic reactions even if the molar absorption ϵ exceeds the trigger values for phototoxicity and photomutagenicity studies.

-The result of the phototoxicity study conducted with foramsulfuron was negative. Since the mechanisms underlying the photochemical effects, like phototoxicity and photomutagenicity are the same, a photomutagenic reaction is not expected.

Conclusion

RMS agrees with the applicant that there is no evidence of a photoreactivity potential of foramsulfuron and thus no further testing is required.

B.6.4.1 In vitro studies

B.6.4.1.1 Bacterial assay for gene mutation

Previous evaluation	This study was evaluated in the original DAR. For transparency, mutagenicity data has been added in tabular form. Conclusion has not been changed.
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Report: Müller W., 1996 (TOX2000-1055)
Hoe 130360 Code: Hoe 130360 00 ZC98 0001: Bacterial reverse mutation test
Testing facility: Hoechst Marion Roussel GmbH, Preclinical Development, Germany
Report No. 96.0667, Doc.No. (Aventis): A57619, unpublished
(Experimental work: 9–19 July 1996)

Test Material: Foramsulfuron, batch no: H 2037; purity 98.4% (w/w)

Test System: *S. typhimurium* (strains TA 1535, TA 1537, TA 98 and TA100);
E. coli (strain WP2uvrA)

GLP: Yes

Test Method: OECD TG 471 and TG 472, adopted 26 May 1983

Deviations: No deviations from current TG 471 (adopted 21 July 1997)

Acceptability: The study is considered to be acceptable.

Material and Methods:

Two independent mutation tests were conducted in both the presence and absence of metabolic activation.

In the first test, histidine dependent auxotrophic mutant strains TA 1535, TA 1537, TA 98 and TA100 of *Salmonella typhimurium* and a tryptophan dependent auxotrophic mutant strain of *Escherichia coli*, WP2uvrA, were exposed to foramsulfuron dissolved in ethanol. For each bacterial strain and dose level, triplicate plates were used in both the presence and absence of an Aroclor 1254-induced rat liver metabolic activation system (S-9 mix). After 48 hours of incubation at 37°C, the numbers of revertant plates were scored using an automated colony counter.

For both experiments negative (untreated) controls and vehicle controls were used, along with positive controls. Positive control compounds used in the absence of metabolic activation were sodium azide (for TA 100 and TA 1535), 9-aminoacridine (TA 1537), 2-nitrofluorene (TA 98) and 1-methyl-3-nitro-1-nitrosoguanidine (WP2uvrA). In the presence of the S9 mix, 2-aminoanthracene was used for all strains.

Dose levels of technical foramsulfuron used in the first test for all bacterial strains were 0, 4, 20, 100, 500, 2500 and 5000 µg/plate. In the second test, concentrations for all the *Salmonella typhimurium* strains were 0, 0.032, 0.16, 0.8, 4, 20 and 100 µg/plate to account for the differences in the sensitivities of these strains. For *Escherichia coli* WP2uvrA, the concentrations were the same as those in the first test i.e. 0, 4, 20, 100, 500, 2500 and 5000 µg/plate.

A toxicity test with *Salmonella* strain TA 100 was conducted in parallel with the second mutation test both with and without S-9 mix. It used triplicate plates of 0.1 ml of a 10⁶ dilution of an overnight culture of TA 100 (designated TA 100 D) and the solvent plated on to histidine and biotin rich top agar. The dose levels of foramsulfuron evaluated were 0, 0.032, 0.16, 0.8, 4, 20 and 100 µg/plate.

Prior to the start of the study the stability of a 5 and 20% concentration of the test compound in ethanol was confirmed over 4 hours. For the 5% concentration the mean percentage of nominal was 115% after 4 hours compared with 108% at time '0', and 114% after 4 hours compared with 113% at time '0' for the 20% concentration. Thus foramsulfuron was stable at these concentrations in ethanol over 4 hours.

Findings:

Foramsulfuron was toxic in both mutation tests to all *Salmonella typhimurium* strains at concentrations of 20 µg/plate and above both with and without metabolic activation. In the toxicity test with a dilution of the 10⁶ overnight culture of strain TA 100 (designated TA 100 D), toxicity was observed at concentrations of 4 µg/plate and above in the absence of metabolic activation. However, there was no toxicity in the presence of metabolic activation at dose levels up to 100 µg/plate, the highest evaluated. The test compound was not toxic to *Escherichia coli* WP2uvrA at any concentration tested.

Foramsulfuron did not cause any significant increases in the number of revertant colonies in either the presence or absence of metabolic activation. All the positive control compounds produced expected increases in the number of revertant colonies, thereby demonstrating the sensitivity of the assay and the efficacy of the S-9 mix.

Table B.6.4-2: Ames test; first experiment

Strain	S9	Dose level µg/plate	Mean	Standard deviation	Ratio: test/control	No revertant/plate		
						Plate 1	Plate 2	Plate 3
TA 100	+	0	188.0	28.6		172	171	221
	+	4	155.7	38.6	0.8	113	188	166
	+	20	83.3	9.3	0.4	94	77	79
	+	100	5.0	4.6	0.0	6	9	0
	+	500	0.0	0.0	0.0	0	0	0
	+	2500	0.0	0.0	0.0	0	0	0
	+	5000	0.0	0.0	0.0	0	0	0
TA 100	-	0	118.7	20.3		105	109	142
	-	4	194.0	27.8	1.6	162	208	212
	-	20	89.0	25.9	0.7	117	66	84
	-	100	0.0	0.0	0.0	0	0	0
	-	500	0.0	0.0	0.0	0	0	0
	-	2500	0.0	0.0	0.0	0	0	0
	-	5000	0.0	0.0	0.0	0	0	0

TA 1535	+	0	11.3	2.1		13	9	12
	+	4	11.3	2.5	1.0	14	11	9
	+	20	2.7	1.2	0.2	4	2	2
	+	100	0.0	0.0	0.0	0	0	0
	+	500	0.0	0.0	0.0	0	0	0
	+	2500	0.0	0.0	0.0	0	0	0
	+	5000	0.0	0.0	0.0	0	0	0
TA 1535	-	0	10.7	0.6		11	11	10
	-	4	12.0	3.5	1.1	8	14	14
	-	20	1.0	1.0	0.1	2	0	1
	-	100	0.0	0.0	0.0	0	0	0
	-	500	0.0	0.0	0.0	0	0	0
	-	2500	0.0	0.0	0.0	0	0	0
	-	5000	0.0	0.0	0.0	0	0	0
TA 1537	+	0	9.0	1.7		8	8	11
	+	4	15.0	1.7	1.7	17	14	14
	+	20	4.0	2.0	0.4	2	6	4
	+	100	0.0	0.0	0.0	0	0	0
	+	500	0.0	0.0	0.0	0	0	0
	+	2500	0.0	0.0	0.0	0	0	0
	+	5000	0.0	0.0	0.0	0	0	0
TA 1537	-	0	9.7	2.5		10	7	12
	-	4	12.3	5.1	1.3	11	18	8
	-	20	4.0	1.7	0.4	3	3	6
	-	100	0.0	0.0	0.0	0	0	0
	-	500	0.0	0.0	0.0	0	0	0
	-	2500	0.0	0.0	0.0	0	0	0
	-	5000	0.0	0.0	0.0	0	0	0
TA 98	+	0	23.3	4.2		20	28	22
	+	4	20.0	3.6	0.9	21	16	23
	+	20	5.0	1.0	0.2	5	6	4
	+	100	0.0	0.0	0.0	0	0	0
	+	500	0.0	0.0	0.0	0	0	0
	+	2500	0.0	0.0	0.0	0	0	0
	+	5000	0.0	0.0	0.0	0	0	0
TA 98	-	0	26.3	6.8		21	24	34
	-	4	23.7	1.5	0.9	22	24	25
	-	20	4.7	0.6	0.2	4	5	5
	-	100	0.0	0.0	0.0	0	0	0
	-	500	0.0	0.0	0.0	0	0	0
	-	2500	0.0	0.0	0.0	0	0	0
	-	5000	0.0	0.0	0.0	0	0	0
WP2uvrA	+	0	30.0	4.6		26	29	35
	+	4	29.3	7.6	1.0	31	21	36
	+	20	26.0	3.6	0.9	22	29	27
	+	100	27.0	4.6	0.9	22	31	28
	+	500	27.3	4.2	0.9	26	24	32
	+	2500	27.0	2.0	0.9	25	27	29
	+	5000	24.7	3.8	0.8	29	23	22
WP2uvrA	-	0	23.3	4.5		28	23	19
	-	4	23.7	3.5	1.0	27	20	24
	-	20	20.0	2.6	0.9	22	21	17
	-	100	26.0	2.0	1.1	24	26	28
	-	500	23.0	2.0	1.0	25	23	21
	-	2500	15.7	3.1	0.7	15	13	19
	-	5000	23.7	2.1	1.0	22	26	23

Table B.6.4-3: Ames test; second experiment

Strain	S9	Dose level µg/plate	Mean	Standard deviation	Ratio: test/control	No revertant/plate		
						Plate 1	Plate 2	Plate 3
TA 100	+	0	202.7	14.0		204	188	216
	+	0.032	141.3	19.7	0.7	129	131	164
	+	0.16	127.3	4.7	0.6	122	131	129
	+	0.8	137.0	5.6	0.7	143	136	132
	+	4	103.3	15.5	0.5	121	97	92
	+	20	42.0	8.0	0.2	34	50	42
	+	100	0.0	0.0	0.0	0	0	0
TA 100	-	0	169.3	16.8		184	173	151
	-	0.032	148.7	24.4	0.9	154	122	170
	-	0.16	178.3	4.5	1.1	174	183	178
	-	0.8	176.3	14.8	1.0	160	189	180
	-	4	130.7	23.5	0.8	151	105	136
	-	20	17.7	5.1	0.1	22	19	12
	-	100	0.0	0.0	0.0	0	0	0
TA 1535	+	0	12.3	2.9		14	9	14
	+	0.032	10.3	0.6	0.8	10	11	10
	+	0.16	15.0	2.6	1.2	16	12	17
	+	0.8	13.3	2.9	1.1	15	15	10
	+	4	8.0	1.7	0.7	9	6	9
	+	20	0.7	1.2	0.1	2	0	0
	+	100	0.0	0.0	0.0	0	0	0
TA 1535	-	0	11.0	3.0		14	11	8
	-	0.032	11.7	3.2	1.1	14	8	13
	-	0.16	10.3	2.1	0.9	8	12	11
	-	0.8	10.7	0.6	1.0	10	11	11
	-	4	9.7	0.6	0.9	9	10	10
	-	20	0.3	0.6	0.0	1	0	0
	-	100	0.0	0.0	0.0	0	0	0
TA 1537	+	0	10.0	2.6		13	9	8
	+	0.032	10.7	3.2	1.1	7	13	12
	+	0.16	11.0	4.0	1.1	7	15	11
	+	0.8	11.7	4.2	1.2	13	7	15
	+	4	10.3	3.5	1.0	14	10	7
	+	20	3.0	2.6	0.3	6	1	2
	+	100	0.0	0.0	0.0	0	0	0
TA 1537	-	0	11.3	4.2		10	16	8
	-	0.032	9.7	3.1	0.9	9	7	13
	-	0.16	13.3	1.2	1.2	12	14	14
	-	0.8	12.0	4.4	1.1	14	15	7
	-	4	10.7	3.1	0.9	10	14	8
	-	20	2.3	1.5	0.2	4	1	2
	-	100	0.0	0.0	0.0	0	0	0
TA 98	+	0	24.7	3.5		21	25	28
	+	0.032	31.7	6.4	1.3	28	28	39
	+	0.16	27.7	6.1	1.1	21	33	29
	+	0.8	30.7	7.5	1.2	31	23	38
	+	4	26.3	6.0	1.1	32	20	27
	+	20	2.3	1.5	0.1	1	4	2
	+	100	0.3	0.6	0.0	1	0	0

TA 98	-	0	28.7	1.5		30	29	27
	-	0.032	23.7	3.8	0.8	28	21	22
	-	0.16	24.3	3.8	0.8	20	27	26
	-	0.8	24.3	5.0	0.8	19	25	29
	-	4	20.7	6.4	0.7	17	28	17
	-	20	2.3	2.3	0.1	1	1	5
	-	100	0.0	0.0	0.0	0	0	0
WP2uvrA	+	0	28.0	6.0		22	28	34
	+	4	27.7	3.8	1.0	32	26	25
	+	20	30.7	4.0	1.1	35	30	27
	+	100	25.0	3.5	0.9	27	27	21
	+	500	31.0	4.0	1.1	31	27	35
	+	2500	24.3	4.0	0.9	20	28	25
	+	5000	23.7	4.0	0.8	28	20	23
WP2uvrA	-	0	24.3	4.0		28	20	25
	-	4	21.3	1.2	0.9	20	22	22
	-	20	24.3	1.5	1.0	23	26	24
	-	100	26.7	1.5	1.1	28	25	27
	-	500	23.7	1.5	1.0	22	25	24
	-	2500	25.7	2.1	1.1	24	25	28
	-	5000	22.3	0.6	0.9	23	22	22

Conclusion:

Foramsulfuron, dissolved in ethanol, was not mutagenic in this *in vitro* bacterial mutation test in either the presence or absence of exogenous metabolic activation.

B.6.4.1.2 Test for clastogenicity in mammalian cells

Previous evaluation	This study was evaluated in the original DAR. The study deviates from the OECD TG 473 (adopted 21 July 1997) in the sense that the cells were not exposed to the test substance for 3 hours in the absence of metabolic activation. As foramsulfuron showed clastogenic activity in assays where cells were treated continuously until sampling in the absence of S9 mix, this deviation has no significant effect to the result of the study. No conclusion has been changed: Foramsulfuron, dissolved in ethanol, showed evidence of clastogenic activity in the absence of S9 mix at the highest test concentration of 2400 µg/ml. The study is considered to be acceptable.
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Report:

██████████, 1997 (TOX2000-1056)
Hoe 130360 (AE F130360); Code: Hoe 130360 00 ZC98 0001 -
In vitro human lymphocyte chromosome aberrations
Study No.: 96106, Doc.No. (Aventis): A58266, unpublished;
Testing facility: ██████████;
(Experimental work: 12 June to 20 September 1996)

Test Material:

Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w)

Test System:

Human blood lymphocytes

GLP:

Yes

Test Method: OECD TG 473, adopted 26 May 1983

Deviations: No significant deviations from current OECD TG 473 (adopted 21 July 1997)

Acceptability: The study is considered to be acceptable.

Material and Methods:

Human blood collected from healthy male donors was pooled and diluted with RPMI tissue culture medium containing 16.7% foetal calf serum (PAA). These cultures were incubated at 37 °C for 48 h in the presence of phytohaemagglutinin (0.4 ml blood: 4.5 ml media: 0.1 ml phytohaemagglutinin) to stimulate cell division. The cycle time for human lymphocytes in the testing facility was approx. 15 h.

Three separate tests were carried out both with and without an exogenous metabolic activation system, S-9 mix, derived from the livers of rats induced with Aroclor 1254. The exposure scheme and test concentrations applied are summarised in Table B.6.4-:

Table B.6.4-4: Exposure scheme and test concentrations applied

Incubation period:	With S9-mix		Without S9-mix	
	With foramsulfuron	Total	With foramsulfuron	Total
Test I	3 h	21 h	21 h	21 h
Test IIa	3 h	21 h	21 h	21 h
Test IIb	3 h	45 h	45 h	45 h
Test III	–	–	21 h	21 h
Test concentrations:				
Test I	0 (ethanol solvent)–18.8–37.5–75–150–300–600–1200–2400 µg/ml			
Test IIa+b	0 (ethanol solvent)–600–1200–2400 µg/ml			
Test III	0 (ethanol solvent)–2400 µg/ml			

Duplicate cultures were used for each treatment with the test substance. Four other cultures were treated with ethanol as the solvent control, while Mitomycin C, the positive control used in the absence of S-9 mix, was added to duplicate cultures at final concentrations of 0.2, 0.4 and 0.8 µg/ml. In the presence of metabolic activation, the positive control cyclophosphamid was added to duplicate cultures at final concentrations of 20, 25 and 30 µg/ml. 2 hours before the cells were harvested, mitotic activity was arrested by addition of colchicine (colcemid) to each culture at a final concentration of 0.1 µg/ml. Cells were subsequently harvested and processed for scoring.

Slides were initially examined to record the proportion of mitotic cells per 1000 cells in each culture (except for the positive control cultures). This was used to establish the highest dose level for metaphase analysis. The intermediate and low dose levels for analysis were also chosen. Following coding, 100 metaphase figures in each culture were evaluated for aberrations. Only cells with 44 to 46 chromosomes were analysed. The number of aberrant metaphase figures in each treated group was compared statistically with the solvent control group using a Fisher's Exact test.

Findings:

In the presence of S-9 mix, for the 21-h harvest time, dose levels selected for metaphase analysis were 600, 1200 and 2400 µg/ml both the first and second tests. For the 45-h harvest of the second test conducted both with and without S-9 mix, and for the third test conducted only in the absence of S-9 mix, the highest test concentration of 2400 µg/ml was evaluated.

First assay (I): Foramsulfuron was non-toxic in both the absence and presence of S-9 mix. The relative mitotic index at 2400 µg/ml was 121% in the absence of S-9 mix and 85% in its presence. Therefore, dose levels of 600, 1200 and 2400 µg/ml were selected for metaphase analysis.

No statistically significant increases in the proportion of aberrant cells, when compared to the solvent controls, were seen in cultures treated with foramsulfuron in either the presence or absence of S-9 mix. Both the positive control compounds caused statistically significant ($p < 0.001$) increases in the proportion of aberrant cells, demonstrating the efficacy of the S-9 mix and the sensitivity of the test system.

Table B.6.4-5: Foramsulfuron metaphase analysis data – tests without S-9 mix

Compound / Concentration			No. of aberrant cells ¹		Rel. Mitotic index %
Test-No.	Incubation period (h)	Concentration	Excl. gaps Mean %	Incl. gaps Mean %	
Solvent control ² [µl/ml]					
I	21-h	10	0.75	0.75	100
IIa	21-h	10	0.5	0.5	100
IIb	45-h	10	0.75	0.75	100
III	21-h	10	0.5	0.5	100
Foramsulfuron [µg/ml]					
I	21-h	600	0.0	0.0	141
		1200	0.0	0.0	127
		2400	0.5	0.5	121
IIa	21-h	600	0.0	1.0	115
		1200	0.5	1.0	74
		2400	5.5*	6.0*	79
IIb	45-h	2400	6.5*	8.5*	55
III	21-h	2400	7.0*	7.0*	74
Mitomycin C[µg/ml]					
I	21-h	0.8 0.4	13.0*	13.0*	—
IIa	21-h	0.8	11.0*	11.0	—

¹ 100 cells were examined for aberrations per culture. Four cultures incubated with solvent control only were evaluated per assay, while duplicate cultures were assayed in the case of foramsulfuron and for positive control Mitomycin C incubations.

² Only negative control assay results of cultures are presented which harboured aberrations.

* $p < 0.001$, otherwise $p > 0.01$

Second test, 21-h harvest (IIa): 2400 µg/ml foramsulfuron reduced the mitotic index to 79% and 82% of the solvent control value in the absence and presence of S-9 mix, respectively.

In the absence of S-9 mix, foramsulfuron caused a slight increase in the number of aberrant cells at 2400 µg/ml. In the presence of S-9 mix, there were no statistically significant increases in the proportion of aberrant cells when compared to the solvent control, at any dose level. Both positive control compounds caused statistically significant increases in aberrant cells.

Second test, 21-h harvest (IIa): In the absence of S-9 mix at 2400 µg/ml reduced the mitotic index to 55% of the control. However, in the presence of S-9 mix the mitotic index showed no toxicity. In the absence of S-9 mix, 2400 µg/ml caused a statistically significant increase in the number of aberrant cells (6.5%) at the 45-hour harvest time. In the presence of S-9 mix, foramsulfuron showed no statistically significant increases in the number of aberrant cells compared to the control.

Third test, 21-h harvest (III): At the 21-hour harvest time in the absence of S-9 mix, 2400 µg/ml was not toxic since the relative mitotic index was 74%. An increase in the number of aberrant cells (7%) was observed.

Measurement of osmolality indicated no difference in the treated and solvent control cultures.

Note:

According to the authors of the study report, the increased mean percentage of cells with chromosomal aberrations in cultures exposed to 2400 µg/ml foramsulfuron lie just outside the upper range of historical control data. However, only a brief summary of historical control data was presented in the study report, which did not include any information (1) whether or which underlying studies were compliant with GLP or OECD Test Guideline requirements, (2) whether or which of the studies used ethanol as control solvent, or (3) the duration of incubation with solvent performed in each study. Therefore, the reported historical control data was regarded to be unreliable by the Rapporteur and could not be considered for the overall assessment of the study results.

Conclusion:

Foramsulfuron, dissolved in ethanol, showed evidence of clastogenic activity in the absence of S-9 mix at the highest test concentration of 2400 µg/ml only, while a negative test result was obtained in the presence of a metabolic activation system in this *in vitro* cytogenetic test.

B.6.4.1.3. Test for gene mutation in mammalian cells

Previous evaluation	This study was evaluated in the original DAR. For transparency, mutagenicity data has been added in tabular form. Conclusion has not been changed.
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Report:

██████████, 1996 (TOX2000-1057)
Hoe 130360, Code: Hoe 130360 00 ZC98 0001:
In vitro Chinese hamster lung V79 cell HPRT mutation
Report No. 96.0781, Doc.No. (Aventis): A58125, unpublished
Testing facility: ██████████
(Experimental work: July 29 to August 19 1996)

Test Material:

Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w)

Test System:

Chinese hamster lung (V79) cells

GLP:

Yes

Test Method:

OECD 476, adopted 4 April 1984

Deviations:

None which is considered to have impact on the validity of the study

Acceptability:

The study is considered to be acceptable.

Material and Methods:

In preliminary assessment of cytotoxicity (determination of cell survival via crystal violet extinction) for selection of appropriate dose levels for the mutation assay, evaluation of the solubility of foramsulfuron showed that 2000 µg/ml produced a slight precipitate and was therefore the highest practicable test concentration. Accordingly, the preliminary toxicity study was carried out using a dose range from 1–2000 µg/ml. The cell cultures were subjected to the same treatment conditions as in the

subsequent mutation assays. Both in the presence or absence of exogenous metabolic activation system (S9-mix) derived from rat livers induced with Aroclor 1254, there was no indication of toxicity up to the limit of solubility.

Ethanol was used as solvent control. The stability of 5% and 20% concentrations of foramsulfuron in ethanol were established. At the 5% concentration, the mean percentage of nominal was 115% at 4 hours compared with 108% at time '0', and 114% of nominal at 4 h compared with 113% at time '0' for the 20% concentration. Thus both concentrations of foramsulfuron were stable over 4 h.

Based on these results, two independent assays for mutation to 6-thioguanine resistance were performed in the presence and absence of S9 metabolic activation using dose levels of 250, 500, 1000 and 2000 µg/ml. Before treatment, the pH values and osmolality of the treatment media were determined. The addition of test compound solutions did not have any effect on these parameters. Negative and solvent controls were used for each test. Ethyl methane sulphonate and 9,10-dimethyl-1,2-benzanthracene were used as positive controls in the absence and presence of metabolic activation, respectively.

The mutation tests were conducted as follows:

- Day 1: A) Exponentially growing cultures of Chinese hamster lung V97 cells were subcultured to establish cultures of about 4500 cells per well of the microtitre plate for plating efficiency.
- B) For the mutation test, a single 175 cm² flask with 30 ml medium containing 6×10^5 to 1×10^6 cells were established for each concentration and time point. Two sets of cultures were prepared, one for treatment in the absence of S9-mix and one for treatment in its presence.
- Day 2: Cell cultures A) and B) were treated with foramsulfuron, the solvent or positive control in both the presence and absence of S9-mix for 4 hours.
- Day 3: Fixation and staining of the cells from the plating efficiency culture a) to determine plating efficiency.
- Day 5: Subculturing of the main mutation test cultures b).
- Day 9: Subculturing of B) in five 75 cm² flasks with culture medium containing 6-thioguanine (about 11 µg/ml) for mutant selection (approx. 300000 cells/flask) and of two 25 cm² flasks for plating efficiency (about 400 cells per flask).
- Day 16: Cell colonies from the Day 9 plating efficiency cultures were fixed and stained with methylene blue stain in 0.01% w/v KOH solution.

All incubations were at approximately 37 °C and in a 4% CO₂ atmosphere. Only colonies with more than 50 cells were counted.

Findings:

No relevant reproducible dose-related increases in the mutant colonies or mutant frequency were seen at any of the concentrations of foramsulfuron tested, in either the presence or absence of metabolic activation. The sensitivity of the test system was demonstrated by statistically significant increases in mutation frequency in the cell cultures treated with the positive control compounds.

Table B.6.4-6: Mutagenicity data (Main experiment)

	Dose µg/ml	S9- mix	Number of mutant colonies					mean	Stand. dev.	Mut. freq.	Stat. sig.
			I	II	III	IV	V				
Negative control	0.0	-	8	10	6	7	5	7.2	1.92	25.7	
Solvent control (ethanol)	0.0	-	15	14	5	8	7	9.8	4.44	38.8	
Positive control (EMS)	1000.0	-	102	115	131	127	125	120.0	11.66	659.3	*
Hoe 130360	250.0	-	4	6	4	3	3	4.0	1.22	16.2	
	500.0	-	2	0	0	1	0	0.6	0.89	2.3	
	1000.0	-	1	2	4	0	4	2.2	1.79	8.5	
	2000.0	-	1	0	2	2	2	1.4	0.89	6.7	
Negative control	0.0	+	3	3	3	4	4	3.4	0.55	12.6	
Solvent control (ethanol)	0.0	+	4	3	2	2	4	3.0	1.00	13.3	
Positive control (DMBA)	7.7	+	21	12	18	20	17	17.6	3.51	70.5	*
Hoe 130360	250.0	+	4	3	6	5	1	3.8	1.92	18.0	
	500.0	+	1	6	5	6	7	5.0	2.35	21.4	
	1000.0	+	1	2	0	1	1	1.0	0.71	4.1	
	2000.0	+	3	3	3	8	3	4.0	2.24	19.1	

Mutation frequency (mutant colonies per 1 million cells): mean value / cells surviving

* Statistical significant ($p \leq 0.05$) Mann-Whitney-U-Test

Table B.6.4-7: Mutagenicity data (Repeat)

	Dose µg/ml	S9- mix	Number of mutant colonies					mean	Stand. dev.	Mut. freq.	Stat. sig.
			I	II	III	IV	V				
Negative control	0.0	-	1	2	1	4	2	2.0	1.22	8.2	
Solvent control (ethanol)	0.0	-	9	4	6	5	6	6.0	1.87	22.9	
Positive control (EMS)	1000.0	-	157	164	149	136	164	154.0	11.81	775.1	*
Hoe 130360	250.0	-	2	2	1	0	1	1.2	0.84	5.8	
	500.0	-	0	1	4	2	2	1.8	1.48	9.1	
	1000.0	-	1	2	2	2	0	1.4	0.89	8.4	
	2000.0	-	3	2	3	2	1	2.2	0.84	11.3	
Negative control	0.0	+	7	2	7	5	4	5.0	2.12	26.9	
Solvent control (ethanol)	0.0	+	1	0	3	3	2	1.8	1.30	8.9	
Positive control (DMBA)	7.7	+	24	26	23	22	17	22.4	3.36	93.3	*
Hoe 130360	250.0	+	0	0	0	1	0	0.2	0.45	0.8	
	500.0	+	1	2	1	2	0	1.2	0.84	4.9	
	1000.0	+	1	3	1	2	2	1.8	0.84	7.6	
	2000.0	+	3	3	0	1	2	1.8	1.30	8.7	

Mutation frequency (mutant colonies per 1 million cells): mean value / cells surviving

* Statistical significant ($p \leq 0.05$) Mann-Whitney-U-Test

Conclusion:

Foramsulfuron was not mutagenic in Chinese hamster lung V79 cells either in the presence or absence of an exogenous metabolic activation system in this *in vitro* test.

B.6.4.2 In vivo studies in somatic cells

B.6.4.2.1 Metaphase analysis in rodent bone marrow, or micronucleus test in rodents

Previous evaluation	<p>This study was evaluated in the original DAR. For transparency, mutagenicity data has been added in tabular form.</p> <p>The study does not fulfil current data requirements. Only 1000 polychromatic erythrocytes were examined for the number of micronuclei which is too little according to the current OECD Test Guideline 474 (1997) where testing on 2000 polychromatic</p>
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	erythrocytes is required. However, no increases in the number of micronuclei in polychromatic erythrocytes was observed. Taken together that no carcinogenic, reproductive toxic and teratogenic effects of foramsulfuron were observed, performing a new study is not considered necessary.
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Report: [REDACTED], 1997 (TOX2000–1058)
Hoe 130360, Code: Hoe 130360 00 ZC98 0001: Mouse micronucleus test
Report No. 96.0865, Doc.No. (Aventis): A58340, unpublished
Testing facility: [REDACTED]
[REDACTED] (Experimental work: 22 July – 26 September, 1996)

Test Material: Foramsulfuron, (batch no H 2037; purity 98.4% (w/w))

Test Animals: SHOE: NMRI mice; age (Day 1): approx. 7 wk, mean bw(Day 1): 37.6 g (males), 30.3 g (females)
Source: [REDACTED]

GLP: Yes

Test Method: OECD TG 474, adopted 1983
USEPA Subdivision F § 84-2, November 1984
EU 92/69/EEC, B12

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Groups of 5 male and 5 female NMRI mice were given a single oral dose by gavage of either 200, 1000 or 2000 mg/kg body weight of foramsulfuron suspended in 1% w/v aqueous methylcellulose. A similar sized negative control group received a single oral dose of the vehicle alone. Another group of 5 males and 5 females was given a single gavage dose of 50 mg/kg body weight of Endoxan (cyclophosphamide) as the positive control. In all cases the dose volume was 10 ml/kg body weight.

All positive control animals were sacrificed 24 hours post-dosing whilst 5 males and 5 females from each of the test and negative control groups were sacrificed 12, 24 and 48 hours after dosing. A bone marrow smear was prepared from the femur of each animal. Following fixation and staining with Giemsa, the slides were air-dried then examined for the number of micronuclei in 1000 polychromatic erythrocytes and, as a control measure, the incidence in 1000 normochromatic erythrocytes from each mouse. In addition, the ratio of polychromatic to 1000 normochromatic erythrocytes was determined. The incidences of micronucleated polychromatic erythrocytes and of normochromatic erythrocytes were statistically evaluated using Wilcoxon tests.

The highest dose level of foramsulfuron, 2000 mg/kg bw, was based on the results of a range finding study in which no mortality and no clinical signs of toxicity were observed at this dose level. Therefore, since this level was defined as the international limit dose according to guidelines, it was chosen as the highest dose for the micronucleus test.

This dose level was prepared as a 20% suspension concentration in the vehicle, 1% w/v aqueous methylcellulose. This was tested for stability of the test substance over 3 hours prior to the start of the study. After 3 hours the mean percent of nominal was 103% compared with 108% at time '0'. Thus a

20% concentration of AE F1309360 in 1% aqueous methylcellulose was stable over this 3-hour time period.

Findings:

There was no mortality in any of the dose groups treated with foramsulfuron. Moreover, no clinical signs of toxicity were observed and there were no macroscopic findings at necropsy.

There were no statistically significant increases in micronucleated polychromatic and normochromatic erythrocytes in animals treated with foramsulfuron. All values were within the normal range of the negative control groups. No treatment-related change of the ratio of polychromatic to normochromatic erythrocytes was observed. The positive control cyclophosphamide induced a marked and statistically significant increase in the number of polychromatic erythrocytes with micronuclei, confirming the sensitivity of the test system.

Table B.6.4-8: Summary of findings in bone marrow erythrocytes

Sex	Dose mg/kg	Sample time	No. of animals	Erythrocytes P/N		Erythrocytes with micronuclei							
				Mean	SD	Polychromatic (mean)			Mut.I.	Normochromatic (mean)			Mut.I.
						No.	%	SD		No.	%	SD	
Pooled	0	12 h	10	0.7	0.16	1.50	0.2	0.12	1.0	1.10	0.1	0.09	1.0
	200	12 h	10	0.9	0.13	1.60	0.2	0.12	1.1	0.70	0.1	0.08	0.6
	1000	12 h	10	0.7	0.08	0.90	0.1	0.06	0.6	1.50	0.2	0.11	1.4
	2000	12 h	10	0.9	0.07*	1.60	0.2	0.10	1.1	1.10	0.1	0.09	1.0
Pooled	0	24 h	10	0.7	0.20	1.70	0.2	0.09	1.0	1.10	0.1	0.10	1.0
	200	24 h	10	1.0	0.15	1.10	0.1	0.10	0.6	1.70	0.2	0.14	1.5
	1000	24 h	10	0.9	0.21	0.70	0.1	0.08	0.4	1.20	0.1	0.11	1.1
	2000	24 h	10	0.8	0.18	0.70	0.1	0.07	0.4	1.40	0.1	0.10	1.3
	P.contr.	24 h	10	0.9	0.09	34.0	3.4	0.90*	20.0	1.80	0.2	0.06	1.6
Pooled	0	48 h	10	0.9	0.16	1.20	0.1	0.14	1.0	1.20	0.1	0.04	1.0
	200	48 h	10	0.8	0.17	0.80	0.1	0.08	0.7	1.00	0.1	0.12	0.8
	1000	48 h	10	0.9	0.15	1.00	0.1	0.13	0.8	1.10	0.1	0.09	0.9
	2000	48 h	10	0.9	0.11	1.00	0.1	0.11	0.8	1.10	0.1	0.09	0.9

Mut.I. = Mutagenic index = erythrocytes with micronuclei in dose group / erythrocytes with micronuclei in control

Control = Vehicle

P.contr = Positive control = endoxan * = Significantly different from control (P < 0.05)

Table B.6.4-9: Summary of findings in bone marrow erythrocytes

Sex	Dose mg/kg	Sample time	No. of animals	Erythrocytes P/N		Erythrocytes with micronuclei							
				Mean	SD	Polychromatic (mean)			Mut.I.	Normochromatic (mean)			Mut.I.
						No.	%	SD		No.	%	SD	
Male	0	12 h	5	0.8	0.15	1.40	0.1	0.15	1.0	1.20	0.1	0.11	1.0
	200	12 h	5	1.0	0.09	1.60	0.2	0.09	1.1	0.80	0.1	0.11	0.7
	1000	12 h	5	0.7	0.07	0.60	0.1	0.05	0.4	1.40	0.1	0.13	1.2
	2000	12 h	5	0.9	0.08	1.60	0.2	0.11	1.1	1.00	0.1	0.10	0.8
Female	0	12 h	5	0.7	0.18	1.60	0.2	0.09	1.0	1.00	0.1	0.07	1.0
	200	12 h	5	0.9	0.15	1.60	0.2	0.15	1.0	0.60	0.1	0.05	0.6
	1000	12 h	5	0.7	0.09	1.20	0.1	0.04	0.8	1.60	0.2	0.09	1.6
	2000	12 h	5	0.9	0.08	1.60	0.2	0.09	1.0	1.20	0.1	0.08	1.2
Male	0	24 h	5	0.6	0.19	1.40	0.1	0.11	1.0	1.20	0.1	0.08	1.0
	200	24 h	5	1.0	0.08	1.20	0.1	0.13	0.9	1.80	0.2	0.18	1.5

	1000	24 h	5	1.0	0.21	0.80	0.1	0.08	0.6	1.40	0.1	0.15	1.2
	2000	24 h	5	0.8	0.25	0.40	0.0	0.09	0.3	1.20	0.1	0.11	1.0
	P.contr.	24 h	5	0.9	0.09	37.2	3.7	0.61	26.6	2.00	0.2	0.07	1.7
Female	0	24 h	5	0.9	0.06	2.00	0.2	0.07	1.0	1.00	0.1	0.12	1.0
	200	24 h	5	1.0	0.20	1.00	0.1	0.07	0.5	1.60	0.2	0.11	1.6
	1000	24 h	5	0.9	0.23	0.60	0.1	0.09	0.3	1.00	0.1	0.07	1.0
	2000	24 h	5	0.8	0.09	1.00	0.1	0.00	0.5	1.60	0.2	0.09	1.6
	P.contr.	24 h	5	0.8	0.05	30.8	3.1	1.09	15.4	1.60	0.2	0.05	1.6
Male	0	48 h	5	0.8	0.16	1.40	0.1	0.11	1.0	1.20	0.1	0.04	1.0
	200	48 h	5	0.8	0.10	1.00	0.1	0.10	0.7	1.80	0.2	0.13	1.5
	1000	48 h	5	0.8	0.03	1.60	0.2	0.15	1.1	1.20	0.1	0.08	1.0
	2000	48 h	5	0.9	0.13	0.60	0.1	0.09	0.4	0.80	0.1	0.08	0.7
Female	0	48 h	5	1.0	0.06	1.00	0.1	0.17	1.0	1.20	0.1	0.04	1.0
	200	48 h	5	0.7	0.22	0.60	0.1	0.05	0.6	0.20	0.0	0.04	0.2
	1000	48 h	5	0.9	0.23	0.40	0.0	0.09	0.4	1.00	0.1	0.10	0.8
	2000	48 h	5	0.8	0.08	1.40	0.1	0.11	1.4	1.40	0.1	0.09	1.2

Mut.I. = Mutagenic index = erythrocytes with micronuclei in dose group / erythrocytes with micronuclei in control

Control = Vehicle

P.contr. = Positive control = endoxan

Conclusion:

Foramsulfuron did not induce micronuclei, i.e., was not clastogenic or aneugenic, in this mouse bone marrow erythrocyte micronucleus test.

B.6.4.2.2 Unscheduled DNA synthesis

Previous evaluation	This study was evaluated in the original DAR. For transparency, mutagenicity data has been added in tabular form. Conclusion has not been changed.
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Report:

██████████, 1996 (TOX2000-1059)
Hoe 130360, Code: Hoe 130360 00 ZC98 0001: *In vivo* rat hepatocyte unscheduled DNA synthesis
Study No.: TOX 96107 Doc.No. (Aventis): A57435, unpublished;
Testing facility: ██████████
(Experimental work: 17–26 June, 1996)

Test Material:

Foramsulfuron, batch no. H 2037, purity: 98.4% (w/w)

Test Animals:

SPF Hsd/Ola Sprague-Dawley male rats; age (Day 1): 6 wk old
██

GLP:

Yes

Test Method:

OECD TG 482, adopted 23 Oct. 1986 and
September 1995 draft of OECD TG 486 (adopted 21 July 1997)

Deviations:

Deviations from OECD TG 486 (21 July 1997): None that compromised the validity of the study.

Acceptability:

The study is considered to be acceptable.

Material and Methods:

In the preliminary USD test four males were given a single oral gavage dose of 2000 mg/kg bw by gavage and observed for 4 days for mortality or clinical signs of toxicity. The vehicle used for the test substance was 1% w/v aqueous methyl cellulose. For the main test, groups of 8 males were given a single gavage dose of either 600 or 2000 mg/kg bw in aqueous 1% w/v methyl cellulose. The negative control group was given the vehicle only. The two positive control groups, each consisting of 2 male rats, were given a single gavage dose of either 4 mg dimethylnitrosamine/kg bw (2-h sampling time) or 50 mg 2-acetylaminofluorene/kg bw (14-h sampling time). In all cases the dose volume was 10 ml /kg bw. The highest dose level, 2000 mg/kg, was selected in the absence of clinical signs and mortality in the preliminary test. It is also the limit dose recommended in the OECD and EEC testing guidelines for acute oral toxicity testing.

Groups of 4 rats from each of the negative control and foramsulfuron-treated groups were sacrificed 2 and 14 hours post dosing together with all animals from the relevant positive control group. Following perfusion and subsequent excision of the liver, isolated hepatocytes were prepared and suspended in Williams' medium E, complete (WEC). A viable cell count was performed after diluting an aliquot of the cells with an equal volume of trypan blue. The cell yield was also calculated.

Twelve replicate cultures of the isolated hepatocytes from each animal were established in multi-well plates, each well containing a glass coverslip and Williams' medium E supplemented with 10% foetal calf serum (WEC). They were incubated for 90 minutes at 37 °C and in a humid atmosphere of 5% CO₂ to allow the cells to attach to the coverslip. The medium was then replaced with Williams' medium C without foetal calf serum (WEI) containing high specific activity (methyl-³H) thymidine at a final activity of 10 µCi/ml. Following 4 hours of incubation, the medium was replaced with 'cold' thymidine in WEI for a 24-hour 'chase' period. The coverslips were then removed from the culture medium, given three 5-minute washes in Hanks' balanced salts solution then fixed in 2.5% v/v acetic acid in ethanol and allowed to dry. They were then mounted on glass microscope slides. Autoradiographs were prepared from six cultures per animal per dose level and sampling point. These slides were then randomised and grain count analysis conducted on three slides per animal using image analysis. A total of 150 (50 from each of 3 cultures per animal) hepatocytes were scored for the foramsulfuron-treated animals. Only 75 cells for the positive controls were examined because of evident cell toxicity. Only results from hepatocytes not in S-phase with normal morphology (i.e., not pyknotic or lysed) without staining artifacts or debris were recorded. For each cell the number of silver grains overlying the nucleus was estimated then the number of grains in an equivalent sized, most heavily grained adjacent area of cytoplasm was scored. The net nuclear grain count was derived by subtracting the cytoplasmic grain count from the gross nuclear grain count. For slides with a strong response, i.e., the mean net grain count was above 10, only 25 cells were examined. The number of cells with a net grain count greater than or equal to 5 was recorded in the raw data. Both gross and net nuclear grain counts for treated animals were compared with the vehicle control counts statistically (one-way analysis of variance followed by a Student's t test with appropriate transformation if necessary).

Findings:Preliminary toxicity test:

No mortality and no clinical signs of toxicity were observed in animals treated with 2000 mg/kg body weight.

Main UDS test:

No mortality and no clinical signs of toxicity were observed in either the preliminary toxicity animals treated with foramsulfuron.

There were no significant increases in the gross or net nuclear grain count at either dose level of foramsulfuron at either the 2- or 14-hour sampling times. Grain counts were similar to the vehicle control values and were within the historical control values.

Animals treated with the positive controls dimethylnitrosamine and 2-acetylaminofluorene showed a significant increase ($P < 0.001$) in the net nuclear grain count and accompanying substantial increases in the gross nuclear grain count. Values were comparable with those from previous studies. Therefore the sensitivity of the test was confirmed.

Table B.6.4-10 : Results for the 2 hour expression time

Test substance	Dosage (mg/kg)	Gross nuclear grain count					Cytoplasmic grain count			Net nuclear grain count				
		x ¹	x ²	x ³	Mean/animal	Mean/group	x ¹	x ²	x ³	x ¹	x ²	x ³	Mean/animal	Mean/group
Vehicle	-	16.6	16.6	16.3	16.5	16.5	19.0	18.4	18.6	-2.4	-1.8	-2.3	-2.2	-1.7
		14.5	15.7	14.4	14.9		14.7	17.8	16.3	-0.2	-2.1	-1.9	-1.4	
		17.1	14.0	16.1	15.7		20.3	14.6	16.6	-3.2	-0.6	-0.5	-1.4	
		19.4	18.5	19.1	19.0		20.5	20.3	21.4	-1.1	-1.8	-2.2	-1.7	
HOE 130360	600	14.7	14.1	12.9	13.9	15.3ns	16.7	15.7	15.0	-2.0	-1.5	-2.1	-1.9	-1.7ns
		17.2	18.0	16.6	17.3		18.6	20.2	19.0	-1.4	-2.2	-2.4	-2.0	
		16.2	16.4	14.5	15.7		16.9	17.6	16.7	-0.8	-1.3	-2.2	-1.4	
		13.0	14.4	15.0	14.1		15.3	15.7	16.2	-2.3	-1.3	-1.2	-1.6	
	2000	15.9	14.3	15.2	15.1	15.9ns	17.0	15.4	16.9	-1.0	-1.0	-1.7	-1.2	-1.7ns
		15.6	15.7	18.1	16.5		18.5	16.9	19.0	-2.8	-1.2	-0.9	-1.6	
		14.5	17.8	18.6	17.0		18.7	17.5	20.0	-4.2	0.3	-1.4	-1.8	
		14.7	14.2	15.7	14.9		17.7	16.2	17.5	-3.0	-2.0	-1.8	-2.3	
Dimethyl-nitrosamine	4	51.0	52.1	47.8	50.3	50.4**	19.9	19.8	20.3	31.1	32.3	27.5	30.3	31.2**
		48.8	52.8	49.5	50.4		18.6	18.9	17.6	30.2	33.9	31.9	32.0	

x¹, x², x³ Mean results for each replicate culture

Results of statistical analysis (one-way analysis of variance followed by a Student's *t* test with critical one-sided probability levels):

** P < 0.001 (highly significant)

* P < 0.01 (significant)

ns P > 0.01 (not significant)

For each cell examined, Net nuclear grain count = Gross nuclear grain count - Cytoplasmic grain count. An occasional apparent discrepancy of 0.1 net grains may occur due to rounding of mean values for presentation in the table.

Table B.6.4-11: Results for the 14 hour expression time

Test substance	Dosage (mg/kg)	Gross nuclear grain count					Cytoplasmic grain count			Net nuclear grain count				
		x ¹	x ²	x ³	Mean/animal	Mean/group	x ¹	x ²	x ³	x ¹	x ²	x ³	Mean/animal	Mean/group
Vehicle	-	15.7	14.6	16.4	15.6	16.4	18.0	18.7	18.2	-2.4	-4.1	-1.8	-2.8	-3.2
		15.8	15.6	14.6	15.3		18.3	18.9	17.8	-2.5	-3.3	-3.2	-3.0	
		15.9	21.7	19.0	18.9		18.1	24.2	21.9	-2.1	-2.6	-2.9	-2.5	
		15.2	15.3	16.2	15.6		19.1	20.5	20.6	-3.9	-5.3	-4.4	-4.5	
HOE 130360	600	12.7	16.9	15.8	15.1	16.7ns	15.5	19.5	17.0	-2.8	-2.5	-1.2	-2.2	-2.8ns
		20.0	19.9	18.7	19.5		22.8	22.5	21.7	-2.8	-2.6	-3.0	-2.8	
		14.5	16.5	16.3	15.8		18.9	19.8	19.3	-4.4	-3.3	-3.0	-3.6	
		15.8	16.3	17.1	16.4		18.7	18.2	19.8	-2.9	-1.8	-2.7	-2.5	
	2000	14.2	12.9	15.7	14.3	14.8ns	17.7	15.1	17.9	-3.5	-2.3	-2.3	-2.7	-3.6ns
		15.8	17.4	14.2	15.8		19.4	20.3	18.2	-3.6	-2.9	-4.0	-3.5	
		16.7	14.8	13.9	15.1		21.1	20.0	18.3	-4.5	-5.2	-4.4	-4.7	
		12.6	14.2	15.0	13.9		15.3	18.2	18.4	-2.7	-4.1	-3.5	-3.4	
2-Acetyl-aminofluorene	50	55.0	48.4	45.0	49.5	45.5**	25.2	24.6	22.5	29.8	23.8	22.5	25.4	22.9**
		42.4	43.7	38.4	41.5		22.6	22.8	18.2	19.8	21.0	20.1	20.3	

x¹, x², x³ Mean results for each replicate culture

Results of statistical analysis (one-way analysis of variance followed by a Student's *t* test with critical one-sided probability levels):

** P < 0.001 (highly significant)

* P < 0.01 (significant)

ns P > 0.01 (not significant)

For each cell examined, Net nuclear grain count = Gross nuclear grain count - Cytoplasmic grain count. An occasional apparent discrepancy of 0.1 net grains may occur due to rounding of mean values for presentation in the table.

Conclusion:

Foramsulfuron did not cause unscheduled DNA synthesis (indicative of DNA repair) in rat hepatocytes following *in vivo* oral treatment with up to 2000 mg/kg, the international dose limit for such studies.

B.6.4.3 In vivo studies in germ cells

As all of the aforementioned genotoxicity studies were essentially negative, an *in vivo* study in germ cells was not triggered under the EC Commission Directive 94/79/EC of 21 December 1994, 5.4.3: *In vivo* studies in germ cells.

As no genotoxic potential was observed in adequate genotoxicity studies and no genotoxic potential is anticipated, *in vivo* studies in germ cells are not required according to the data requirements (EU) No 283/2013

B.6.5. LONG-TERM TOXICITY AND CARCINOGENESIS

In a combined chronic toxicity and oncogenicity study, rats were subjected to continuous dietary treatment for 2 years with dose levels of up to 20000 ppm, corresponding to 849 mg/kg bw/d in males and 1135 mg/kg bw/d in females. Tumour incidences were slightly increased in some tissues/organs (brain, thyroid, uterus, malignant lymphoma), but the increases did not follow a dose-response relationship, were not significantly different when compared to control values and similar to historical control data of the test laboratory. Therefore, these effects were considered not to be related to treatment with foramsulfuron.

In mice, dietary treatment with up to 8000 ppm for 80 consecutive weeks provoked no evidence of oncogenic activity. This high dose level also approximated to the international regulatory limit dose.

Results obtained in these long-term studies are presented below.

Table B.6.5-1: Summary of long-term toxicity studies

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

B.6.5.1 Rat dietary combined chronic toxicity and oncogenicity study

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 453 has been adopted 7th September, 2009. The study fulfils these data requirements.
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Report: [REDACTED], 2000 (TOX2000-1060)
Rat dietary combined chronic toxicity and oncogenicity study:
AE F130360 (Hoe 130360), Code: AE F130360 00 1C95 0001
Report No. TOX/99/262-42, Doc.No. (Aventis): C006180, unpublished
Test facility: [REDACTED]
(Experimental work: November 1996 – December 1999)

Test Material: Foramsulfuron, batch no 1/96, purity: 94.6% (w/w)

Test Animals: Sprague Dawley CRL:CD (IGS) BR rats; age (Day 1): approx. 6 wk,
bw range (Day 1): males: 60–184 g; females: 114–163 g
Source: [REDACTED]

GLP: Yes

Test Method: OECD TG 453, adopted 12 May 1981

Deviations: No deviations from OECD TG 453 that were considered to have
compromised the validity or integrity of the study.

Acceptability: The study is considered to be acceptable.

Material and Methods:

The end points of long-term toxicity and carcinogenicity were tested in a combined study in rats. Groups of 50 male and 50 female Sprague Dawley rats were given dietary concentrations of either 0, 100, 600, 6000 or 20000 ppm of foramsulfuron for 104 - 108 consecutive weeks. Further groups of 20 males and 20 females were treated at the same dose levels for 52-53 weeks. Animals were housed in groups of five by sex and dose level.

Animals were observed twice daily for mortality and clinical signs except on weekends and on public holidays when they were observed once. They were given a detailed physical examination, which included palpation for masses, at weekly intervals immediately prior to weighing. Individual body weights were recorded immediately prior to the start of treatment, at weekly intervals to week 14, every second week thereafter and at necropsy. Cage group food consumption was measured weekly for the first 13 weeks of treatment and approximately every four weeks thereafter.

Ophthalmoscopy was conducted on all animals prior to the start of treatment, on all animals in the control and highest dose group in Week 52 and on all surviving animals prior to termination (month 24).

Blood samples for biochemistry and haematology and samples of urine for analysis were obtained from numerically the first ten surviving rats of each sex in each group at 3, 6, 12, 18 and 24 months.

After 52 weeks of treatment, the first 20 surviving animals of each sex and dose level were sacrificed for assessment of chronic toxicity; survivors remaining after 104 weeks were assessed for oncogenic potential.

All animals, including decedents, were necropsied. Each animal was examined thoroughly for macroscopic abnormalities, the weights of discrete organs recorded and an extensive range of tissues preserved. A bone marrow smear was also prepared from all animals except decedents. Subsequently all tissues from all decedents and animals surviving to the scheduled necropsy were examined histopathologically.

Findings:

At the end of the chronic toxicity phase (after 54 weeks of treatment), the group mean achieved intakes of foramsulfuron at 0, 100, 600, 1000 and 20000 ppm 5.0, 30, 291 and 976 mg/kg bw/d for males and 6.7, 40, 397 and 1305 mg/kg bw/d for females, respectively.

After 104 wk, the group mean achieved daily intakes of foramsulfuron at 0, 100, 600, 1000 and 20000 ppm were 4.5, 25, 246 and 849 mg/kg bw/d for males and 5.6, 34, 339 and 1135 mg/kg bw/d for females, respectively.

There were no treatment-related effects on survival. There were no treatment-related clinical signs of toxicity, no effects on palpable masses body weight, food consumption, biochemistry, haematology, urinalysis, organ weights or macroscopic findings.

In treatment groups, the incidence of pituitary cysts, endometrial stromal polyps, and of tumours of the brain, thyroid and hematopoietic tissue were slightly increased, and spermatozoa were reduced or absent in the epididymides when compared to control levels (see Table B.6.5-2). However, the incidences did not follow a dose-response relationship, the differences to control values were statistically not significant and were comparable to historical control data of the testing laboratory. Therefore, these effects were considered not to be related to treatment with foramsulfuron.

Table B.6.5-2: Incidence of selected non-neoplastic and neoplastic lesions

Effect	Sex	Dose level (ppm)					*Historical controls Min–Max
		0	100	600	6000	20000	
Epididymides , reduced or absent spermatozoa	M	10/50 (20%)	9/50 (18%)	5/50 (10%)	9/50 (18%)	13/50 (26%)	6–56%
Epididymides , reduced or absent spermatozoa, severe	M	6/50 (12%)	5/50 (10%)	4/50 8%	8/50 (16%)	9/50 (18%)	2–12%
Uterus , endometr. stromal polyp	F	6/50 (12%)	7/50 (14%)	6/50 (12%)	5/50 (10%)	10/50 (20%)	0–12%
Pituitary , cysts present	M	3/50 (6%)	3/50 (6%)	3/50 (6%)	3/50 (6%)	7/50 (14%)	0–8%
	F	2/50 (4%)	3/50 (6%)	5/50 (10%)	1/50 2%	1/50 2%	0–4%
Brain , astrocytoma, malignant	M	1/50 (2%)	0/50 (0%)	2/50 (4%)	3/50 (6%)	1/50 (2%)	0–2%
	F	1/50 (2%)	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/50 (6%)	0–4%
Malignant lymphoma	M	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	2/50 (4%)	0–4%
	F	0/50 (0%)	0/50 (0%)	2/50 (4%)	0/50 (0%)	1/50 (2%)	0–5%
Thyroid , follicular cell adenoma	M	2/50 (4%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	4/50 (8%)	2–8%
	F	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	0–4%
Thyroid , follicular cell carcinoma	M	1/50 (2%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0–4%
	F	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)	1/50 (2%)	0–2%
Thyroid , c cell adenoma	M	11/50 (22%)	16/50 (32%)	5/50 (10%)	14/50 (28%)	11/50 (22%)	2–22%
	F	6/50 (12%)	6/50 (12%)	10/50 (20%)	6/50 (12%)	11/50 (22%)	4–22%
Thyroid , c cell carcinoma	M	0/50 (0%)	0/50 (0%)	2/50 (4%)	0/50 (0%)	2/50 (4%)	0–8%
	F	0/50 (0%)	1/50 (2%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	0–6%

*Historical control histopathology data from 9 studies conducted between 1982–1998 by the same laboratory that conducted the rat chronic toxicity and oncogenicity study with foramsulfuron

Conclusion:

Dietary administration of foramsulfuron to rats did not result in any statistically significant increased incidences of adverse effects at dose levels up to 20000 ppm. This was equivalent to 976 and 1305 mg/kg bw/d in males and females, respectively over 54 weeks, and to 849 mg/kg bw/d in males and 1135 mg/kg bw/d in females over 104 weeks.

B.6.5.2 Carcinogenicity study in the mouse

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 451 has been adopted 7th September, 2009. The study fulfils these data requirements.
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Report: [REDACTED], 1999 (TOX2000–1061)
Mouse dietary oncogenicity study: AE F130360, Code: AE F130360 00 1C96 0001;
Study-No.: TOX 96120, Doc.No. (Aventis): C006435, unpublished;
Testing facility: [REDACTED]
(Experimental work: 21 July 1997 to 10 February 1999)

Test Material: Foramsulfuron, batch no. 1-4/97, purity: 96.4% (w/w)

Test Animals: Crl:CD-1(ICR)BR mice, age (Day 1): approx. 6 wk;
male bw (Day 1): 21.8–33.9 g; female bw (Day 1): 19.8–28.0 g
Source: [REDACTED]

GLP: Yes

Test Method: OECD 451, adopted 12 May 1981

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Groups of 51 male and 51 female CD-1 mice housed in groups of three by sex and dose level were given dietary concentrations of either 0, 40, 800 or 8000 ppm of foramsulfuron for 80 consecutive weeks.

Animals were observed twice daily for morbidity and mortality. They were observed daily for clinical signs of toxicity and were given a detailed physical examination at weekly intervals, including palpation for masses. Individual body weights were recorded immediately prior to the start of treatment, at weekly intervals for the first 16 weeks, once every four weeks thereafter, and at necropsy. Cage group food consumption was measured weekly for the first 16 weeks of treatment, then one week in four thereafter. A blood smear was prepared from all animals in Weeks 52 and 53. Blood samples were obtained from numerically the first ten mice of each sex in each group at necropsy and the white blood cell count determined. However, practical difficulties meant that the count was actually scored in 8 to 10 per sex per group, apart from in females from the intermediate dose group where only 5 were evaluated. Blood smears were also taken from all animals at the scheduled terminal necropsy but were not examined. All animals, including decedents were necropsied. Each animal was examined thoroughly for macroscopic abnormalities, the weights of adrenals, brain, heart, kidney, liver, spleen and testes (incl. epididymides) recorded and an extensive range of tissues preserved. Subsequently tissues from all animals, including decedents, were examined histopathologically. Bone marrow smears were also prepared from all the terminal sacrifice animals and examined.

Findings:

The group mean achieved daily intakes of foramsulfuron for the combined sexes were 0, 6.0, 121 and 1236 mg/kg bw/d at 0, 40, 800 and 8000 ppm, respectively. The corresponding values for each sex were 5.4, 109 and 1115 mg/kg bw/d for males and 6.5, 134 and 1358 mg/kg bw/d for females.

There were no clinical signs of toxicity and no treatment-related effects on survival, body weight, food consumption, haematology, organ weights or macroscopic findings. No evidence of an increased incidence of any tumour or hyperplasia indicative of oncogenicity was observed. In addition, there were no microscopic non-neoplastic findings indicative of toxicity induced by foramsulfuron.

Conclusion:

Dietary administration of foramsulfuron for 80 weeks to the CD-1 mouse at up to 8000 ppm was not oncogenic and did not cause toxicity. This high dose level was slightly higher than the international regulatory limit dose. NOEL (80-wk oral, mouse): 8000 ppm (1115 mg/kg bw/d).

B.6.5.3 Mechanism of action and supporting data

There was no evidence of untoward toxicological findings. Therefore no mechanism of action was identified.

B.6.6. REPRODUCTIVE TOXICITY

The reproductive toxicity studies were conducted during 1997 and 1998 in accordance with OECD and EU testing guidelines and were GLP compliant. A summary of the results is presented in Table B.6.6-1.

A two-generation reproduction study in rats evaluated continuous dietary dose levels of 0, 100, 1225 and 15000 ppm of technical foramsulfuron. No treatment-related effects were observed, including no effects on reproductive parameters (fertility, mating, gestation, parturition, litter size sex ratios), parental toxicity, neonatal toxicity or on markers of endocrine function (oestrous cycling, balanopreputial separation, vaginal opening, spermatogenetic function and capacity). Therefore, the NOEL and NOAEL was 15000 ppm, equivalent to a mean daily intake of 1038 mg/kg bw/d for F₀ and F₁ males and 1430 mg/kg bw/d for F₀ and F₁ females combined (about 1234 mg/kg bw/d for the study overall).

A rat developmental toxicity (teratogenicity) study was conducted with dose levels of 0, 5, 71 and 1000 mg/kg bw/d. There was no evidence of any maternal, embryonal or foetal toxicity up to and including the 1000 mg/kg dose level, the international limit dose for this type of study. Therefore the no observed effect level (NOEL) for both maternal and embryonal/foetal toxicity was 1000 mg/kg bw/d. Foramsulfuron was not teratogenic in rats.

The rabbit developmental toxicity (teratogenicity) study was conducted with dose levels of 0, 5, 50 and 500 mg/kg bw/d. Maternal toxicity was seen at the high dose of 500 mg/kg bw/d, as evidenced by reduced body weight gain and slightly decreased food consumption during the treatment period. There was no embryonal or foetal toxicity at any dose level. The no observed effect level (NOEL) for maternal toxicity was 50 mg/kg bw/d and 500 mg/kg bw/d for developmental toxicity (teratogenicity). Foramsulfuron was not teratogenic in the rabbit.

Table B.6.6-1: Summary of reproductive toxicity studies

Study and dose levels	Target	NOEL/ NOAEL	LOAEL	Effects
Rat 2-generation study 0–100–1225–15000 ppm	Parental + reproductive tox.	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

Results of the two-generation and the developmental toxicity (teratogenicity) studies, show that foramsulfuron gives no evidence of reproductive, embryonal/foetal or neonatal toxicity. Therefore, foramsulfuron was of very low reproductive toxicity. Parental (maternal) toxicity was only seen in the rabbit at 500 mg/kg bw/d.

B.6.6.1. Generational studies

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 416 has been adopted 22nd January 2001. The study fulfils these data requirements.
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Report:

██████████ 1999 (TOX2000-1062)
 AE F130360, code AE F130360 00 1C96 0002: Rat dietary two-generation reproductive toxicity study
 Report-No. TOX/99262-35, Study-No. 96123, Unpublished
 Testing facility: ██████████
 (Experimental work: 4 November 1997 to 31 July 1998)

Test Material:

Foramsulfuron, a blend of batch numbers H2075/1-H2075/4 + 1/97, containing 96.1% w/w of active substance

Test Animals:

Sprague Dawley Crl:CD (SD)BR rats
 Source: ██████████

GLP:

Yes

Test Method:

OECD guideline 416, adopted 26 May 1983

Deviations:

None

Acceptability:

The study is considered to be acceptable.

Material and Methods:

Groups of 30 male and 30 female F₀ and F₁ Sprague Dawley Crl:CD rats, received dietary concentrations of either 0, 100, 1225 or 15000 ppm of technical foramsulfuron continuously throughout the study. Animals were housed individually except during pairing and lactation.

F₀ and F₁ animals were treated for at least 70 days prior to pairing (one male and one female from same dose group); treatment was continued throughout pairing, gestation and lactation up to termination (following weaning of pups on post-natal Day 22). Treatment commenced when the F₀ animals were 6 weeks of age and commenced at weaning, post-natal Day 22, for the F₁ generation when one male and one female from each of the F₀ generation litters were selected to form this generation. Mated females were allowed to litter. Pups were individually identified and the litters in excess of 8 pups were adjusted to this maximum as appropriate on post-natal Day 4. At weaning, an additional one male and one female pup per litter were selected for detailed necropsy and organ weights. Surplus F₁ and F₂ pups were sacrificed and necropsied on post-natal Day 21.

Parent animals were subjected to detailed necropsy after their pups had been weaned and selected organs were weighed. Spermatogenic endpoints (sperm motility, morphology and numbers) were recorded for all F₀ and F₁ males. Histopathology was conducted on the reproductive and target organs of 10 males and 10 females from the control and highest dose levels of each generation.

All F₀ and F₁ animals were observed twice daily for clinical signs and behaviour. Body weights and food consumption were recorded weekly prior to pairing. Females were weighed on Days 0, 4, 7, 10 and 20 of gestation and on Days 1, 4, 7, 14 and 21 of lactation. Male body weights were recorded weekly. Food consumption of females and their litters were recorded weekly. Vaginal smears were taken for 21 days prior to pairing, during pairing until mating occurred and at necropsy. Litters were examined twice daily for pup mortality, clinical signs and behaviour. Pups were weighed individually and sexed on post-natal Days 0/1, 4, 7, 14 and 21. Balanopreputal separation and vaginal opening were monitored in the F₁ generation animals.

Findings:

Mean achieved intakes of the test substance for the combined generations were 7, 82 and 1038 mg/kg bw/d for males and 10, 115 and 1430 mg/kg bw/d for females at 100, 1225 and 15000 ppm.

There were no treatment-related findings, including no effects on reproductive parameters (fertility, mating, days between pairing and mating, gestation, parturition, litter size sex ratios, pup mortality), parental toxicity (body weight and body weight gain, food consumption, clinical condition, macroscopic pathology), neonatal toxicity (body weights and clinical condition), or on markers of endocrine function (oestrous cycling, balanopreputal separation, vaginal opening, spermatogenic function and capacity).

Conclusion:

Dietary administration of up to 15000 ppm of foramsulfuron to rats for two successive generations did not cause any parental, neonatal or reproductive toxicity.

The No Observed Adverse Effect Level (NOAEL), and No Observed Effect Level (NOEL) of reproductive toxicity and parental toxicity was 15000 ppm, equivalent to an achieved mean daily intake of 1038 mg/kg bw/d for F₀ and F₁ males combined and 1430 mg/kg bw/d for F₀ and F₁ females combined (1234 mg/kg bw/d for the study overall).

B.6.6.2. Developmental toxicity studies**B.6.6.2.1 Teratogenicity study by the oral route in the rat****Previous evaluation**

This study was evaluated in the original DAR. No new evaluation

	has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 414 has been adopted 22nd January, 2001. The study fulfils these data requirements except that the exposure period was on days 7 to 16 and not days 5-15 as mentioned in the current OECD Test Guideline.
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Report: [REDACTED] 1997 (TOX2000-1063)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001:
Rat oral development toxicity (teratogenicity) study
Report-No. TOX/98/262-24; 97.0320; 96.0760; Unpublished
Testing facility: [REDACTED]
[REDACTED]
(Experimental work: 18 November to 5 December, 1996)

Test Material: Foramsulfuron, batch number H 2037, containing 98.4% w/w of active substance

Test Animals: Hoe: WISKf(SPF71) Wistar rats
Source: [REDACTED]

GLP: Yes

Test Method: OECD 414, adopted 12 May 1981

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Groups of 23 mated female Wistar rats, weighing 206 to 235 g and aged approximately 8-10 weeks on Day 1 of pregnancy, were used. Each was given a daily oral dose by gavage of either 0, 5, 71 or 1000 mg/kg bw/d, suspended in 1% w/v aqueous methylcellulose, on Days 7 to 16 of pregnancy inclusive (Day 1 = day sperm detected). The control animals received the vehicle alone. A dose volume of 5 ml/kg bw was used.

Animals were examined several times each day (once daily on weekends and on public holidays) for clinical signs and mortality. Body weights were recorded on Days 1, 4, 7, 10, 14, 17, 19 and 21 of pregnancy. Food consumption was measured between Days 1-4, 4-7, 7-10, 10-14, 14-17, 17-19 and 19-21 of pregnancy. Animals were sacrificed on Day 21 of pregnancy and examined externally and internally for macroscopic abnormalities. Gravid uterus weight was determined. The uterus was opened and the number of live and dead foetuses, and the number of conceptuses undergoing resorption were recorded. The number of corpora lutea were counted and examined macroscopically. Implantation sites in the uterus were counted after staining with ammonium sulphide. Foetal body weights, crown-rump lengths and sex ratios were recorded together with placental weights. Any external abnormalities were also documented. About 50% of the foetuses in each litter were examined for skeletal anomalies. The remaining foetuses were examined for visceral anomalies.

Doses were prepared daily. For each foramsulfuron concentration, samples were taken towards the start, middle and end of the dosing period. Those from the start and end were analysed for homogeneity stability of foramsulfuron and its achieved concentration. Concentrations of 1 and 200 mg/ml (equivalent to the dose levels 5 and 1000 mg/kg bw/d) were within the acceptable range of 80% to 120% of nominal, i.e., they were homogeneous and the test compound was stable over a 4 hour

period in 1% w/v aqueous methylcellulose. Similarly, achieved concentrations at all dose levels were within the range of 96% to 99% of nominal, i.e. entirely acceptable.

Findings:

There were no deaths and no treatment-related clinical signs of toxicity.

Body weights and food consumption were not affected, and no compound-related effects were observed at necropsy of the animals.

Gravid uterus weights, crown-rump lengths, litter size, sex ratios, foetal and placental weights were unaffected by administration of the test compound. There was no increase in the number of early or late conceptuses undergoing resorption.

Morphological examination of the foetuses did not reveal any compound-related effect.

Conclusion:

Oral administration of foramsulfuron to the pregnant rat up to and including 1000 mg/kg bw/d, the international limit dose, did not cause maternal, embryonal or foetal toxicity. Therefore, foramsulfuron was not teratogenic in the rat.

The NOEL was 1000 mg/kg bw/d for both maternal and developmental toxicity.

B.6.6.2.2 Teratogenicity study by the oral route in the rabbit

Previous evaluation	This study was evaluated in the original DAR. No new evaluation has been performed. Conclusion has not been changed. After the study was performed, a new version of the OECD Test Guideline 414 has been adopted 22nd January, 2001. The main study fulfils these data requirements except that the number of 15 animals with implantation sites at necropsy is just under the required count (16-20 dams) mentioned in the current OECD Test Guideline.
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Report:

██████████ 1997 (TOX2000-2126)
Hoe 130360 (AE F130360), Code: Hoe 130360 00 ZC98 0001: Rabbit oral developmental toxicity (teratogenicity) range finding study
Report-No. TOX/97/262-17; 96.0564; TOX 95391; Unpublished
Testing facility: ██████████
(Experimental work: 26 August to 24 September, 1996)

Test Material:

Foramsulfuron, batch number H 2037, containing 98.4% w/w of active substance

Test Animals:

Himalayan (Chbb: HM SPF Kleinrusse) rabbits
Source: ██████████

GLP:

Yes

Acceptability:

The study is acceptable as a range-finding study.

Test Material:	Foramsulfuron, batch number H 2037, containing 98.4% w/w of active substance
Test Animals:	Himalayan (Chbb: HM SPF Kleinrusse) rabbits Source: [REDACTED]
GLP:	Yes
Test Method:	OECD 414, adopted 12 May 1981
Deviations:	Live foetuses were incubated for 24 hours after delivery to monitor their survival. This was standard practice at the testing facility at the time this study was conducted but it is not a regulatory requirement.
Acceptability:	The study is considered to be acceptable.

Material and Methods:

Groups of 15 mated female Himalayan (Chbb: HM SPF Kleinrusse) rabbits, about 5-10 months old and weighing 2.2-3.0 kg at mating were used. Each rabbit received a daily oral dose, by gavage, of either 0, 5, 50 or 500 mg/kg bw/d, suspended in 1% w/v aqueous methyl cellulose, on Days 6 to 18 of pregnancy inclusive (Day 0 = day of sperm detection i.e., mating). Control animals received the vehicle alone. A dose volume of 5 ml/kg bw/d was used in all cases.

Animals were examined several times each day (once daily on weekends and on public holidays) for clinical signs of toxicity and mortality. Body weights were recorded on Days 0, 3, 6, 8, 10, 13, 16, 19, 23, 26 and 29 of pregnancy. Food consumption was recorded between Days 0-3, 3-6, 6-8, 8-10, 10-13, 16-19, 19-23, 23-26 and 26-29 of pregnancy. Animals were sacrificed on Day 29 of pregnancy and examined externally and internally for macroscopic abnormalities. Gravid uterus weight was determined. The uterus was opened and the number of live and dead foetuses and the number of conceptuses undergoing resorption and corpora lutea were recorded. Foetal body weights, crown-rump lengths and the sex ratio were recorded together with placental weights. Any external macroscopic abnormalities were documented. Live foetuses were incubated for 24 hours to determine their viability. All foetuses were necropsied and examined for visceral anomalies. Subsequently, their skeletons were also examined for anomalies.

Doses were prepared daily. For each foramsulfuron concentration, samples were taken towards the start, middle and end of the dosing period and stored deep frozen prior to analysis. Those from the start and end were analysed for homogeneity stability of foramsulfuron and its achieved concentration. Concentrations of 1 and 200 mg/ml (equivalent to the dose levels 5 and 1000 mg/kg bw/d) were within the acceptable range of 80% to 120% of nominal, i.e., they were homogeneous and the test compound was stable over a 4 hour period in 1% w/v aqueous methylcellulose. Similarly, achieved concentrations at all dose levels were 98% to 99% of nominal, i.e., entirely acceptable.

Findings:

No deaths occurred throughout the study. At the high dose level, 500 mg/kg bw/d, reddish coloured urine was observed in six animals for 1 to 3 days between Days 10 and 12, and in one animal on Days 15 to 17. No treatment-related clinical signs were observed in animals from the other groups.

At the high dose level, body weight gain was only 1.8 g during the treatment period compared with 81.9 g in the controls (see Table B.6.6-3). Statistical evaluation revealed decreased body weight gain in all treated groups on Day 19 of the study, but there was no dose-related response in the intermediate dose groups.

Food consumption was slightly decreased in the animals from the high dose group during the treatment period. Consumption between Days 6 and 19 was 24% lower than in controls. Relative consumption (intake/100 g bw) was statistically significant from Days 6-8, 8-10, 10-13 and 16-19.

Table B.6.6-3: Group mean maternal body weight gain and food consumption

Parameter (Days 6-19 of gestation)	Dose level [mg/kg body weight]				
	0	5	50	500	Historical control* Mean \pm SD (Min – Max)
Body weight gain (g) (% control)	81.9 (100)	47.4 (58)	53.8 (66)	1.8 (2)	64.1 \pm 32.1 (-20.7 – 117.7) [< 31.4 in 1 of 18 studies]
Food consumption (g/animal/d) (% control)	201.6 (100)	184.0 (91)	193.5 (96)	153.8 (76)	–

* Historical control data based on 18 studies conducted between 1995–1997 at the same test facility (Hoechst Marion Roussel, Global Preclinical Development, Germany) using the same rabbit strain (Himalayan) as the rabbit oral developmental toxicity study with foramsulfuron.

No compound-related effects were observed at necropsy of the animals.

Gravid uterus, the number of live foetuses, foetal and placental weights, crown-rump lengths and sex ratios were unaffected by administration of the test compound. No significant differences in the incidence of the numbers of early and late conceptuses undergoing resorption were detected. Therefore, pre- and post- implantation rates were unaffected. Survival rates of the foetuses over 24 hours were comparable in all groups.

No compound-related external, visceral or skeletal anomalies were detected in the foetuses at necropsy. One control foetus exhibited microphthalmia and one foetus in each of two litters from the intermediate dose level had aplasia of the lens of the eye. However, in the absence of any dose-response relationship, the findings in the treated group were considered to be fortuitous.

Discussion of maternal toxicity findings:

Interpretation of the results on maternal toxicity is difficult due to high variability of individual body weight gain and food consumption data. For example the body weight during Days 0-3 (i.e. before the application of the test substance) was decreased by 218 g in Animal No.484 and increased by 223 g in Animal No.485 in the same study group (500 mg/kg bw/d). Similar fluctuations were observed in the other dose groups and the controls. In the course of the study increases and decreases of the body weight of the same animal often changed within only few days without regularity.

During the treatment period (gestation days 6–19), the mean body weight gain of the control group was 81.9 g while the mean value of the highest dose group was only 1.8 g. Corresponding historical control data of the test facility was available for comparison (see Table B.6.6-3), which indicated that the reduced body weight gain at 500 mg/kg bw/day was an adverse treatment-related effect. Furthermore a relevant decrease of the food consumption of the high dose group (500 mg/kg bw/d) was observed. The mean value was only 76 % of the control value.

The dose group 500 mg/kg bw/d must therefore be considered to be the LOAEL of maternal toxicity in this rabbit study.

In the teratogenicity study in rabbits the mean body weight gain during Days 6-19 was also lower in the intermediate dose groups than in the controls. These differences from the control group were well within historical control ranges and not dose-dependent. Taking into account the high fluctuation rate of the individual animal data, the differences are not considered to be substance related effects.

Conclusion:

Embryonal or foetal toxicity was not observed in the teratogenicity study in rabbits. The NOEL for developmental toxicity was 500 mg/kg bw/d. Foramsulfuron was not teratogenic in rabbits. The NOEL for maternal toxicity in rabbits is considered to be 50 mg/kg bw/d, based on reduced body weight gain and reduced food consumption at 500 mg/kg bw/d.

B.6.6.3 Separate male and female studies

Foramsulfuron did not cause any effects on reproduction in the rat two-generation reproduction toxicity study (see Point B.6.6.1). Consequently separate male and female studies were not triggered.

B.6.6.4 Three segment designs

End points evaluated in segments 1 (fertility) and 3 (peri- and post-natal) are covered by the rat two-generation reproduction toxicity study. No effects on fertility or pre-natal and post-natal survival of the offspring were observed in this study at dose levels approximating to the international regulatory limit dose, 1000 mg/kg bw/d. Segment 2 relates to the developmental toxicity (teratogenicity) studies. Again, foramsulfuron showed no potential to impair development in the rat and rabbit.

B.6.6.5 Dominant lethal assay for male fertility

There was no evidence for effects on male or female fertility or dysfunction of the male or female reproductive organs in the rat two-generation reproduction study. Therefore no separate dominant lethal assay for male fertility was considered necessary.

B.6.6.6 Cross-matings of treated males with untreated females and vice versa

There was no evidence for effects on male or female fertility or dysfunction of the male or female reproductive organs in the rat two-generation reproduction study. Therefore no separate investigations on cross matings of treated male with untreated females and vice versa were considered necessary.

B.6.6.7 Effects on spermatogenesis

There was no evidence for effects on male or female fertility or dysfunction of the male or female reproductive organs in the rat two-generation reproduction study. Therefore no separate study on effects on spermatogenesis was considered necessary.

B.6.6.8 Effects on oogenesis

There was no evidence for effects on male or female fertility or dysfunction of the male or female reproductive organs in the rat two-generation reproduction study. Therefore no separate study on effects on oogenesis was considered necessary.

B.6.6.9 Sperm motility, mobility and morphology

There was no evidence for effects on male or female fertility or dysfunction of the male or female reproductive organs in the rat two generation reproduction study. Therefore no separate study on effects on sperm motility, mobility and morphology was considered necessary.

B.6.6.10 Investigation of hormonal activity

There was no evidence for effects on male or female fertility or dysfunction of the male or female reproductive organs in the rat two generation reproduction study. Therefore no separate investigation of hormonal activity was considered necessary.

B.6.7. NEUROTOXICTY

In a 28-day neurotoxicity study in rat, there were no treatment related effects on brain weights and no treatment related ophthalmic abnormalities were observed. There were no findings in FOB results related to treatment at any dietary level in either sex. Results of home cage observations, observations during handling, open field observations, reflex / physiologic observations as well as landing foot splay and grip strength measurements were not affected. For the overall 60-minute test session, motor and locomotor activity were not affected by treatment at any dietary level in either sex. The NOAEL for neurotoxicologic endpoints in rats was 15000 ppm (1208 and 1415 mg/kg bw/day for males and females, respectively).

B.6.7.1. Neurotoxicity studies in rodents

Report: [REDACTED] 2009
A 28-day dietary neurotoxicity study with technical grade foramsulfuron in Wistar rats
Report No.: 09-N72-QZ; unpublished
[REDACTED]
(Study completion date: 28 July, 2009)

Test Material:	Foramsulfuron, batch number AE F130360-01-01 (origin batch no. ELIR004130), purity 97.6 % (w/w)
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Test Animals: Wistar Han Crl:WI (HAN) rats
Source: [REDACTED]

GLP: Yes

Test Method: OECD 424, adopted 21st July 1997

Deviations: None.

Acceptability: The study is considered to be acceptable.

Material and methods

Dose selection was based on the results of a 90-day toxicity study conducted with foramsulfuron which was administered via the diet to male and female Sprague Dawley rats at nominal concentrations of 20, 200, 5000 and 20000 ppm. The 15000 ppm dietary level was selected as a limit dose (~1000 mg/kg bw/day) that most likely would produce no evidence of toxicity following 28-days

of exposure in both sexes. The 3750 ppm dietary level was selected to produce no evidence of toxicity (NOAEL) for endpoints measured in this neurotoxicity study.

Foramsulfuron Technical (batch: ELIR004130; purity: 97.6 % w/w) was mixed in the diet and given for 28 days to young-adult male and female Wistar Han Crl:WI (HAN) rats (12/sex/dietary level), using nominal concentrations of 0, 3750 and 15000 ppm (0, 307.0 and 1208 mg/kg bw/day for males and 362.4 and 1415 mg/kg bw/day for females). 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 twice daily (once daily on holidays and weekends). Functional observational battery (FOB) and automated measurements of activity (figure-eight maze) were conducted the week prior to treatment and again during week 4. Ophthalmologic examinations were conducted prior to exposure and then again on all study animals during week 4. Animals were subjected to a gross necropsy during week 5. The brain was weighed in order to calculate the brain/body weight ratio. Six rats/sex/dose group were allocated for nervous tissue collection. Micropathology examinations were conducted on neural tissues from control and high-dose rats (six/sex/dose level). The following tissues were examined: brain (eight levels), spinal cord (four levels), gasserian ganglia, spinal nerve roots and dorsal root ganglia from the cervical and lumbar swellings, sciatic nerves, tibial nerves, sural nerves, optic nerves, eyes and gastrocnemius muscle. Gross findings in tissues other than neural tissues or skeletal muscle were not collected or processed for microscopic evaluation.

Results

There were no deaths and no treatment-related clinical observations at any dietary level in either sex. Body weight and food consumption was not affected. There were no treatment related effects on brain weights and no treatment related ophthalmic abnormalities were observed. No gross lesions or micropathologic observations were related to test substance administration.

There were no findings in FOB results related to treatment at any dietary level in either sex. Results of home cage observations, observations during handling, open field observations, reflex / physiologic observations as well as landing foot splay and grip strength measurements were not affected.

Table 6.7-01 Summary Body Weight, Grip Strength (kg) and Footsplay (mm)

	Dose level PPM (mg/kg bw/day)		
	Control	3750 (♂ 307.0) (♀ 362.4)	15000 (♂ 1208) (♀ 1415)
Males			
Pretreatment			
Body weight	210 ± 13	208 ± 15	213 ± 17
Grip strength; forelimb	0.83 ± 0.10	0.80 ± 0.11	0.85 ± 0.12
Grip strength; hindlimb	0.87 ± 0.10	0.80 ± 0.11	0.84 ± 0.06
Footsplay	85 ± 17	88 ± 15	81 ± 13
Week 4			
Body weight	306 ± 36	308 ± 30	327 ± 47
Grip strength; forelimb	1.11 ± 0.24	1.14 ± 0.17	1.19 ± 0.18
Grip strength; hindlimb	1.14 ± 0.20	1.11 ± 0.21	1.16 ± 0.17
Footsplay	83 ± 18	86 ± 18	82 ± 10
Females			
Pretreatment			
Body weight	149 ± 6	150 ± 10	150 ± 11

Grip strength; forelimb	0.69 ± 0.11	0.69 ± 0.11	0.65 ± 0.09
Grip strength; hindlimb	0.69 ± 0.10	0.70 ± 0.09	0.66 ± 0.09
Footsplay	80 ± 15	73 ± 14	72 ± 14
Week 4			
Body weight	199 ± 12	203 ± 15	197 ± 10
Grip strength; forelimb	0.94 ± 0.19	0.89 ± 0.24	0.80 ± 0.12
Grip strength; hindlimb	0.88 ± 0.18	0.99 ± 0.25	0.86 ± 0.15
Footsplay	76 ± 13	70 ± 17	70 ± 11

Mean ± S.D.

* Significantly different from control ($p \leq 0.05$, ANOVA)

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. 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. These differences are within the range of normal variability (approximately ± 20 %) in the laboratory for groups of 10-12 rats/sex/dietary level and, therefore, are not biologically significant. (Table 6.7.1.1-01 and Table 6.7.1.1-02)

Table 6.7-02 Summary Session Motor Activity Results (percent difference from control)^a

Test week	Dose level PPM (mg/kg bw/day)	
	3750 (♂ 307.0)	15000 (♂ 1208)
Males^b		
Pretreatment	-1	+3
Week 4	-6	-7
Females^b		
Test week	3750 (♀ 362.4)	15000 (♀ 1415)
Pretreatment	-10	-6
Week 4	-3	-2

^a Percent greater (+) or less (-) than concurrent control.

^b N=12. Summary session motor activity was not statistically different from control ($p \leq 0.05$; ANOVA).

Table 6.7-03 Summary Session Locomotor Activity Results (percent difference from control)^a

Test week	Dose level PPM (mg/kg bw/day)	
	3750 (♂ 307.0)	15000 (♂ 1208)
Males^b		
Pretreatment	-3	+6
Week 4	-8	-8
Females^b		
Test week	3750 (♀ 362.4)	15000 (♀ 1415)

Pretreatment	-2	-8
Week 4	-3	-13

^a Percent greater (+) or less (-) than concurrent control.

^b N=12. Summary session locomotor activity was not statistically different from control ($p \leq 0.05$; ANOVA).

For the overall 60-minute test session, motor and locomotor activity were not affected by treatment at any dietary level in either sex.

Table 6.7-04 Motor Activity (total activity counts for session)

Test week	Dose level PPM (mg/kg bw/day)		
	Control	3750 (♂ 307.0) (♀ 362.4)	15000 (♂ 1208) (♀ 1415)
Males			
Pretreatment	547±193	543±232	562±145
Week 4	678±154	634±133	628±182
Females			
Pretreatment	714±270	644±243	674±268
Week 4	772±158	745±220	753±207

Mean ± S.D.

N=12. Summary session motor activity was not statistically different from control ($p \leq 0.05$; ANOVA).

Table 6.7-05 Locomotor Activity (total activity counts for session)

Test week	Dose level PPM (mg/kg bw/day)		
	Control	3750 (♂ 307.0) (♀ 362.4)	15000 (♂ 1208) (♀ 1415)
Males			
Pretreatment	311±112	301±144	329±86
Week 4	343±101	316±85	315±90
Females			
Pretreatment	354±134	347±156	325±172
Week 4	401±93	388±152	350±137

Mean ± S.D.

N=12. Summary session locomotor activity was not statistically different from control ($p \leq 0.05$; ANOVA).

Conclusion

The NOAEL for neurotoxicologic endpoints in rats was 15000 ppm (1208 and 1415 mg/kg bw/day for males and females, respectively).

B.6.7.2. Delayed polyneuropathy studies

No study performed and not required.

Foramsulfuron is a sulfonylurea herbicide. This well-known class of compounds is devoid of any neurotoxic effects. Furthermore, the chemical structure of foramsulfuron has no structural relationships with any known neurotoxicants.

No evidence of clinical signs indicative of neurotoxicity was seen in the acute, subacute, subchronic (90-day) or long term toxicity studies, even at international regulatory limit dose levels. Furthermore, there were no neuropathological changes. Similarly, in the two generation reproduction toxicity study, no clinical signs were seen in either the F1 or F2 offspring or their parents.

B.6.8. OTHER TOXICOLOGICAL STUDIES

B.6.8.1. Toxicity studies on metabolites and relevant impurities

There are no significant plant or soil-specific metabolites. All significant metabolites detected in these systems have also been found in mammals. Therefore no studies with metabolites have been conducted.

B.6.8.2. Supplementary studies on the active substance

No supplementary studies were deemed necessary.

B.6.8.3. Studies on endocrine disruption

In the studies performed, 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.

B.6.9. MEDICAL DATA AND INFORMATION

B.6.9.1. Medical surveillance on manufacturing plant personnel and monitoring studies

Foramsulfuron has been manufactured in various pilot plants since 1996. This work was undertaken using up to about 75 kg/batch and up to 350 kg/campaign involving about 4-6 people per campaign. Manufacture was carried out in closed systems that virtually preclude any possibility of exposure. Where worker exposure was possible, during sampling, or dryer filling, or emptying procedures for example, appropriate personnel protection measures were used to minimise this. There have been no reports of adverse effects on human health caused by foramsulfuron in the work-place. Foramsulfuron has been formulated in several campaigns in Germany since. About 3 workers were involved in total. Formulation was carried out in closed systems that practically exclude any possibility of worker exposure. Where exposure was possible (during sampling and filling operations for example), precautions were taken to minimise exposure to the operators through suitable exhaustion equipment

and personnel protection measures. Again, no reports of adverse effects on human health caused by foramsulfuron in the work-place have been made. Annual medical examinations of the workers were carried out as a routine procedure by the Department of Occupational Medicine of AgrEvo GmbH (now Aventis CropScience GmbH). Since exposure to other active ingredients and formulants, including solvents, was possible, these workers were also examined in accordance with the requirements of the trade association of the German chemical industry (Berufsgenossenschaft-Chemie). This involved physical examination, blood chemistry, haematology and urinalysis. No substance-related disturbances to human health have been found.

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

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

B.6.9.2. Data collected on humans

No data were collected on humans.

B.6.9.3. Direct observation

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.

B.6.9.4. 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.

B.6.9.5. Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical test

Please refer to point B.6.9.3.

B.6.9.6. Proposed treatment: first aid measures, antidotes, medical treatment

First Aid:

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

B.6.9.7. LITERATURE DATA

The literature search carried out by the applicant was summarised in Document MCA section 9. The RMS considers the literature search provided as acceptable.

Databases: STN, a scientific information platform hosted by CAS, itself a division of the American Chemical Society, was selected as the preferred provider. Following data bases were used for the literature search: Agricola, Biosis, CABA, Chemical Abstracts, Derwent Drug File (DRUGU), EMBASE, Esbiobase, IPA, Medline, Pascal, PQSciTech, Registry, Scisearch, Toxcenter, Ulidat and FSTA.

Time window: January 1st 2004 – August 2nd 2013 for the parent compound and metabolites.

Input parameters: IUPAC name, CAS number, common name, code and abbreviation, molecular structure, molecular formula, molar mass and/or other names/codes, as far as available.

Results: A total of 430 identified and evaluated for potential relevance for foramsulfuron and its metabolites. Of these, 384 summary records were excluded after a rapid assessment of relevance, and 46 full-text documents were assessed in detail.

As a summary 45 studies were excluded from the risk assessment because the publications did not meet the relevance criteria for the detailed assessment. Moreover, one study was unclear of relevance and only one study from the whole literature search was revealed for further examination (KCA 8.6.2).

A reference list containing these 46 documents were included in Doc MCA section 9.

There were no articles with relevance for toxicology section.

B.6.10. REFERENCES RELIED ON

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
B.6.1.1.1	[REDACTED]	1999	Code: AE F130360 00 ZE- Preliminary toxicokinetic studies in the rat. TOX/98/262- 28 ! C004339 GLP, unpublished TOX2000- 1035	Y	N		Bayer Crop Science	In DAR 2001
B.6.1.1.1	[REDACTED]	1999	Code: AE F130360 00 ZE. (14C)-AE F130360: Rat - absorption, distribution, elimination following oral dosing at 10 and 1000 mg/kg bodyweight. TOX/98/262- 29 ! C004352 GLP, unpublished TOX2000- 1036	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.1.1.1	[REDACTED]	1998	(14C)-AE F130360: A study of excretion following oral administration to bile duct cannulated rats. 194/170- D1141 ! A67666 GLP, unpublished TOX2000- 1037	Y	N		Bayer Crop Science	In DAR 2001
B.6.1.1.1	[REDACTED]	2000	1st Amendment to Report TOX/98/262- 33 (14C)-AE F130360: A study of excretion following oral administration to bile duct cannulated rats. Generated by. [REDACTED] Dokument No: C007333 GLP, unpublished TOX2000- 1597	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.1.1.1	[REDACTED]	1999	(14C)-AE F130360: Tissue distribution and clearance in the rat. 194/201- D1141 ! C005630 GLP, unpublished TOX2000- 1038	Y	N		Bayer Crop Science	In DAR 2001
B.6.1.1.1	[REDACTED]	1999	Code: AE F130360 - Metabolism in the rat following a single oral administration of 10 or 1000 mg/kg body weight. TOX/99/262- 38 ! C004971 GLP, unpublished TOX2000- 1039	Y	N		Bayer Crop Science	In DAR 2001




Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.1.1.2		1999	Code: AE F130360. (14C)-AE F130360 - Rat: Absorption, distribution and elimination - repeat oral dose (10 mg/kg day). TOX/99/262- 41 ! C005527 GLP, unpublished TOX2000- 1040	Y	N		Bayer Crop Science	In DAR 2001
B.6.1.3		2013	[Pyrimidine-2- ¹⁴ C]Foramsulfu ron: Metabolic stability and profiling in liver microsomes from rats and humans for inter-species comparison. Report No.: EnSa-13-0827 GLP, unpublished	N	Y		Bayer Crop Science	Submitted for the purpose of renewal

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.2.1		1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Rat acute oral toxicity. AGV 117/963060/A C ! A58267 GLP, unpublished TOX2000- 1041	Y	N		Bayer Crop Science	In DAR 2001
B.6.2.2		1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Rat acute dermal toxicity. AGV 118/963061/A C ! A58268 GLP, unpublished TOX2000- 1042	Y	N		Bayer Crop Science	In DAR 2001
B.6.2.3		1998	AE F130360: code: AE F130360 00 1C94 0002 - Rat acute inhalation toxicity. 374/054 ! A67640 GLP, unpublished TOX2000- 1043	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.2.4		1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Rabbit skin irritancy. AGV 119/962892/SE ! A59370 GLP, unpublished TOX2000- 1044	Y	N		Bayer Crop Science	In DAR 2001
B.6.2.5		1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Rabbit eye irritancy. AGV 120/962960/SE ! A59371 GLP, unpublished TOX2000- 1045	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
B.6.2.6		1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Guinea-pig skin sensitisation (Magnusson and Kligman Test). AGV 121/963533/SS ! A58182 GLP, unpublished TOX2000- 1046	Y	N		Bayer Crop Science	In DAR 2001
B.6.2.7		2013	Foramsulfuron TC: Cytotoxicity assay <i>in vitro</i> with BALB/c3T3 cells: Neutral red (NR) test during simultaneous irritation with artificial sunlight. Report No.: 1561300 GLP, unpublished	N	Y		Bayer Crop Science	Submitted for the purpose of renewal

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.3.1.1	[REDACTED]	1998	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC 90 0001 - Rat 28 day dietary repeat dose study. TOX/96/262-1 ! A67148 GLP, unpublished TOX2000- 1047	Y	N		Bayer Crop Science	In DAR 2001
B.6.3.1.2	[REDACTED]	1998	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC97 0001 - Rat 90-day dietary toxicity study with 4 week off dose period. TOX/96/262-3 ! A67046 GLP, unpublished TOX2000- 1050	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.3.2.1		1998	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC90 0001 - Mouse 28-day dietary toxicity. TOX/96/262-2 ! A67045 GLP, unpublished TOX2000- 1048	Y	N		Bayer Crop Science	In DAR 2001
B.6.3.2.2		1998	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Mouse 90-day dietary toxicity. TOX/96/262-5 ! A67340 GLP, unpublished TOX2000- 1051	Y	N		Bayer Crop Science	In DAR 2001
B.6.3.3.1		1998	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Dog 28-day oral toxicity study. TOX/96/262-4 ! C001562 GLP, unpublished TOX2000- 1049	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.3.3.2		1998	Hoe 130360 (AE F130360) code: Hoe 130360 00 1C93 0001 - Dog 90-day oral toxicity study. TOX/97/262- 18 ! C001108 GLP, unpublished TOX2000- 1052	Y	N		Bayer Crop Science	In DAR 2001
B.6.3.3.3		1999	Hoe 130360 (AE F130360) code: Hoe 130360 00 1C96 0001 - Dog 12 month oral toxicity study. TOX/99/262- 37 ! C003751 GLP, unpublished TOX2000- 1053	Y	N		Bayer Crop Science	In DAR 2001
B.6.3.4.3		1999	Hoe 130360 (AE F130360) code: Hoe 130360 (AE F 130360) 00 1C94 0001 - Rat 28-day dermal toxicity study. TOX/98/262- 34 ! C005128 GLP, unpublished TOX2000- 1054	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.4.1	Bomann, W.	2013	Foramsulfuron - Overview on photosafety and waiver for conduct of a photomutagenicity study	N	Y		Bayer Crop Science	Submitted for the purpose of renewal
B.6.4.1.1	Müller, W.	1996	Hoe 130360 code: Hoe 130360 00 ZC98 0001 - Bacterial reverse mutation test. 96.0667 ! A57619 GLP, unpublished TOX2000-1055	N	N		Bayer Crop Science	In DAR 2001
B.6.4.1.2		1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - <i>In vitro</i> human lymphocyte chromosome aberrations. AGV 102/962804 ! A58266 GLP, unpublished TOX2000-1056	N	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
B.6.4.1.3		1996	Hoe 130360 code: Hoe 130360 00 ZC98 0001 - <i>In vitro</i> Chinese hamster lung V79 cell HPRT mutation. 96.0781 ! A58125 GLP, unpublished TOX2000- 1057	N	N		Bayer Crop Science	In DAR 2001
B.6.4.2.1		1997	Hoe 130360 code: Hoe 130360 00 ZC98 0001 - Mouse micronucleus test. 96.0865 ! A58340 GLP, unpublished TOX2000- 1058	Y	N		Bayer Crop Science	In DAR 2001
B.6.4.2.2		1996	Hoe 130360 code: Hoe 130360 00 ZC98 0001 - <i>In vivo</i> rat hepatocyte unscheduled DNA synthesis. AGV 103/962088 ! A57435 GLP, unpublished TOX2000- 1059	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
B.6.5.1	[REDACTED]	2000	Rat dietary combined chronic toxicity and oncogenicity study. AE F130360 (Hoe 130360) code: AE F130360 00 1C95 0001. TOX/99/262-42 ! C006180 GLP, unpublished TOX2000-1060	Y	N		Bayer Crop Science	In DAR 2001
B.6.5.1	[REDACTED]	2000	1st addendum to document no. C006180 (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. C010585 not GLP, unpublished TOX2000-2125	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.5.2		1999	Mouse dietary oncogenicity study. AE F130360 code AE F130360 00 1C96 0001. 194/176 ! TOX/99/262- 45 ! C006435 GLP, unpublished TOX2000- 1061	Y	N		Bayer Crop Science	In DAR 2001
B.6.6.1		1999	Rat dietary two-generation reproductive toxicity study. AE F130360 code AE F130360 00 1C96 0002. WIL-303004 ! TOX/99/262- 35 ! C004338 GLP, unpublished TOX2000- 1062	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.6.2.1	[REDACTED]	1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Rat oral developmental toxicity (teratogenicity) study. TOX 95390 ! TOX/98/262- 24 ! A67035 GLP, unpublished TOX2000- 1063	Y	N		Bayer Crop Science	In DAR 2001
B.6.6.2.2	[REDACTED]	1997	Hoe 130360 (AE F130360) - Rabbit oral developmental toxicity (teratogenicity) range finding study. 96.0948 ! Tox95391 ! A59486 GLP, unpublished TOX2000- 2126	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
B.6.6.2.2	[REDACTED]	1997	Hoe 130360 (AE F130360) code: Hoe 130360 00 ZC98 0001 - Rabbit oral developmental toxicity (teratogenicity) study. TOX 95392 ! TOX/98/262- 25 ! A67041 GLP, unpublished TOX2000- 1064	Y	N		Bayer Crop Science	In DAR 2001
B.6.6.2.2	[REDACTED]	2000	1st addendum to document no. A67041 (report number Tox/98/262- 25) - Rabbit oral developmental toxicity (teratogenicity) study: Provision of historical control body weight data as requested by the EU. C010603 not GLP, unpublished TOX2000- 2127	Y	N		Bayer Crop Science	In DAR 2001

Data Point	Author(s)	Year	Title Compagny Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation n
B.6.7.1	[REDACTED]	2009	A 28-day dietary neurotoxicity study with technical grade foramsulfuron in Wistar rats Report No.: 09-N72-QZ GLP, unpublished	Y	Y		Bayer Crop Science	Submitted for the purpose of renewal