Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

Sulcotrione

ECHA/RAC/CLH-O-0000002100-96-01/A1

EC number: N/A
CAS number: 99105-77-8

Adopted

27 October 2011

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TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Sulcotrione**

EC Number: **not allocated**

CAS number: 99105-77-8

Registration number (s): -

Purity: minimum 950 g/kg (on a dry weight basis),

minimum 630 g/kg (on an “as received” basis, i.e. water wet paste)

Impurities: There are a number of impurities claimed as confidential by the producer (see confidential Annex).

Classification & Labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
	Sulcotrione (ISO); 2-(2-chloro-4-mesylbenzoyl)cyclohexane-1,3-dione	N/A	99105-77-8	**Skin Sens 1A** **STOT RE 2 (kidney)** **Repr. 2** **Aquatic Acute 1** **Aquatic Chronic 1**	**H317** **H373** **H361d** **H400** **H410**	GHS07 GHS09 Wng	**H317** **H373** **H361d** **H410**		**Acute M=1** **Chronic M=10**	

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	Sulcotrione (ISO); 2-(2-chloro-	N/A	99105-77-8	**R43** **Xn: R48/22** **Repr. Cat. 3; R63**	**Xn; N** **R: 43-48/22-63-50/53**	**N; R50/53: C ≥ 25%** **N; R51/53: 2.5% ≤ C < 25%**	

	4-mesylbenzoyl)cyclohexane-1,3-dione			**N; R50/53**	**S: (2-)22-36-37-60-61**	**R52/53: 0.25%≤ C<2.5%** **R43: C ≥ 0.1%**	

RAC opinion

In their response to the public consultation, the Dossier Submitter clarified that the proposed M-factor was intended to apply to both the short-term and long-term aquatic hazard categories (based on the surrogate approach). However, RAC considers that the M-factor (Chronic) is 10, in line with the 2nd ATP (i.e. based on long-term ecotoxicity data), which had not been implemented at the time the dossier was submitted.

Proposed notes (if any):

None

JUSTIFICATION

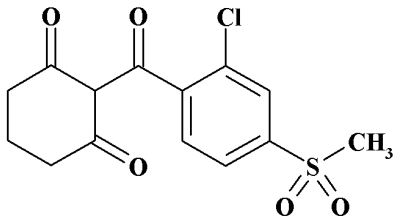
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	**1,3-cyclohexanedione, 2-[2-chloro-4-(methylsulfonyl)benzoyl]-**
EC Name:	-
CAS Number:	99105-77-8
IUPAC Name:	2-(2-chloro-4-mesylbenzoyl)cyclohexane-1,3-dione

1.2 Composition of the substance

For each constituent/ impurity/ additive, fill in the following table (which should be repeated in case of more than one constituent). The information is particularly important for the main constituent(s) and for the constituents (or impurity) which influence the outcome of the dossier.

Chemical Name:	1,3-cyclohexanedione, 2-[2-chloro-4-(methylsulfonyl)benzoyl]-
EC Number:	not allocated
CAS Number:	99105-77-8
IUPAC Name:	2-(2-chloro-4-mesylbenzoyl)cyclohexane-1,3-dione
Molecular Formula:	$C_{14}H_{13}ClO_5S$
Structural Formula:	
Molecular Weight:	328.8 g/mol
Typical concentration (% w/w):	confidential data
Concentration range (% w/w):	min. 950 g/kg (on a dry weight basis)

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	white solid (purity 98.8 %)	Draft Assessment Report / Monograph
VII, 7.2	Melting/freezing point	3.2	139 °C (purity 98.8 %)	
VII, 7.3	Boiling point	3.3	not measureable	
VII, 7.4	Relative density	3.4 density	1.55 g/cm^3 at 20 °C	
VII, 7.5	Vapour pressure	3.6	5x10^{-6} Pa, extrapolated for 25 °C from measurements between 90 … 130 °C	
VII, 7.6	Surface tension	3.10	69 mN/m at 20 °C (purity 99.6 %)	
VII, 7.7	Water solubility	3.8	0.13 g/L (unbuffered, final pH 3.6) 1.67 g/L (buffered, pH 4.8) > 60 g/L (buffered, pH 9, drifting) at 20 °C (98.8 % purity)	
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	log $P_{O/W}$ = 0.2 (pH 4) log $P_{O/W}$ = - 1.7 (pH 7) log $P_{O/W}$ = - 2.0 (pH 9) at 20 ° C and 99.6 % purity	
VII, 7.9	Flash point	3.11	not relevant	
VII, 7.10	Flammability	3.13	not highly flammable in the sense of method EEC A10 (purity 71.5 %)	
VII, 7.11	Explosive properties	3.14	not explosive in the sense of method EEC A14 (purity 71.5 %)	
VII, 7.12	Self-ignition temperature		not detected	
VII, 7.13	Oxidising properties	3.15	No oxidising properties in the sense of method EEC A17 (purity 71.5 %)	
VII, 7.14	Granulometry	3.5	not determined	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not determined	
XI, 7.16	Dissociation constant	3.21	pKa = 3.13 (23 °C)	
XI, 7.17,	Viscosity	3.22	not determined	

	Auto flammability	3.12	no spontaneous combustion, multiple endothermic reactions until the melting point.	
	Reactivity towards container material	3.18	not determined	
	Thermal stability	3.19	Exothermal process starting at about 170 °C (purity 98.8 %) Slight exothermic decomposition was detected at 130 °C, but never exceede the oven temperature (water wet paste, purity 77.6 %)	

2 MANUFACTURE AND USES

2.1 Manufacture

Confidential information.

2.2 Identified uses

Herbicide for selective post-emergence use in maize.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

None

4 ENVIRONMENTAL FATE PROPERTIES

The environmental fate properties assessment for sulcotrione is based on the Draft Assessment Report and Proposed Decision of Germany prepared in the context of the inclusion of sulcotrione in Annex I of Council Directive 91/414/EEC (DAR July 2006 + Final addendum June 2008, RMS Germany).

4.1 Degradation

4.1.1 Stability

Hydrolysis

- Onisko, B.C. et al., 1988, Report No.: RRC 88-10, Doc ID WAS 94-00173

Under sterile aqueous conditions, at temperatures of 25 °C and 40 °C, sulcotrione was found to be hydrolytically stable at pH 5, 7 and 9. The study was performed according to US-EPA Pesticide Assessment Guidelines, Subdivision N, §161-1 (1982) with ^{14}C-radiolabelled sulcotrione dissolved in sterile buffers at a nominal concentration of approximately 30 mg/L.

Photolysis in water

- Onisko, B.C. et al., 1988, Report No.: RRC 88-10, Doc ID WAS 94-00173

Sulcotrione was comparatively stable at pH 7 under the light exposure. Concentrations in irradiated samples of aqueous solutions decreased with an experimental half-life of 100 days natural summer sunlight (USA at latitude, north 38).

- Moffatt, F., 1994, Report No.: RJ1657B, Doc ID LUF 2004-156

The quantum yield of direct phototransformation of sulcotrione was determined to be 6.3×10^{-4}, 2.9×10^{-4} and 1.7×10^{-4} mol/Einstein at pH 4, 7 and 9.

Based on this quantum yield ABIWAS 2.0 calculations for middle Europe (55 ° North) result in DT_{50} values of 1.8 days (June, Minimum) to 309 days (December, Maximum).

Photolysis in soil

- Stupp, H.-P., 2002, Report No.: MR-032/02, Doc ID: BOD 2004-929

The photolytic degradation of radiolabelled [Phenyl-UL-^{14}C]sulcotrione was studied following application to a test soil under artificial sunlight. The samples were incubated at 20 ºC irradiated continuously for 24 hours/day for a maximum period of 192 hrs (8 days). The maximum experimental test duration corresponded to 40 solar midsummer days under environmental conditions in Phoenix (Arizona, USA) or to 61 days related to such conditions in Athens (Greece).

The presence of light slightly will contribute to the degradation of sulcotrione in the environment, but to a rather low extent, only. The experimental DT_{50} value for sulcotrione assuming first order kinetics was 18.3 days under the prevailing light intensity, this corresponds to a DT_{50} of 91 days under environmental light conditions (Phoenix solar summer days). In relation to that the experimental DT_{50} of sulcotrione in the dark controls was shorter (i.e. extrapolated to be 54 days, only).

Photo-oxidative degradation in air

- Hellpointner, E., 2003, Report No.: MEF-003/03, DOC ID: LUF 2004-157

Based on an overall OH reaction rate of 7.5124 x 10^{12} cm^3/molecule-sec obtained by addition reactions to aromatic rings of sulcotrione, and assuming a 24-hours-day with an OH radical concentration of 0.5 x 10^6 OH radicals/cm^3, the half-life of sulcotrione in air was calculated to be 2.136 days (AOPWIN-software version 1.90). More conservative assumptions concerning the OH radical rate constant, assuming an overall OH reaction rate of 6.2 x 10^{-12} cm^3/molecules-sec would result in half-life of sulcotrione in air of 2.6 days, corresponding to a maximum chemical lifetime (τ) of sulcotrione in air of 3.7 days, with respect to the OH radical reaction, only.

The chemical stability of sulcotrione in air is not solely determined by an attack at one single site, but at different parts of the molecule. This should result in the formation of various primary radicals leading to secondary oxidation products, which can be eliminated from the air by wet and/or dry deposition. On account of the short half-life of sulcotrione in air of utmost 2.6 days, it is expected that the active substance cannot be transported in gaseous phase over large distances and cannot accumulate in the air. This indicates that there should be no difference in the behaviour between sulcotrione and other organic substances which are emitted into the air from natural sources (e.g. from plants and soil).

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

No data available.

4.1.2.2 Screening tests

No data available.

4.1.2.3 Simulation tests

Biodegradation in water/sediment systems

The behaviour of [Phenyl-UL-^{14}C]-sulcotrione was studied in two different water-sediment systems, characterised as a loamy sand (Virginia Water system) and a silt loam (Old Basing system), over a period of 100 days according to the BBA Guidelines, Part IV, section 5 – 1 (December 1990). The results of the aerobic incubation are summarised in Table 2.

Table 2: Degradation of sulcotrione in aerobic water/sediment system

Water / sediment system	t °C	pH water	pH sed.	OC[1)] [%]	DT50 water	DT50 sed.	DT50 whole system	Method/ Guideline	Reference

Water / sediment system	**t °C**	**pH water**	**pH sed.**	**OC[1)] [%]**	**DT50 water**	**DT50 sed.**	**DT50 whole system**	**Method/ Guideline**	**Reference**
Virginia Water system I	20	n.d.	6.1	2.1	15	n.d.	48	BBA Guideline for the Official Testing of Plant Protectants, Part IV, 5-1, 1990	Waring, A.R. (1995); report no 38/186-1015; Doc ID: WAS 95-00157
Old Basing system II	20	n.d.	7.3	15.1	6	n.d.	84		
Geometric mean					9.5		63.9		

[1)] organic carbon content of sediment n.d. = no data

Sulcotrione can be described as being not easily degradable in the water/sediment system: The overall degradation half-life in the test systems was on average 64 days (geometric mean, linear regression first order). At the end of study 21 % (41 %) active substance and 61 % (41 %) of the major metabolite CMBA (2-chloro-4-(methylsulfonyl) benzoic acid) are still present in the system. Mineralisation can be described as being negligible.

The DT_{50}-values for the active substance in the water phase are calculated to be 15 and 6 days, respectively, with a geometric mean DT_{50} of 9.5 days (linear regression first order). No data on degradation of the major metabolite CMBA in the water phase is available.

An additional water-sediment study performed with sulcotrione radiolabelled in the cyclohexanedione-ring or evidences to demonstrate that potential metabolites containing the cyclohexanedione ring are labile are required.

Estimation of biodegradation in soil

The rate of biodegradation of sulcotrione and its major metabolite CMBA (2-chloro-4-methanesulfonyl [^{14}C]benzoic acid) in soil under aerobic conditions was estimated from the results of laboratory studies conducted at 25 ºC with test concentration of 1 ppm. Additionally, 2 soils were investigated in darkness (20 ºC and 40% MWHC soil moisture) with non-radiolabelled sulcotrione. Estimated DT50 (single first order non linear regression) were 14.1-74.0 days for sulcotrione (n=5) and 12.2-44.8 days for CMBA (n=5). After normalisation to reference conditions (20 °C and pf2 soil moisture content) these single first order DT50 were in the range 10.8-89.7 days (geometric mean = 25.3 days) for sulcotrione and 9.4-38.3 days (geometric mean = 24.2 days) for CMBA. The experiments are summarised in Table 3 and Table 4.

Mineralisation to CO_2 took place to a great extent (58.3 % CO_2 after 120 days). One degradate (2-chloro-4-(methylsulfonyl) benzoic acid (ICIA0051-CMBA)) was found in major amounts (max. 28.7 % of applied radioactivity at DAT 30, already). Unextracted soil residue did not exceed a portion of 28 % (at DAT-60).

Table 3: Degradation of sulcotrione in aerobic laboratory studies

Soil type	**pH**	**t. °C / % MWHC**	**DT50 /DT90 [d]**	**DT50 [d] 20 °C pF2/10kPa**	**St. [r^2]**	**Method of calcu-lation**	**Method/ Guideline**	**Reference**
silt loam (Iowa)	5.6	25 °C/ 75 % FC	24.0/79.7	29.1	0.979	SFO	U.S.A. EPA, Pesticide Assessment Guidelines, Subdivision N, § 162-1	Subba-Rao, R.V.; Wang, W.W. (1989); report no RR89-029B; Doc ID: BOD 94-00959
sand (Toulouse)	5.2	25 °C/ 75 % FC	15.0/49.8	18.2	0.967	SFO		
sandy loam (San Jose)	7.3	25 °C/ 75 % FC	74.0/245.9	89.7	0.989	SFO		
loamy sand (Speyer 2.2)	5.9	20 °C/40 %	14.1/47	10.8	0.993	SFO	BBA Guideline for the Official Testing of Plant Protectants, Part IV, 4-1, 1986	Newcombe, A.C. (1994); report no RJ1768B; Doc ID: BOD 95-00115
sand (East Anglia)	8.0	20 °C/40 %	23.6/78.4	20.2	0.985	SFO		
Geometric mean			24.5	25.3				

Table 4: Degradation of major metabolite CMBA in aerobic laboratory studies

Soil type	**pH**	**t. °C / % MWHC**	**DT50 /DT90 [d]**	**DT50 [d] 20 °C pF2/10kPa**	**St. [r^2]**	**f.f. k_{dp}/k_f**	**Method of calcu-lation**	**Method/ Guideline**	**Reference**
silt loam (Iowa)	5.6	25 °C/ 75 % FC	23.1/n.a.	28.1	0.979	0.7	SFO	U.S.A. EPA, Pesticide Assessment Guidelines, Subdivision N, § 162-1	Subba-Rao, R.V.; Wang, W.W. (1989); report no RR89-029B; Doc ID: BOD 94-00959
sand (Toulouse)	5.2	25 °C/ 75 % FC	28.1/n.a.	34.1	0.967	0.81	SFO		
sandy loam (San Jose)	7.3	25 °C/ 75 % FC	"increase"						
loamy sand (Speyer 2.2)	5.9	20 °C/40 %	12.2/n.a.	9.4	0.993	0.22	SFO	BBA Guideline for the Official Testing of Plant Protectants, Part IV, 4-1, 1986	Newcombe, A.C. (1994); report no RJ1768B; Doc ID: BOD 95-00115
sand (East Anglia)	8.0	20 °C/40 %	44.8/n.a.	38.3	0.985	0.22	SFO		
Geometric mean			24.4	24.2		0.49 arith. mean			

Soil dissipation field studies were performed in 1990-1993 in Southern France (2 trials, soil cropped with maize), Italy (3 trials, soil cropped with maize) and Germany (4 trials, bare soil) up to a nominal application rate of 600 g a.s./ha. The $DissT_{50}$ values for sulcotrione kinetic modelling analysis (including normalisation procedure to reference conditions of 20 C and pf2 soil moisture content) led to first-order normalised in the range of 1.2-11.4 days. The $DissT_{50}$ values for the major metabolite CMBA (2-chloro-4-methanesulfonyl [^{14}C]benzoic acid) kinetic modelling analysis (including normalisation procedure to reference conditions of 20 C and pf2 soil moisture content) led to first-order normalised in the range of 2.5-45.4 days.

It was noted that in three out of the nine trials (Italy: Emilia Romagna, Lombardia and Veneto) residues of sulcotrione were determined in soil at depths below 10 cm and/or in some soil-pore water samples down to a depth of 90 cm. Therefore, it cannot be excluded that in the Italian trials some fraction of the dose can have leached out of the soil layers that were sampled and the related dissipation DT50 values for sulcotrione cannot be used as degradation rates in soil. Consequently, the appropriate geometric mean normalised DegT50 values are 3.6 days for sulcotrione and 8.5 days for CMBA. The experiments are summarised in Table 5 and Table 6.

Table 5: Degradation of sulcotrione in field dissipation studies

Soil type	**Location**	**pH**	**Depth [cm]**	**DT50 [d] norm.**	**DT90 [d] norm.**	**Chi²**	**Reference**
sandy / clay loam	South France Grisolles	8.1	0-20	1.2	4.0	14.4	Earl, M.; Cary, C. A.; Hepburn, D. F. (1991); report no RJ1045B; Doc ID: BOD 94-00956
coarse sand	South France Ychoux	6.2	0-20	8.9 *	29.3	2.5	
clay	Italy Emilia Romagna	8.1	0-20	10.3 *[3]	34.1	11.2	Earl, M. et al. (1993); report no RJ1549B; Doc ID: BOD 94-00960
loam	Italy Lombardia	7.8	0-20	2.2 [3]	7.4	10.1	
sandy loam	Italy Veneto	7.3	0-20	11.4 [3]	38	17.5	
loamy sand	Germany Bienenbüttel-Varendorf	6.1	0-10	2.1	6.9	10.5	Earl, M.; Runnalls, J.K.; Chamier, O. (1994); report no RJ1673B; Doc ID: BOD 94-00958
sandy loam	Germany Klein-Zecher	6.1	0-10	5.3	17.6	7.5	
clay	Germany Ottersweiher-Unzurst	5.3	0-30	5.2	17.2	8.9	
clay loam	Germany Sollern	6.8	0-30	3.4	11.3	7.5	
Geometric mean/median (SFO)				3.6/4.3			

*) back-calculated from DT90 as conservative DT50 estimate for modelling

3) not considered for DegT50

Table 6: Degradation of major metabolite CMBA in field dissipation studies

Soil type	Location	pH	Depth [cm]	DT50 [d] norm.	DT90 [d] norm.	Chi²	Reference
sandy / clay loam	South France Grisolles	8.1	0-20	4.9	16.3	14.8	Earl, M.; Cary, C. A.; Hepburn, D. F. (1991); report no RJ1045B; Doc ID: BOD 94-00956
coarse sand	South France Ychoux	6.2	0-20	34.7	115.1	16.3	
clay	Italy Emilia Romagna	8.1	0-20	45.4	150.8	14	Earl, M. et al. (1993); report no RJ1549B; Doc ID: BOD 94-00960
loam	Italy Lombardia	7.8	0-20	42.8	142	17.2	
sandy loam	Italy Veneto	7.3	0-20	25.6	85	7.4	
loamy sand	Germany Bienenbüttel-Varendorf	6.1	0-10	10.6	35.5	7.8	Earl, M.; Runnalls, J.K.; Chamier, O. (1994); report no RJ1673B; Doc ID: BOD 94-00958
sandy loam	Germany Klein-Zecher	6.1	0-10	2.5	8.4	4.8	
clay	Germany Ottersweiher-Unzurst	5.3	0-30	30.5	101.5	12.5	
clay loam	Germany Sollern	6.8	0-30	2.8	9.2	8.2	
Geometric mean/median (SFO)				8.5/7.8			

4.1.3 Summary and discussion of persistence

Biodegradation in water

In water/sediment systems sulcotrione was metabolised exhibiting moderate persistence in the whole system with DT_{50} values of 48 days and 84 days. Sulcotrione and its major metabolite CMBA was found to be not readily biodegradable in the water/sediment study. No data on degradation of the major metabolite CMBA in the water phase is available.

Biodegradation in soil

Sulcotrione exhibits moderate to medium persistence in soil under aerobic conditions. Mineralisation of the phenyl ring to carbon dioxide accounted for 2.5-73.8 % applied radioactivity (AR) after 120 days. The formation of unextractable residues was a sink, accounting up to 26.5 % AR after 120 days. The major metabolite CMBA was detected in soil at maximum level of 60% AR.

In aerobic laboratory soil degradation studies the overall geometric mean DT_{50} value of sulcotrione and its major metabolite CMBA is 25.3 days and 24.2 days (SFO, 20 °C, pF2), respectively. In field dissipation studies the overall geometric mean DT_{50} value of sulcotrione and its major metabolite CMBA is 3.6 days and 8.5 days (SFO, 20 °C, pF2), respectively.

Based on the findings from the water/sediment simulation tests and soil studies sulcotrione appears to be susceptible for primary degradation and not ultimate mineralisation. Considering the levels of mineralisation in the simulation studies, sulcotrione is considered not readily biodegradable (a degradation of >70% degradation within 28 days) for purposes of classification and labeling.

4.2 Environmental distribution

4.2.1 Adsorption/desorption

- Simmonds, M.; Early, E., 2004, Report No.: CX/03/062, DOC ID: BOD 2004-934

Sorption properties of sulcotrione in soil were investigated in batch equilibrium tests. The Freundlich adsorption constants K_{OC} determined in the tests performed with in sum 5 different soils ranged from 17 to 58 mL/g, Freundlich coefficients 1/n ranged from 0.812 to 0.888. Thus, low to moderate adsorption of sulcotrione to soil occurred, predominantly influenced by the organic carbon content of the soil but at least also by the pH value, which itself correlates to the organic carbon content. Based on a mean K_{OC} was 36 mL/g (1/n = 0.84) sulcotrione is classified as a mobile compound in soil.

- Subba-Rao, R. V., 1990, Report No.: RB 90-048B, DOC ID: BOD 2004-935

Sorption properties of the major metabolite CMBA (2-chloro-4-methanesulfonyl [^{14}C]benzoic acid) in soil were investigated in batch equilibrium tests. The Freundlich adsorption constants K_{OC} determined in the tests performed with in sum 5 different soils ranged from 1.08 to 8.98 mL/g, Freundlich coefficients 1/n ranged from 0.708 to 0.931. Soil pH and clay content had no apparent influence on the adsorptive nature of CMBA in the five soils investigated. Based on a mean K_{OC} was 4.76 mL/g (1/n = 0.861) CMBA is classified as a high mobile compound in soil.

4.2.2 Volatilisation

- Lee, K. S.; Myers, H. W., 1987, Report No.: RRC 87-76, DOC ID: LUF 2004-153

The vapour pressure of sulcotrione was determined to be 5.3E^{-06} Pa at 25 °C. On the basis of this value it can be concluded that due to the low vapour pressure no significant evaporation of sulcotrione has to be expected after its use.

- Schneider, J., 2003, Report No.: 14 0032 1078, DOC ID: LUF 2004-154

The Henry's law constant of sulcotrione at 20 °C was calculated to be H = 6E-07 Pa m^3 mol^{-1}. Based on this value it can be concluded that significant volatilisation of sulcotrione from water is not to be expected.

- Emburey, G. T.; Hadfield, S. T., 1995, Report No.: RJ1835B, DOC ID: LUF 95-00140

The recoveries of radioactivity (means of duplicates expressed in percent of zero time) obtained from the soil after 1, 3, 6, 20 and 24 hours were 99.7, 99.7, 101.1. 99.3 and 99.9 %, and those obtained from the leaves were 99.3, 98.5, 101.0, 104.2 and 109.5 %, respectively. The results obtained showed that sulcotrione formulated as a suspension concentrate, was not volatilised from either soil or leaf surfaces (i.e. < 2 % volatilisation) over the 24 hour period of the experiment.

4.2.3 Distribution modelling

Not relevant for this dossier.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

- Schneider, J., 2003, Report No.: MO-03-003112, DOC ID: CHE2004-2211

The log Pow of sulcotrione has been determined as ≤ 0.2 (pH 4-9), therefore a bioconcentration in aquatic organisms is unlikely. A BCF study was not required.

- Robson, C. G., 1994, Report No.: RIC0453, DOC ID: WAT2004-1082

The major aquatic metabolite CMBA (M01) has a log P_{ow} of -0.2 and a bioconcentration in fish is also unlikely. A BCF-study is not required.

4.3.1.2 Measured bioaccumulation data

No data available.

4.3.2 Terrestrial bioaccumulation

No data available.

4.3.3 Summary and discussion of bioaccumulation

The log Pow of sulcotrione and of its major metabolite CMBA has been determined as ≤ 0.2 (pH 4-9), therefore a bioconcentration in aquatic organisms is unlikely. Sulcotrione and its major metabolite CMBA do not fulfil the trigger of log Pow ≥ 3 (criterion for bioaccumulating potential conform Directive 67/548/EEC) and log Pow ≥ 4 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not readily biodegradable substances.

4.4 Secondary poisoning

Not relevant for this type of dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

Sulcotrione has been reviewed under Council Directive 91/414/EEC. For more detail on the studies described or mentioned below reference is made to the Draft Assessment Report, the final addendum to the DAR, and the EFSA conclusions.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Sulcotrione is rapidly absorbed and excreted, primarily in the urine, at an average of 93 % of the administered dose in the rat and 50-81 % in the monkey 96 hours after treatment. Excretion via faeces occurs in small amounts (2-6 %) in both species. A comparison of faecal excretion data after intravenous application in rats and measurements of sulcotrione in the bile of monkeys, revealed that absorption from the gastrointestinal tract is complete upon oral administration. Distribution of sulcotrione into tissues and organs is poor, with no evidence of accumulation of residues, not even in the eye which was identified as a target organ for toxicity. In the rat, the majority of the remaining radioactivity is found in the liver and kidneys 96 hours after oral administration. Metabolism studies in rat and monkey showed that sulcotrione is poorly metabolised and over 91 % of the urinary radioactivity corresponded to unchanged parent. Small amounts of the parent molecule were metabolised by hydroxylation of the cyclohexanedione ring, forming either M02 (4-hydroxy-sulcotrione; 1- 6 %) or M04 (5-hydroxy-sulcotrione; < 1 %). The metabolite M01 (2-chloro-4-(methylsulfonyl)-benzoic acid, CMBA) which is formed by hydrolytic cleavage of the benzoyl moiety was detected in small amounts in urine (< 1 %); in the eye however, a different pattern of metabolism was revealed in the rat with 31 % of the radioactivity detected being CMBA. This metabolite may contribute to the corneal changes for which the rat appears to be the most sensitive species. In contrast, monkey's metabolism pattern in ocular tissues does not differ substantially from other tissues and 11 % of the radioactivity was identified as M02 (Peffer, R. C., 1990, report no. T-13011; Peffer, R. C., 1990, report no. T-13223).

Dermal absorption of sulcotrione was measured *in vitro* with human skin exposed for 24 hours to a concentrate (1.512 mg/cm^2) and a diluted formulation (0.0154 mg/ cm^2). Uptake into and through the skin was found to be less than 0.1 % of the dose for the concentrate and 0.5 % for the in-use dilution (Clowes, H.M., 2000, CTL/JV1611/REG/REPT). Indirect support for these *in vitro* findings comes from a comparison of tyrosine blood levels in rats after dermal (Krötlinger 2003) and oral (dietary) exposure (Milburn, 1991), showing that systemic exposure appears to be similar after dermal doses of 250 and 1000 mg/kg bw/day and oral doses of 1.4 and 6.8 mg/kg bw/day, respectively.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Sulcotrione was of very low acute oral toxicity in rats. No mortality occurred in rats and body weight was not affected. Clinical signs in all animals consisted of depression, greasy-appearing fur or rough coats, and piloerection. Some of the female rats showed alopecia (3/5), stained fur (2/5), and wet and yellowish anogenital region (4/5). All signs in male rats had reversed by day 2 after treatment, and all signs in females except for alopecia had reversed by day 6 after treatment. There were no significant findings at necropsy.

Table 7: Summary of acute oral toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 401	Oral	Rat, SD 5M+5F	5000	LD_{50} > 5000	Vehicle: corn oil	Morgan, R.L. (1988); report no T-13151

5.2.2 Acute toxicity: inhalation

Sulcotrione is of low acute inhalation toxicity in rats. No mortalities were observed at the highest attainable concentration. Treatment-related findings during exposure were mucoid nasal discharge and a reduced response to sound. Immediately after exposure, treated animals showed paw flicking, upright tail, salivation and lacrimation, abnormal respiratory noise in some males, and mucoid nasal discharge in nearly all animals. Almost all treatment-related clinical signs had resolved by the second day after treatment, although piloerection and abnormal respiratory noises were fairly persistent. Abnormal respiratory noises were also heard in some of the control males and females, and the study report suggests that this was due to a mild respiratory infection. Neither body weight nor organ weight were affected by inhalation exposure to sulcotrione. No abnormal or treatment-related findings were seen at necropsy.

Table 8: Summary of acute inhalation toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/L)	Value LC_{50} (mg/L)	Remarks	Reference
OECD 403	Inhalative	Rat, Alpk:APfSD 5M+5F	1.63	LC_{50} > 1.63	Dust, 4-h, nose only, highest attainable concentration	Lewis, R.W. (1989); report no CTL/P/2715

5.2.3 Acute toxicity: dermal

Sulcotrione is of low acute dermal toxicity in rabbits. No deaths occurred. Clinical signs were limited to mild depression. All rabbits appeared normal by day 9. Local, mild to moderate erythema was observed following removal of sulcotrione. Body weight was unaffected. At necropsy, one female showed pale kidneys, but no other findings of any significance were observed.

Table 9: Summary of acute dermal toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 402	**Dermal**	**Rabbit, Stauffland albino 5M+5F**	**4000**	**LD_{50} >4000**	**Vehicle: not reported**	**Morgan, R.L. (1988); report no T-13151**

5.2.4 Acute toxicity: other routes

No data are available.

5.2.5 Summary and discussion of acute toxicity

Sulcotrione is of low acute toxicity by oral (LD_{50} > 5000 mg/kg bw) and dermal route (LD_{50} > 4000 mg/kg bw) in rats and by inhalation route (LC_{50} > 5.06 mg/L) in rabbits (LC_{50} > 1.63 mg/L). No classification is required.

RAC opinion

No information to oppose this classification was received during the public consultation or RAC discussion. RAC agrees with the view of the Dossier Submitter that the available information does not support a classification for acute toxicity.

Summary and discussion of specific target organ toxicity – single exposure

RAC opinion

The Dossier Submitter did not include a discussion of specific target organ toxicity – single exposure. Based on the available data, sulcotrione did not meet the criteria for classification as STOT-SE. No information to oppose this evaluation was received during the public consultation or RAC discussion. Therefore, RAC concluded that no classification for specific target organ toxicity – single exposure is required.

5.3 Irritation

5.3.1 Skin

Sulcotrione was not irritating to rabbit skin when applied as dry or moistened powder at a dose of 80 mg/cm^2.

Table 10: Summary of skin irritation

Method / Guideline	Species, Strain, Sex, No/group	Average score 24, 48, 72 h		Reversibility yes/no	Results	Remarks	Reference
		Erythema	Oedema				
OECD 404	**Rabbit, Stauffland albino 1M+5F**	**0-0-0**	**0-0-0**	**Not applicable**	**Not irritating**	**None**	**Morgan, R.L. (1988); report no T-13151**

5.3.2 Eye

Slight irritation, manifested most strongly 1 hour after the application of 100 mg sulcotrione to the eye, was seen in rabbits. The findings included mild iritis (4 rabbits), mild to moderate conjunctival reddening, and mild corneal epithelial erosion (2 rabbits). Five of the six animals showed grade 2 conjunctival redness at 24 and 48 h after instillation of the test material. All of these findings had resolved by 7 days after treatment.

Table 11: Summary of eye irritation

Method/ Guideline	Species, Strain, Sex, No/group	Average Score 24, 48, 72 h				Reversi-bility yes/no	Results	Remarks	Reference
		Cornea	Iris	Redness Conjunc-tiva	Chemo-sis				
OECD 405	Rabbit, NZW 6F	0-0-0	0-0-0	1.8-1.8-0.8	1.2-0.8-0.17	yes	Not irritating	None	Morgan, R.L. (1988); report no T-13151

5.2.4 Respiratory tract

No data are available. A slight potential for respiratory irritation may be deduced from findings in the acute inhalation toxicity study (salivation, lacrimation, abnormal respiratory noise, mucoid nasal discharge).

5.2.5 Summary and discussion of irritation

Sulcotrione is not irritating to the skin but produced slight eye irritation shortly after dosing. According to the criteria in council directive 67/548/EEC no classification is required. As the mean scores following grading at 24, 48 and 72 hours after instillation of the test material were < 2 and full reversibility was attained within 7 days the classification criteria of the CLP Regulation are not met.

RAC opinion

One comment received during the public consultation requested more information to clarify whether or not the classification criteria for eye irritation had been met. RAC checked the original

test report (Morgan 1988, T-13151) containing the individual animal data, and were satisfied that classification for eye irritation under CLP is not supported. Effects in all animals were reversed by day 7 (post treatment). There were no mean scores (over 24, 48 and 72h) above the cut-off values for classification in any animals.

RAC agrees that classifications for skin and respiratory irritation are not supported by the available information.

5.3 Corrosivity

In skin and eye irritation studies there was no evidence for a corrosive action of sulcotrione.

RAC opinion

RAC agrees that a classification for corrosivity is not supported.

5.4 Sensitisation

5.4.1 Skin

In the Magnusson and Kligman test, Guinea pigs were induced intradermally with 0.3 % sulcotrione, followed by topical induction with a 75 % solution. A sensitisation rate of 80 % was noted after challenging with a 30 % sulcotrione solution in corn oil.

Table 12: Summary of skin sensitisation

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/Total number of animals	Results	Remarks	Reference
OECD 406 GPMT	Guinea pig, Alpk:Dunkin Hartley 20F (treated) 10F (control)	0/10 (control) 10% sulcotrione: 14/20 30% sulcotrione: 16/20 scattered mild to intense redness, swelling	Sensitising	Vehicle: intradermal induction: Freund' s Complete Adjuvant/ 3 % dimethylformamide/ corn oil; topical induction and challenge: corn oil	Rattray, N.; Robinson, P. (1989); report no. CTL/P/2714

5.4.2 Respiratory system

No data are available.

5.4.3 Summary and discussion of sensitisation

Sulcotrione was sensitising in the Guinea pig maximisation test. Therefore, a classification is required.

Classification and Labelling for acute toxicity [DOSSIER SUBMITTER ERROR: skin sensitisation] according to Directive 67/548/EEC:

Xi; R43 (Irritant; May cause sensitisation by skin contact)

Classification and Labelling for acute toxicity [DOSSIER SUBMITTER ERROR: skin sensitisation] according to GHS:

Skin Sens. 1; H317 (May cause an allergic skin reaction)

RAC opinion

No information to oppose this evaluation was received during the public consultation and RAC discussion. However, one comment received during the public consultation highlighted that, with the publication of the second ATP to the CLP Regulation, sub-categories had been introduced to the sensitisation end-point, and that sufficient information was available in the dossier for sulcotrione to place it in category 1A: a sensitisation rate of 80% after intradermal induction with 0.3% sulcotrione. This is consistent with the criterion for classification in category 1A (≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose). Therefore, RAC supports the following classification, with a specific concentration limit (SCL) of 0.1% under the DSD in line with the generic concentration limit for the sub-category 1A (under CLP according to the 2nd ATP).

CLP, taking into account the 2nd ATP: Skin Sens. 1A (H317): **May cause an allergic reaction**

R43: May cause sensitisation by skin contact (DSD)

SCL (DSD): R43: C ≥ 0.1%

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

Sulcotrione is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD), a key enzyme of the tyrosine catabolic pathway. Inhibition of this enzyme results in increased 4-hydroxyphenyl pyruvate (the proximal tyrosine metabolite) and tyrosine concentrations in blood. The primary toxic effects were an increased incidence of corneal lesions and increased liver and kidney weights, generally more prominent in males than in females. The effects observed in the liver and kidneys (increased organ weight, minor to slight hepatocellular hypertrophy) may in part be related to increased metabolic load or excretion of the test substance, respectively, as well as tyrosine concentrations. However, a direct effect of sulcotrione on these organs cannot be ruled out and the NOAEL in rats at the dose level of 3.3 mg/kg bw/day is based on these findings.
Corneal opacity was also seen in dogs albeit at higher doses than in rats. The overall NOAEL from two acceptable studies in dogs was 50 mg/kg bw/day.

Table 13: Summary of oral repeat dose toxicity

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels ppm (mg/kg bw /d)	NO(A)EL ppm (mg/kg bw /d)	LO(A)EL ppm (mg/kg bw /d)	Results, Main effects/ Target organs	Remarks	Reference
OECD 407 with deviations	Oral/diet, 28 days	Rat, SD; 10M+10F	0-5000-7500-10000 (M: 0-574-756-1160; F: 0-581-741-1107)	< 5000 (M: < 574; F: < 581)	5000 (M: 574; F: 581)	Kidney weight ↑; liver: weight ↑, hepato-cellular hypertrophy	Range-finding study; insufficient endpoints and reporting	Pavkov, K. L. (1986); report no T-12736
No Guideline	Oral/diet 35 days	Rat, Alpk:APfS, 12M Recovery group: 12 M	0-10-50-1900-12000 (0-1.4-6.8-253-1590)	Overall: < 10 (< 1.4) Relevant: 1900 (253.4)	Overall: 10 (1.4) Relevant: 12000 (1590)	≤ 10 ppm: plasma tyrosine ↑, corneal opacity, corneal keratitis 12000 ppm: food consumption, bw ↓	Recovery 4 weeks; effects reversible	Milburn, G.M. (1991); report no. CTL/P/3223
OECD 408	Oral/diet 90 days	Rat, Crl:CD (SD)BR 10M+10F	0-50-300-800-1900-4800-12000 (M: 0-3.3-21.2-55.5-128.7-328.3-792.2; F: 0-3.5-21.5-58.7-134.3-364.6-848.6)	Overall: < 50 (M: < 3.3) Relevant: M: 50 (3.3) F: 4800 (364.6)	Overall: 50 (M: 3.3) Relevant: M: 300 (21.2), F: 12000 (848.6)	Overall: corneal opacity and keratitis Relevant: M: liver and kidney weights ↑; F: food consumption ↓		Pavkov, K.L., Taylor, D.O.N (1991); report no. T-12900SC
OECD 409	Oral/ capsule 90 days	Dog, Beagle, 4M+4F	(0-40-100-300-800)	(40)	(100)	Corneal opacity, keratopathy, microcytosis, hypochromia	None	Sauerhoff, M.W. et al. (1989); report no. T-12964
OECD 452	Oral/ capsule 1 year	Dog, Beagle, 4M+4F	(0-5-50-300)	(50)	(300)	Corneal opacity; platelet count ↑	None	Moxon, M.E. (1993); report no. CTL/P/3834

5.5.2 Repeated dose toxicity: inhalation

No data are available. Based on the results of the acute toxicity study, a repeated dose inhalation toxicity study has not been required.

5.5.3 Repeated dose toxicity: dermal

Dermal application of sulcotrione to rats resulted in few findings but gave evidence for dermal absorption of the test substance. Absolute and relative liver weight were generally increased at 1000 mg/kg bw/day in the absence of any histopathological findings. Plasma tyrosine concentration increased at all doses; the extent of the increase was greater in males than in females. No corneal opacities were seen. Thus the NOAEL was 1000 mg/kg bw/day.

Table 14: Summary of dermal repeat dose toxicity

Method/ Guideline	**Route of exposure, Duration**	**Species, Strain, Sex, No/group**	**Dose levels mg/kg bw/d**	**NO(A)EL mg/kg bw/d**	**LO(A)EL mg/kg bw/d**	**Results, Main effects/ Target organs**	**Remarks**	**Reference**
OECD 410	Dermal, 28 days	Rat, Wistar HsdCpb:WU; 5M+5F	0-50-100-250-1000	1000	> 1000	≥50: Blood tyr ↑ 1000: Liver wt ↑	Moistened solid; 6 h/d, 5 d/week	Chevalier, G. (2002); report no 21601TSR

5.5.4 Other relevant information

No eye lesions developed upon oral administration of sulcotrione up to 750 mg/kg bw/day in monkeys for one year and in rabbits after a treatment of three months.
The EU Commission Scientific Committee on Plants summarised a number of volunteer studies in its 2002 evaluation of mesotrione (a moderately strong HPPD inhibitor structurally very similar to sulcotrione), and concluded that a tyrosine concentration threshold exists for the development of ocular lesions after HPPD inhibition, and further that in humans even complete inhibition of HPPD activity through administration of NTBC does not produce tyrosine concentrations greater than this threshold. Thus, corneal opacities and keratitis resulting from administration of sulcotrione to rats or dogs are not relevant for human risk assessment.

Table 15: Summary of other oral repeat dose toxicity studies

Method/ Guideline	**Route of exposure, Duration**	**Species, Strain, Sex, No/group**	**Dose levels ppm (mg/kg bw /d)**	**Results**	**Remarks**	**Reference**
No Guideline	Oral/diet 90 days	Rat, Wistar HsdCpb:WV 10M+9M for satellite groups	Sulcotrione: 0-225 NTBC: 0.2-10 Tyr: 20000 NTBC+Tyr: 0.2+20000	Sulcotrione; NTBC+Tyr; NTBC10 : Bw gain ↓; corneal opacity, keratitis, neovascularisation; blood and urinary tyr ↑; liver wt ↑, hepatocellular hypertrophy (also in NTBC0.2); kidney wt ↑ Renal cortex gene expression (mRNA): Day 1: up-regulation of inflammatory signals, growth signals, transcriptional activation, HNF1 beta ↑; downregulation of metabolic function, energy production. Day 4-7: up-regulation apoptosis, regenerative processes	Mechanistic study	Kroetlinger, F. et al. (2003); report no. AT00590

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels ppm (mg/kg bw /d)	Results	Remarks	Reference
No Guideline	Oral/ gavage 1 year	Rhesus monkey, control: 8M+8F low dose: 5M+5F high dose: 8M+8F	(0-75-750)	No relevant toxicity, no eye lesions NOAEL 750 mg/kg bw/d	5 days/week	Pettersen, J. C. (1990); report no. T-12986
No Guideline	Oral/ gavage 90 days	Rabbit, NZW 10M+10F	(0-50-250-750)	No relevant toxicity, no eye lesions NOAEL 750 mg/kg bw/d	Endpoints: food consumption, bw, ophthalmology	Potrepka, R.F (1988); report no. T-13251

5.5.5 Summary and discussion of repeated dose toxicity:

The primary finding after exposure to sulcotrione is hypertyrosinaemia. The cornea, the liver and the kidney have been identified as main target organs. The corneal lesions seen with the administration of HPPD inhibitors in rats have been accepted as a result of increased blood tyrosine or tyrosine metabolite concentration. Due to species-specific differences in tyrosine catabolic pathways humans are less susceptible to the hypertyrosinaemic effect of HPPD inhibitors and therefore unlikely to develop corneal lesions. Corneal effects are considered not relevant for humans. In contrast, direct effects of sulcotrione are at least partially responsible for the liver and kidney findings, consistent with the involvement of these organs in metabolism and excretion of the compound. Accumulating tyrosine is excreted via urine and contributes to the renal load. The increased organ weights in males only are likely to be adaptive and the hepatocellular hypertrophy observed in the mechanistic study was described as minor to slight. No classification for repeated dose toxicity is required.

RAC opinion

RAC made a detailed evaluation of the repeated dose toxicity of sulcotrione, given that several members of the Committee commented that classification may be appropriate. Although neither the Dossier Submitter nor those who responded to the public consultation made such a proposal, it appears that they did not take into account the full range of findings from the standard repeat dose toxicity studies *and* the carcinogenicity and reproductive toxicity studies.

Sulcotrione has been tested for repeated dose toxicity by the oral and dermal routes in rats, dogs, monkeys and rabbits. The cornea, the liver and the kidney were identified as the main target organs; some of the effects were postulated by the Dossier Submitter to be a consequence of hypertyrosinaemia, which occurs in rats after exposure to sulcotrione.

Effects on the Cornea

In a 90-day study in the rat, there was an increased incidence of corneal opacities and keratitis at doses below the guidance values for classification for repeated dose toxicity. Corneal opacity also occurred in a 90-day study in the dog, albeit at higher doses than in rats. No eye lesions developed upon oral administration of sulcotrione in doses up to 750 mg/kg bw/day in monkeys for one year and in rabbits after a treatment of three months.

Sulcotrione is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD), a key enzyme of the tyrosine catabolic pathway. Inhibition of this enzyme results in increased 4-hydroxyphenyl pyruvate (the proximal tyrosine metabolite) and tyrosine concentrations in the blood. The corneal lesions seen with the administration of HPPD inhibitors in rats have been accepted as the result of increased blood tyrosine or tyrosine metabolite concentration. Owing to species-specific differences in tyrosine catabolic pathways, the rat, and especially the male, is extremely sensitive to these effects, whereas mice are known to be quite insensitive. The absence of corneal effects in monkeys at high and prolonged doses of sulcotrione indicates that this effect would not be expected in humans at doses relevant for classification.

Another enzyme involved in tyrosine metabolism, tyrosine aminotransferase (TAT), accounts for species differences in tyrosine levels and, therefore, the sensitivity of the rat to sulcotrione. TAT activity in humans is relatively high compared with that of the rat, therefore humans are less sensitive to sulcotrione-mediated increases in tyrosine levels.

Studies on mesotrione (a moderately strong HPPD inhibitor that is structurally very similar to sulcotrione) demonstrated that a tyrosine concentration threshold exists for the development of ocular lesions after HPPD inhibition, and further that in humans even complete inhibition of HPPD activity does not produce tyrosine concentrations greater than this threshold (European Commission Opinion, Opinion of the Scientific Committee for Plants, OJ L 230, 19.8.1991, p. 1). Thus, corneal opacities and keratitis resulting from administration of sulcotrione to rats or dogs are not considered relevant for humans.

Effects on the Liver and Kidney

In a 90-day study in the rat, liver and kidney weights were generally increased. In a two-year carcinogenicity study in rats, kidney effects were noted at gross necropsy from 0.04 mg/kg/d. They also occurred in pups and parents in two two-generation reproductive toxicity studies. During the public consultation and RAC discussions, comments referred to these findings of kidney effects in rats and requested their clarification in relation to the potential of sulcotrione to cause repeated-dose toxicity. In contrast to the corneal effects, where increased tyrosine levels were the proposed cause, direct effects of sulcotrione were likely to be at least partially responsible for the liver and the kidney findings, consistent with the involvement of these organs in metabolism and excretion of the substance. The observed liver effects consisted of increased organ weight and minor to slight hepatocellular hypertrophy; since both of these are indicative of adaptive rather than adverse responses by the liver, they will not be considered further in deciding upon a classification.

Additional information, taken from the Draft Assessment Report produced for the review of sulcotrione in accordance with Directive 91/414/EEC, provides a greater understanding of the nature of the renal effects: cystic kidneys; kidney enlargement; pelvis dilatation, calcification; papillary necrosis and tubule dilatation. The renal findings from the relevant studies are summarised in the table below.

Table R1. Renal findings from the oral repeated dose, carcinogenicity and reproductive toxicity studies

Study design	Doses (mg/kg/d)	Severe renal effects	Other renal effects
Repeated dose toxicity studies			
28 days, dietary (range-	M: 0, 574, 756,	None	Increased kidney weight

finding study) Rat, Sprague Dawley, 10/sex/group [Pavkov, 1986]	1160 F: 0, 581, 741, 1107		from 574 mg/kg/d
35 days, dietary Rat, Wistar-derived, 12 males/group, plus recovery groups of 12/group Conducted at ICI Central Toxicology Laboratory [Milburn, 1991]	0, 1.4, 6.8, 253, 1590	None	None
90 days, dietary Rats, Sprague Dawley-derived, 10/sex/group Conducted at Richmond Toxicology Laboratory [Pavkov, 1991]	M: 0, 3.3, 21.2, 55.5, 128.7, 328.3, 792.2 F: 0, 3.5, 21.5, 58.7, 134.3, 364.6, 848.6	None	Increased kidney weights from 21.2 mg/kg/d
90 days, dietary mechanistic study Rats, Wistar, 10 males/group [Kroetlinger, 2003]	0, 225	None	Increased kidney weights at 225 mg/kg/d
90 day, capsule Dogs, Beagle, 4/sex/group Conducted at Richmond Toxicology Laboratory [Sauerhoff, 1989]	0, 40, 100, 300, 800	None	None
1 year, capsule Dogs, Beagle, 4/sex/group Conducted at Zeneca Central Toxicology Laboratory [Moxon, 1993]	0, 5, 50, 300	None	None
Carcinogenicity studies			

24 months, dietary Rats, Sprague Dawley-derived, 60/sex/group Conducted at Richmond Toxicology Laboratory [Pavkov, 1990]	M: 0, 2, 72, 484 F: 0, 2.2, 91, 555	Increased severity of chronic progressive nephrosis of males at 484 mg/kg/d (2nd year of study only).	Increased kidney weights in males at 72 mg/kg/d at 1-year interim sacrifice. Gross necropsy and histopathology: males from 2 mg/kg/d: increased incidence of kidney cysts, kidney enlargement, enlarged renal lymph nodes (2nd year of study only). Pelvis dilatation in males from 2 mg/kg/d.
24 months, dietary Rats, Sprague Dawley-derived, 50/sex/group Conducted at Richmond Toxicology Laboratory [Potrepka, 1991]	M: 0, 0.04, 0.4, 0.8, 2 F: 0, 0.05, 0.5, 0.9, 2.4	None	Gross necropsy only. In males from 0.04 mg/kg/d: increased incidences of kidney cysts, enlarged kidneys and distended renal pelves. No renal effects in females.
18 months, dietary Mice, CD-1, 50/sex/group Conducted at Richmond Toxicology Laboratory [Pettersen, 1990]	M: 0, 4.2, 38, 332, 797 F: 0, 5.2, 46, 409, 909	At 797/909 mg/kg/d, increased incidence and/or severity of papillary necrosis and calcification.	Gross necropsy and histopathology: at 797/909 mg/kg/d, increased incidences of rough or pitted kidneys, pelvis and tubule dilatation.
Reproductive toxicity studies			
Two-generation study, dietary Rats, Sprague Dawley-derived, 25/sex/group [Gilles, 1989]	0, 0.5, 15, 340 Administered to P0 animals for 56 days prior to mating	<u>Adults</u> None <u>Pups</u> None	<u>Adults</u> Gross necropsy and histopathology: P0 males: pelvis dilatation and tubular basophilia at 340 mg/kg/d, protein filtrate from 0.5 mg/kg/d. P1: pelvis dilatation, tubular basophilia, protein filtrate from 0.5 mg/kg/d. <u>Pups</u> Gross necropsy: urinary

			tract abnormalities (unidentified white material, which may have been protein filtrate or sulcotrione; pelvis dilatation) from 0.5 mg/kg/d at PND 4 (F2B) and at weaning (F1B and F2B). At 340 mg/kg/d, small kidneys in F2B and misshapen kidneys in F1B. Increased pup deaths at 340 mg/kg/d.
Two-generation study, dietary Rats, Sprague dawley-derived, 25/sex/group [Minor, 1990]	0, 0.06, 0.7, 17 Administered to P0 animals for 56 days prior to mating	Adults None Pups None	Adults Gross necropsy and histopathology: pelvis dilatation at 17 mg/kg/d in P1 males. Nephropathy (not further defined) at histopathology in P0 and P1 males from 0.7 mg/kg/d. Pups Gross necropsy: urinary tract abnormalities (dilated renal pelves, convoluted and/or dilated ureters, white material in the urinary tract) from 0.7 mg/kg/d at PND 4 and weaning (F1B and F2B). At weaning, small and/or misshapen kidneys at 17 mg/kg/d (F1B and F2B). No statistically significant increase in pup deaths.
Developmental study (GD 6-20) Rat, CD, 23 females [Gilles, 1988]	0, 10, 100, 1000	None	None

Developmental study (GD 7-19) Rabbit, New Zealand White, 18 females [Minor, 1988]	0, 30, 100, 300	None	None

In repeated dose studies of up to 90 days' duration, the only observed effect on the kidneys was increased weight, which was likely to be an adaptive change. There were no renal changes in dogs that were exposed for up to one year. In the two rat carcinogenicity studies, of two years' duration, consistent renal findings were obtained: kidney cysts, enlargement, pelvis dilatation, from 0.04 mg/kg/d, which, in the study that included an interim sacrifice, occurred in the second year of the study only. In an 18-month mouse study, such renal effects were only seen in the high-dose group (797/909 mg/kg/d). Indications of more severe effects (increased severity of chronic progressive nephrosis, papillary necrosis and calcification) in rats and mice occurred only in the high-dose groups, and in the rat study, only in the second year.

The information obtained from the two-generation reproductive toxicity studies also indicated that longer durations of exposure resulted in higher incidences of renal effects in adults (P0 compared with P1). Renal changes were not noted in pups at delivery in the developmental toxicity studies, but were observed by post natal day 4. At weaning, the additional finding of small and/or misshapen kidneys was reported in a few animals. These data are discussed further in the section on reproductive toxicity.

From these data, it is concluded that prolonged exposure of adults to sulcotrione is necessary for the adverse renal effects to become apparent. The severity of these effects was not reported in the dossier submitter's report or the Draft Assessment Report. Subsequently, industry provided the rapporteurs with additional information on the nature of the effects observed in the two rat carcinogenicity studies (Pavkov, 1990; Potrepka, 1991). In the first study, it was shown by histopathology that the severity of the cystic change was increased in the high-dose group (484 mg/kg/d). The incidence of the pelvis dilatation in males was increased from 2 mg/kg/d, but the severity was not, even at the high dose (the changes at 484 mg/kg/d were mostly scored as 2, whereas mores severe scores were obtained from some of the control animals). Histopathology was not performed on the kidneys of animals in the second rat carcinogenicity study. However, the data provided by industry indicated, although there were increased incidences in some renal findings from 0.04 mg/kg/d, the number of animals affected was small and only slightly greater than the control values. The absence of overt clinical signs and indications that renal function was affected would seem to support the view that the effects observed at gross necropsy and histopathology were not severe.

Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

The guidance cut-off value for a classification for STOT-RE under CLP is 100 mg/kg/d (for a classification in category 2), obtained in a 90-day rat study. For a classification in category 1, the guidance value is $\leq$ 10 mg/kg/d. STOT-RE is assigned on the basis of a substance demonstrating evidence of significant or severe toxicity, generally at or below one of these guidance values. When the guidance values are adjusted from a 90-day study to one of two years' duration, a value of 12.5 mg/kg/d is obtained for STOT-RE2 and a value of 1.25 mg/kg/d is obtained for STOT-RE1. 'Significant' toxicity is taken to mean changes that clearly indicate functional disturbance or

morphological changes that are toxicologically relevant. 'Severe' toxicity is considered to be more profound or serious and indicates changes that are of a considerably adverse nature with a significant impact on health.

At doses below these guidance values, sulcotrione did not result in any toxicity that could be regarded as severe according to this definition. Renal toxicity that could be viewed as significant (i.e., toxicologically relevant) occurred only in carcinogenicity and reproductive studies.

Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

a) Morbidity or death resulting from repeated or long-term exposure

There were no treatment-related deaths or cases of moribund animals below the guidance value. A statistically significant increase in pup deaths occurred only at a dose above the guidance value.

b) Significant functional changes in the central or peripheral nervous systems or other organ systems

There were no such changes in any organ systems.

c) Any consistent and significant adverse change in clinical biochemistry, haematology or urinalysis parameters

There were no such changes.

d) Significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination

At doses below the guidance value (adjusted for studies of two years' duration), some kidney changes were noted at necropsy and, in some cases, confirmed at histopathology. These included increased incidences of kidney cysts, kidney enlargement and pelvis dilatation from 0.04 mg/kg/d in carcinogenicity and two-generation studies. Whilst it was recognised that these effects were observed from very low doses (below the adjusted guidance cut-off value for category 1), additional factors were taken into account in deciding upon a category. Firstly, the nature and severity of the effects, and the absence of overt clinical toxicity, indicated that the effects induced by sulcotrione were significant rather than severe. Secondly, the fact that the severity and incidence of the effects was generally not greatly increased in the top-dose group compared with the low-dose group indicated that there was a shallow dose-response curve. Thirdly, a very long duration of exposure was necessary before the effects became apparent.

e) Multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity

There were no such effects.

f*) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver)*

There were no morphological changes that provided evidence of marked organ dysfunction.

g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration

There were no such effects.

There were no generalised changes that involved several organ systems or significant/severe changes in the general health status of the animals.

After considering the above information on the potential of sulcotrione to cause renal toxicity, as evidenced by gross and histopathological changes at doses below the guidance value for classification, the overall conclusion of RAC is that sulcotrione best meets the CLP criteria for a classification as STOT RE 2 (kidneys); H373.

Classification with R48 (DSD) is reserved for substances that cause serious damage to health. In the sulcotrione carcinogenicity studies, the severe effects occurred only at doses that were far in excess of the adjusted threshold value (6.25 mg/kg/d for a study of two years' duration for Xn; R48). It is doubtful if the effects observed below the guidance value, and in the two-generation studies, could be regarded as serious. However, significant effects occurred at doses below the cut-off value. Accordingly, as discussed under STOT-RE, RAC considers that classification as Xn; R48/22 is appropriate.

CLP: STOT RE 2 (H373): May cause damage to kidneys through prolonged or repeated exposure

DSD: R48/22: Danger of serious damage to health by prolonged exposure

5.6 Mutagenicity

5.6.1 In vitro data

There were positive responses in two of the four Ames Salmonella/microsomal assays; the positive responses were observed with material of higher purity in studies conducted under GLP while older, non-GLP studies conducted with test substance of lower purity were negative. Strain TA1535 was consistently negative in the presence and in the absence of S9 and TA 98 gave a positive response under both conditions. Results for the other strains were less congruous. Sulcotrione was mutagenic in a mouse lymphoma cell forward mutation assay in the presence of S9. Sister chromatid exchanges were increased in the presence of metabolic activation with no correlation to the incidences of chromosomal aberrations in the same cultures. A cytogenetic test in human lymphocytes was negative.

Table 16: Summary of in vitro mutagenicity

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks give information on cytotoxicity and other	Reference
			+ S9	- S9		
OECD 471	*S. typhimurium*: TA1535, TA1537, TA1538, TA98, TA100	0-5000 µg/plate	Positive TA1537 TA1538 TA98 TA100	Positive TA1538 TA98	Reduced backgroung lawn at 5000 µg/plate –S9 Revertant rate 3-4fold over control Test material purity 92.4 %	Callander, R.D., Priestley, K.P. (1989); report no. CTL/P/2634
OECD 471	*S. typhimurium*: TA1535,	0-5000 µg/plate	Positive TA1537	Positive TA1537	Reduced backgroung lawn at 5000 µg/plate –S9	Callander, R.D. (1992); report no.

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks give information on cytotoxicity and other	Reference
			+ S9	- S9		
	TA1537, TA98, TA100 *E. coli*: WP2P, WP2PuvrA		TA98 TA100	TA98 TA100	Revertant rate 2-8fold over control Test material purity 95.1 %	CTL/P/3739
Similar to OECD 471	*S. typhimurium*: TA1535, TA1537, TA98, TA100	0-5000 µg/plate	Negative	Negative	No cytotoxicity Test material purity 90 %	Majeska, J.B. (1984); report no. T-11960
Similar to OECD 471	*S. typhimurium*: TA1535, TA1537, TA98, TA100	0-10000 µg/plate	Negative	Negative	No cytotoxicity Test material purity 90 %	Majeska, J.B. (1985); report no. T-11964
OECD 473	Human lymphocytes	0-600 µg/mL	Negative	Negative	Cytotoxicity at 600 µg/mL	Howard, C.A. (1989); report no. CTL/P/2437
Similar to OECD 476 (Forward mutation)	L5178Y mouse lymphoma cells	0-3000 µg/mL	Positive	Negative	Cytotoxicity at 750 µg/mL	Majeska, J.B. (1985); report no. T-11961
Similar to OECD 479 (SCE induction)	L5178Y mouse lymphoma cells	0-3000 µg/mL	Positive	Negative	Cytotoxicity at 1500 µg/mL	Majeska, J.B. (1985); report no. T-11962

5.6.2 In vivo data

One mouse micronucleus study with C57BL mice (Mackay, 1990) gave reproducible, weak positive findings in males only at doses above the current limit dose of 2000 mg/kg bw. The reason for the finding is unclear, it may be due to the observed variability in the mouse strain used. Two further micronucleus studies with the CD-1 strain were negative. The *in vivo* UDS test did not show any increase in DNA repair.

Table 17: Summary of in vivo mutagenicity

Method/ Guideline	Species, Strain, Sex, No/group	Route, Frequency of application	Sampling times	Dose levels mg/kg bw	Results	Remarks	Reference
OECD 474 (Micronucle-us assay)	Mouse, C57BL/6Jf CD-1/Alpk, 5M+5F	Oral, single dose	24, 48, 72 hours	0-3125-5000	Weak positive at 48 and 72 h	MPCE counts highly variable between and within animals	Mackay, J.M. (1990); report no. CTL/P/2784
OECD 474 (Micronucle-us assay)	Mouse, CD-1 5M+5F	Oral, single dose	24, 48, 72 hours	0-3200-5000	Negative	None	Griffiths, K., Mackay, J.M. (1992); report no. CTL/P/3820
Similar to OECD 474 (Micronucle-us assay)	Mouse, CD-1 5M+5F	Oral, single dose	16, 24, 48 hours	0-333-1000-3000	Negative	None	Majeska, M.S (1986); report no. T-12775

Method/ Guideline	Species, Strain, Sex, No/group	Route, Frequency of application	Sampling times	Dose levels mg/kg bw	Results	Remarks	Reference
OECD 486 (UDS test)	Rat, Alpk:APfSD 5M	Oral, single dose	4, 12 hours	0-1000-2000	Negative	None	Trueman, R.W. (1989); report no. CTL/P/2495

5.6.3 Human data

A test for clastogenicity in vitro was performed with human lymphocytes (Howard, 1989). Sulcotrione did not produce chromosome aberrations in this assay. No other human data are available regarding this endpoint.

5.6.4 Other relevant information

No other relevant information is available.

5.6.5 Summary and discussion of mutagenicity

Inconsistent results were obtained from the genotoxicity studies conducted with sulcotrione. Positive *in vitro* tests results were found in two out of four Ames tests, a mouse lymphoma assay and a Sister Chromatid Exchange assay. One out of three *in vivo* micronucleus tests gave a positive result which is probably spurious. The lack of test substance-induced repair processes in highly exposed liver tissue of rats argues against a clastogenic and mutagenic potential of sulcotrione *in vivo*. Taking into account that no evidence for carcinogenicity had been found in long term studies and that the exposure of liver tissue is much higher than that of blood and bone marrow it is concluded that sulcotrione had no genotoxic potential *in vivo*. Classification for genotoxicity is not required.

RAC opinion

No further data or comments relating to the mutagenicity of sulcotrione were received during the public consultation or the RAC discussions.

Sulcotrione gave inconsistent results in the package of genotoxicity studies conducted. In the in vitro studies, positive responses were seen in two of the four Ames Salmonella/microsomal assays, both with and without exogenous metabolic activation. A positive result for gene mutations was also observed in mouse lymphoma cells (in the presence of S9 only). In contrast, a test for chromosome aberrations in human lymphocyte cultures was negative. From these in vitro studies, there are concerns about the potential genotoxicity of sulcotrione; therefore, a careful scrutiny of the *in vivo* data was made. In the in vivo studies, one mouse micronucleus study (C57BL mice) appeared to give reproducible, weak positive findings in males. However, the frequencies of micronuclei observed in this study were highly variable between animals and within animal replicates and accordingly the validity of the positive result is questionable. Significantly, two further micronucleus studies with the CD-1 strain were negative. In addition, a UDS-test using rat liver tissue was also negative.

RAC judged overall that the weight and strength of the available negative *in vivo* data were sufficient to conclude that no classification for mutagenicity was justified; a robust case for classification cannot be made given the clearly negative findings. RAC therefore agrees with the Dossier Submitter that the available data do not support classification for mutagenicity.

5.7 Carcinogenicity

5.7.1 Carcinogenicity: oral

Long term toxicity was examined in a two-year study in rats and an 18-month study in mice. A supplementary study was conducted to determine whether the corneal opacities and keratitis observed in the rat were due to housing conditions or to sulcotrione administration. Rats developed increased incidences of corneal opacities and keratitis as well as liver and kidney toxicity (increased liver weight, liver and kidney histopathology). In the supplementary study, the lowest dose level of 0.04 mg/kg bw/day still resulted in an increased incidence of kidney findings in males (enlargement, cystic changes and pelvis dilation) while ocular findings were evident only from the next higher dose level of 0.4 mg/kg bw/day. Although kidney changes are common to ageing rats the increase in all sulcotrione exposed groups indicates that the long term NOAEL for the rat is below 0.04 mg/kg bw/day. In the mouse, no corneal opacities were observed at any dose; the NOAEL was 5.2 mg/kg bw/day based on increased liver weight at the next higher dose of 46 mg/kg bw/day; further dose increases (≥ 409 mg/kg bw/day) reduced survival in females and thus exceeded the tolerated dose. No evidence of treatment-related oncogenicity was found in either rats or mice.

Table 18: Summary of oral carcinogenicity

Method/ Guideline Route of exposure	**Route of exposure, duration**	**Species, Strain, Sex, No/group**	**Dose levels ppm (mg/kg bw/d)**	**Results Main effects/ Target organs/ Tumors**	**NO(A)EL ppm (mg/kg bw/d)**	**LO(A)EL ppm (mg/kg bw/d)**	**Remarks**	**Reference**
OECD 453	Oral/diet 24 months	Rat, Crl:CD (SD)BR 60M + 60F	0-50-1900-12000 (M: 0-2-72-484; F: 0-2.2-91-555)	≥50 ppm: corneal opacity, keratitis (M+F); liver wt ↑ (M); bile duct hyperplasia (M+F) 12000 ppm: cystic kidneys (M)	< 50 (M: < 2; F: < 2.2)	50 (M: 2; F: 2.2)	None	Pavkov, K.L., Taylor, D.O.N (1990); report no. T-12900C
OECD 453 with deviations	Oral/diet 24 months	Rat, Crl:CD (SD)BR 50M + 50F	0-1-10-20-50 (M: 0-0.04-0.4-0.8-2; F: 0-0.05-0.5-0.9-2.4)	≥ 1 ppm: kidney enlarge-ment,cysts, pelvis dilation (M) ≥ 10 ppm: corneal inflammat-ion and vascularisat-ion (M)	M: < 1 (< 0.04)	M: 1 (0.04)	Reduced number of tissues weighed; histopatho-logy only for eyes and Harderian glands	Potrepka, R. F., Turnier, J.C. (1991); report no. T-13242
OECD 451	Oral/diet 18 months	Mouse, Crl:CD-1(ICR) BR 50M + 50F	0-40-350-3000-7000 (M: 0-4.2-38-332-797; F: 0-5.2-46-409-909)	≥ 350 ppm: liver wt ↑ (F); mammary gland hyperplasia (F) ≥ 3000 ppm: survival ↓ (F) 7000 ppm: liver: single cell necrosis; kidney: papillary necrosis and tubule dilation (M+F), papillary calcification and pelvis dilation (F)	M: 3000 (332) F: 40 (5.2)	M: 7000 (797) F: 350 (46)	None	Pettersen, J.C., Turnier, J.C. (1990); report no. T-12904

5.7.2 Carcinogenicity: inhalation

No data are available.

5.7.3 Carcinogenicity: dermal

No data are available.

5.7.4 Carcinogenicity: human data

No data are available.

5.7.5 Other relevant information

No other relevant information is available.

5.7.6 Summary and discussion of carcinogenicity

No carcinogenic potential of sulcotrione was observed and classification for carcinogenicity is not required.

RAC opinion

A comment received during the public consultation highlighted the occurrence of mammary adenocarcinomas from 3000 ppm (409 mg/kg/d) in female mice, as reported in the Draft Assessment Report (DAR) produced for the review of sulcotrione in accordance with Directive 91/414/EEC, that may be relevant for classification.

The relevant data from the three carcinogenicity studies that were presented in the DAR are given in the table below.

Table R2: Summary of oral carcinogenicity

Method	**Dose levels**	**Observations and remarks** **(effects of major toxicological significance)**
Oral/diet 24 months Rat, Crl:CD (SD)BR 60M + 60F OECD 453 Pavkov, K.L., Taylor, D.O.N (1990); report no. T-12900C	0, 50, 1900, 12 000 ppm Equivalent to: Males: 0, 2, 72, 484 mg/kg/d Females: 0, 2.2, 91, 555 mg/kg/d	Sulcotrione did not affect survival of either males or females. The only treatment-related clinical signs were those associated with corneal lesions. By the end of the study, total body weight gain was reduced compared with the controls by up to 16 % in males and up to 10.5 % in females. Food consumption was unaffected. There were no effects on the organ weights of females at either one year or two years. In males, liver and kidney weights were increased. Haematological and clinical chemistry parameters were unaffected by treatment. Apart from corneal lesions, findings at the two-year sacrifice were largely limited to the renal system: increased incidence of kidney cysts, kidney enlargement, enlarged renal lymph nodes in males of all dose groups; and increased incidence of pelvis dilatation in all dose groups. An increased severity of chronic progressive nephrosis during the second year of the study, which was statistically significant at 12 000 ppm, suggested a treatment-related effect, as did the similar pattern of

<table>
<tr><td></td><td></td><td>cystic kidney change.

Additional findings were focal stomach discolouration at 12 000 ppm and an increase in bile duct hyperplasia (males at 50 and 12 000 ppm; females of all dose groups).</td></tr>
<tr><td>Oral/diet

24 months

Rat, Crl:CD (SD)BR 50M + 50F

OECD 453 with deviations

Potrepka, R. F., Turnier, J.C. (1991); report no. T-13242</td><td>0, 1, 10, 20, 50 ppm

Eequivalent to:

Males: 0, 0.04, 0.4, 0.8, 2 mg/kg/d

Females: 0, 0.05, 0.5, 0.9, 2.4 mg/kg/d</td><td>Reduced number of tissues weighed; histopathology only for eyes and Harderian glands.

Survival was not affected by sulcotrione administration.

Non-tumour findings

Food consumption was largely unaffected, but body weight gain was reduced from 20 ppm. Mean liver weight was increased in male rats at 50 ppm.

At gross necropsy, male rats of all dose groups showed increased incidences of kidney cysts, enlarged kidneys and distended renal pelves. Focal discolourations of the stomach were observed in males at 20 and 50 ppm. In males, corneal vascularisation and inflammation were noted at histopathology.

Tumour findings

Only limited histopathology was performed. In the tissues investigated, there were no tumour-related findings.</td></tr>
<tr><td>Oral/diet

18 months

Mouse, Crl:CD-1(ICR) BR 50M + 50F

OECD 451

Pettersen, J.C., Turnier, J.C. (1990); report no. T-12904</td><td>0, 40, 350, 3000, 7000

Equivalent to:

Males: 0, 4.2, 38, 332, 797 mg/kg/d

Females: 0, 5.2, 46, 409, 909 mg/kg/d</td><td>There were no treatment-related clinical signs in males or females at any dose. Survival of males was unaffected by treatment, but the survival of females in the 3000 and 7000 ppm groups was reduced between weeks 50 and 65.

Non-tumour findings

There were no consistent effects on food consumption. Decreases in the body weight of male mice in the 7000 ppm group reached a magnitude of 13-19% on occasion, although the changes were not consistent throughout the study. There was not a dose-response relationship in the changes in female body weight.

No treatment-related ocular effects occurred during the study. There were no treatment-related changes in the haematology parameters.

Organ weights of males were unaffected by treatment. The absolute and relative liver weights of females were increased at 3000 (relative increase of 28%) and 7000 (relative increase of 128.5%) ppm, and also slightly increased at 350 ppm (relative increase of 16%).

At gross necropsy, there were no treatment-related observations in males. In females, the incidence of rough or pitted kidneys was increased at 7000 ppm. On histopathology, there was an increased incidence of individual hepatic cell necrosis in males and females at 7000 ppm. In the kidneys, findings at 7000 ppm included an increased incidence and/or severity of papillary necrosis and tubule dilation in males, and of papillary calcification and necrosis, and pelvis and tubule dilation in females. There was a slight increase in the incidence of mammary gland hyperplasia in the females, scored as very slight to slight: 2/46, 2/45, 9/46, 11/47, 11/46 at 0, 40, 350, 3000 and 7000 ppm.

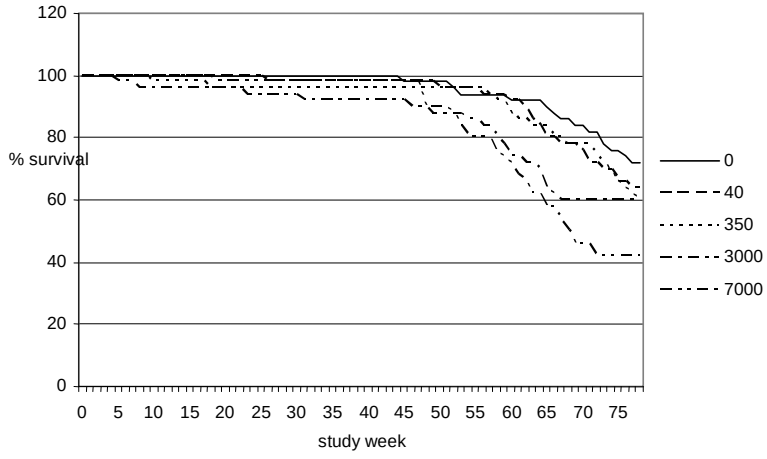
Tumour findings

There was a slight increase in the incidence of primary malignant mammary tumours in females at 3000 and 7000 ppm, none of which was statistically significant, as indicated below:
<table>
<tr><th>Sulcotrione (ppm)</th><th>Tumour incidence</th><th>Day of death</th><th>Diagnosis</th></tr>
<tr><td>0</td><td>0/46 (0%)</td><td>-</td><td>-</td></tr>
<tr><td>40</td><td>1/45 (2.2%)</td><td>TS</td><td>Adenocarcinoma</td></tr>
<tr><td>350</td><td>0/46 (0%)</td><td>-</td><td>-</td></tr>
</table></td></tr>
</table>

		3000	3/47 (6.4%)	435 TS TS	Adenocarcinoma Adenocarcinoma Adenocarcinoma
		7000	3/46 (6.5%)	TS TS 481	Carcinosarcoma Adenocarcinoma Adenocarcinoma
		The historical control range from 6 studies was 0% to 2%. There were no mammary tumours in male mice. There were no other tumour findings.			

In the 18-month study by Pettersen and Turnier (1990), the incidences of mammary adenocarcinomas in female mice were: 0%, 2.2%, 0%, 6.4%, 6.5% at 0, 40, 350, 3000, 7000 ppm, respectively; none of the increased incidences was statistically significant. The historical control range for this tumour type in mice was 0 to 2%. The tumours were seen only late in the study, the majority of them occurring in terminal-kill animals. There were no tumours in the mammary glands of male mice. Clinical signs of toxicity were not noted in any dose group, and there were no consistent changes in the body weights of female mice. At necropsy, absolute and relative liver weights were statistically significantly increased in females at 3000 and 7000 ppm. Non-neoplastic findings in females, which occurred with an increased incidence only in the 7000 ppm group, included rough/pitted kidneys, hepatic cell necrosis and renal pelvis and tubule dilation. Survival of male mice was unaffected by sulcotrione. The survival of female mice during the study is shown in the figure below (copied from the DAR).

Figure 1. Percent survival in female mice over 78 weeks of sulcotrione administration



Because of the reduced survival of female mice in the 3000 and 7000 ppm groups, it was concluded in the DAR that the maximal tolerated dose (MTD) was exceeded at both of these doses.

RAC has considered the information provided in the CLH report together with the additional information included above. A classification for carcinogenicity in Category 1A (based on human

evidence) is clearly not appropriate. Considerations that lead to the conclusion that Category 1B is also not appropriate are the non-genotoxic nature of the substance; an increased tumour incidence only in one tissue, in one sex of one species; and the late stage of the study at which the tumours were observed, indicating that the tumour latency was not reduced. It therefore remains to decide between Category 2 and no classification.

A key issue pertinent to the interpretation of the tumour findings in mice was the general toxicity observed at the higher two dose levels. In its assessment, the Dossier Submitter considered that both 3000 and 7000 ppm were above the MTD in female mice, based on the reduced survival of both these groups (survival of both groups was reduced by at least 33% compared with the controls at week 65). In contrast, the submitter of the comment received during the public consultation questioned this view, stating that, because the survival of the 3000 ppm group was similar to the controls at the end of the study and the body weight was unaffected, this dose was not above the MTD. As is clear from the graph above, death rates in the top two dose groups increased drastically between approximately weeks 50 to 65. In contrast, in males, survival was not affected and there were no signs of toxicity. On reflection, therefore, RAC is of the opinion that 3000 and 7000 ppm were probably excessive doses in female mice, and as a consequence the relevance of any tumours at these doses should be interpreted with caution. Additional factors were that the increased tumour incidences were low and without statistical significance, were just outside the historical control range, and they were sex- and species-specific, occurring only in toxicologically compromised animals. Overall, therefore, RAC agrees with the Dossier Submitter that the available information does not support a classification of sulcotrione for carcinogenicity

5.8 Toxicity for reproduction

5.8.1 Effects on fertility

As in other rat studies, the adults (mainly the males) in the 2-generation studies showed effects on cornea, kidney and liver. The overall NOAEL for parental toxicity was 0.06 mg/kg bw/day based on increased liver and kidney weights, renal pelvis dilation and nephropathy observed at 0.6 mg/kg bw/day. No adverse effect on reproductive parameters was observed, therefore the NOAEL for reproductive effects was the highest dose tested of 340 mg/kg bw/day. Based on increased pup mortality, decreased body weight gain, delay in eye opening and urinary tract abnormalities apparent at 14 mg/kg bw/day, the NOAEL for offspring was 0.6 mg/kg bw/day. Small or misshaped kidneys were noted in a few offspring exposed to sulcotrione at a dose of 14 mg/kg bw/day (225 ppm) or higher.

Table 19: Summary of effects on fertility

Method/ Guideline	**Route of exposure**	**Species, Strain, Sex, No/group**	**Dose levels ppm**	**Critical effect Parental, Offspring (F1, F2)**	**NO(A)EL Parental toxicity ppm (mg/kg bw/d)**	**NO(A)EL reproductive toxicity ppm (mg/kg bw/d)**	**NO(A)EL offspring toxicity ppm (mg/kg bw/d)**	**Reference**
Similar to OECD 416	Oral/diet	Rat, Crl:CD (SD)BR VAF/Plus, 25M + 25F	0-10-225-5000	P: corneal opacity, vascularisation, keratitis (M); liver wt ↑, hepatocellular vacuolation kidney wt ↑ F1, F2: mortality ↑; bw gain ↓, eye opening delayed; corneal opacity; renal pelvis dilation (M), protein filtrate (M), kidney abnormalities	< 10 (M: < 0.5; F: < 0.7)	5000 (340)	10 (0.6)	Gilles, P.A., Minor, J.L., Taylor, D.O.N. (1989); report no. T-12962
OECD 416	Oral/diet	Rat, Crl:CD (SD)BR VAF/Plus 25M + 25F	0-1-10-225	P: bw gain ↓; corneal opacity; liver wt ↑; kidney wt ↑, nephropathy F1, F2: mortality ↑; bw gain ↓, eye opening delayed; corneal opacity; renal pelvis dilation, kidney abnormalities	M: 1 (0.06) F: 10 (0.7)	225 (M: 16; F: 18)	10 (0.7)	Minor, J.L., Morrissey, R.L. (1990); report no. T-13219

5.8.2 Developmental toxicity

Sulcotrione was not teratogenic in rats and, specifically, did not induce kidney malformations when administered to pregnant females, indicating that renal pelvis dilation and other urinary tract

abnormalities develop (or are induced) postnatally in the rat. Maternal toxicity was limited to decreased body weight and food consumption, and increased liver weight at the highest dose of 1000 mg/kg bw/day. In the foetuses, the high dose produced a slight decrease in foetal weight and a slight increase in incomplete sternal ossification. Thus, both the maternal and the foetal NOAEL was 100 mg/kg bw/day. In rabbits, a decreased maternal food consumption and body weight loss were observed during early pregnancy at 300 mg/kg bw/day, resulting in a maternal NOAEL of 100 mg/kg bw/day. No adverse effect was observed in the foetuses and the NOAEL for developmental toxicity was the highest dose tested (300 mg/kg bw/day).

Table 20: Summary for developmental toxicity

Method/ Guideline	**Route of exposure, Duration**	**Species, Strain, No/group**	**Dose levels mg/kg bw**	**Critical effects 1) dams 2) fetuses**	**NO(A)EL Maternal toxicity mg/kg bw/d**	**NO(A)EL Teratogenicity Embryotoxicity mg/kg bw/d**	**Remarks**	**Reference**
OECD 414	Oral, pregnancy day 6-20	Rat, Crl:CD(SD)BR VAF/Plus 23F	0-10-100-1000	1) Food ↓; liver wt ↑ 2) Bw ↓; sternum ossification ↓;	100	100	Vehicle: corn oil	Gilles, P.A. (1988); report no. T-12976
OECD 414	Oral, pregnancy day 7-19	Rabbit, Hrp: (NZW)SPF 18F	0-30-100-300	1) Food ↓; bw loss (initial) 2) -	100	300	Vehicle: water	Minor, J.L. (1988); report no. T-12959

5.8.3 Human data

No data are available.

5.8.4 Other relevant information

Based on the urinary tract abnormalities observed in rat offspring at weaning and as adults, the EFSA Scientific Report (2008) 150, Conclusions on the Peer Review of Sulcotrione, proposed classification as **Xn; R63 "Possible risk of harm to the unborn child"**.

5.8.5 Summary and discussion of reproductive toxicity

Sulcotrione was not teratogenic and did not affect reproduction. Postnatal viability and development were influenced only at doses that also induced organ toxicity in the parents. Renal pelvis dilation was not apparent at birth but became a frequent finding in high dose pups from postnatal day 4 to adult age. This abnormality can be induced prenatally with other substances and is then indicative either of retarded development (usually associated with lower foetal weight) or of a functional impairment in the urinary tract which leads to retention of urine, dilation of ureters and distension of the developing kidney pelvis due to the increase in pressure. However, with sulcotrione no such effects occurred in the prenatal toxicity study even though the highest dose administered to the rats dams was 3 times the dose achieved in the two-generation study. Similarly, small or misshaped kidneys were found in a few high dose offspring in the two-generation studies after the lactation period but not in the developmental toxicity study where evaluation of foetuses is performed at term of pregnancy. This suggests that the urinary tract abnormalities seen in the offspring in the two-

generation studies were of postnatal origin and not a consequence of exposure in utero. As no specific impairments of fertility and embryo-foetal development have been observed a classification for fertility effects or developmental toxicity is not proposed.

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Effects on or via lactation

This end-point was not addressed by the Dossier Submitter. See the considerations and conclusions of RAC below

RAC opinion

Reproductive Toxicity

Fertility

Sulcotrione did not demonstrate any adverse effects on fertility in two two-generation studies in rats. The Dossier Submitter did not propose a classification for fertility effects.

No information opposing this evaluation was received during the public consultation or RAC discussions. It was therefore confirmed by RAC not to support a classification for fertility effects.

Developmental toxicity

The possibility of the kidney effects seen post-natally in pups in the two-generation studies being a consequence of *in utero* exposure was raised during the public consultation and discussed by RAC. During these discussions, further information on and an assessment of the increases in pup death in some sulcotrione-treated groups was also requested.

The renal findings and information on pup deaths in the two-generation studies are summarised in the tables below (information taken by the Rapporteur from the Draft Assessment Report produced for the review of sulcotrione in accordance with Directive 91/414/EEC).

Table R3. Renal findings in the first two-generation study in rats (dietary exposure)

	P0 (males)				**P1 (males)**			
approx mg/kg/d	**0**	**0.5**	**15**	**340**	**0**	**0.5**	**15**	**340**
gross necropsy:								
kidney, pelvis dilated	4%	0%	4%	8%	4%	32%*	64%*	44%*
histopathology:								
protein filtrate	20%	64%*	68%*	60%*	40%	72%*	88%*	80%*
tubular basophilia	64%	60%*	64%	80%	60%	88%	88%*	92%*
pelvis dilatation	0%	0%	0%	4%	4%	28*	64%*	48%*
	F1B (males & females)				**F2B (males & females)**			
pups day 4:								
urinary tract abnormalities	11%	11%	20%	8%	10%	23%	23%	33%

dilated kidney pelvis	2%	0%	9%	3%	3%	7%	14%	27%
<u>pups at weaning:</u>								
urinary tract abnormalities	6%	11%	17%	18%	11%	24%	30%	19%
dilated kidney pelvis	6%	11%	17%	16%	6%	11%	25%	12%
kidney misshaped	0%	0%	0%	4%[1]	0%	0%	0%	0%
small kidneys	0%	0%	4%	0%[2]	0%	0%	0%	8%

* = statistically significant. [1] = finding also occurred in two P1 parents. [2] = finding occurred in one P1 parent.

Table R4. Renal findings in the second two-generation study in rats (dietary exposure)

	P0 (males)				**P1 (males)**			
approx mg/kg/d	**0**	**0.06**	**0.7**	**17**	**0**	**0.06**	**0.7**	**17**
<u>gross necropsy:</u>								
kidney, pelvis dilated	8%	0%	12%	4%	0%	4%	8%	40%*
<u>histopathology:</u>								
nephropathy as a summation of several histopathology findings (as reported in the DAR)	24%	20%	60%	48%	24%	12%	72%	64%
	F1B (males & females)				**F2B (males & females)**			
<u>pups day 4:</u>								
urinary tract abnormalities	12%	24%	18%	38%	19%	35%	27%	48%
dilated kidney pelvis	9%	15%	10%	23%	12%	15%	17%	30%
<u>pups at weaning:</u>								
urinary tract abnormalities	6%	8%	11%	31%	11%	12%	14%	24%
dilated kidney pelvis	4%	7%	12%	30%	6%	10%	12%	15%
kidney misshaped	0%	4%	0%	8%	0%	0%	0%	4%
small kidneys	0%	0%	0%	12%	0%	0%	0%	12%

* = statistically significant

Table R5. Pup mortality – first two-generation study in rats

	F1A				**F1B**			
mg/kg/d	**0**	**0.5**	**15**	**340**	**0**	**0.5**	**15**	**340**
Litters with pup mortality > 1 (PND 0-21)	1	2	9*	5*	1	2	0	7*
Pre-weaning losses	-	-	-	-	9%	9%	2%	17%
Pup wt PND 0		NC	NC	NC		NC	NC	NC
Pup wt PND 21		-4%	-5%	-12%*		-5%	-7%*	-21%*

Total maternal total food intake during lactation		NC	NC	-13%		NC	NC	-10%
	F2A				**F2B**			
Litters with pup mortality > 1 (PND 0-21)	3	1	6	10%	0	0	5*	7*
Pre-weaning losses	-	-	-	-	3%	5%	13%	14%
Pup wt PND 0		NC	NC	NC		NC	NC	NC
Pup wt PND 21		NC	-10%*	-13%*		NC	-11%*	-21%*
Total maternal food intake during lactation		NC	NC	-12%*		NC	NC	-13%*

* = statistically significant. NC = no change from controls

Table R6. Pup mortality – second two-generation study in rats

	F1			
mg/kg/d	**0**	**0.06**	**0.7**	**17**
Litters with pup mortality > 1 (PND 0-21)	1	1	3	7
Pre-weaning losses	5%	3%	5%	13%
Pup wt PND 0		NC	NC	NC
Pup wt PND 21		NC	NC	-6%
Maternal food intake pregnancy		NC	NC	-9%*
Maternal terminal body weight		NC	-5%	-9%*
	F2			
Litters with pup mortality > 1 (PND 0-21)	4	2	1	4
Pre-weaning losses	9%	5%	3%	13%
Pup wt PND 0		NC	NC	NC
Pup wt PND 21		NC	NC	-6%*
Maternal food intake pregnancy		NC	NC	-7%*
Maternal terminal body weight		NC	NC	-3%

* = statistically significant. NC = no change from controls

In both of the two-generation studies, abnormalities of the urinary tract were increased in the P1 adult males relative to the controls (there were no statistically significant differences in any of the female dose groups), but were generally less apparent in the P0 parental animals. This was particularly true in the case of the gross necropsy findings (pelvis dilatation). The increased incidence of histopathology findings in the P0 animals treated with sulcotrione could not have been the result of developmental toxicity. The increased incidence of kidney effects in the P1 compared with the P0 animals was likely to be a consequence of the longer overall exposure of the P1 animals to sulcotrione (i.e., *in utero*, through lactation, into adulthood) compared with the P0 (where dosing started in adulthood); this is consistent with the findings of repeated dose studies, in which adverse renal effects only became apparent after a long duration of exposure.

Similar urinary tract findings were observed in F1 and F2 pups examined at post natal day (PND) 4 and at weaning. During the EFSA review of sulcotrione in accordance with Directive 91/414/EEC, it was noted that hepatocyte nuclear factor 1 beta (HNF1β), a transcription factor associated with congenital abnormalities of the kidney and urinary tract in humans (including solitary functioning kidney, renal dysplasia, glomerulocystic kidney disease and oligomeganephronia; Bohn S. *et al*., 2003, Journal of American Society of Nephrology, **14**, 2033-2041), is induced by HPPD inhibitors. Gene expression analyses in a mechanistic study (Kroetlinger *et al.*, 2003) indicated that sulcotrione resulted in the up-regulation of HNF1β. Although it could be concluded that the kidney effects observed in pups exposed *in utero* were thus a developmental effect, a confounding point is that similar findings were not observed in standard developmental toxicity studies, in which sulcotrione was administered at doses up to 1000 mg/kg/d, which were far higher than those employed in the two-generation studies. Although small and misshapen kidneys were observed in some pups, they were only apparent at weaning. Rather, the kidney findings in the two-generation studies were consistent with the results of the repeated dose studies, in which increased organ weight, pelvis dilatation and tubular basophilia were reported, indicating that the observed effects were more likely to be the result of direct toxicity rather than a specific developmental effect.

The significance of the renal findings is difficult to interpret. As discussed in the section on repeated dose toxicity, there is insufficient information to judge their severity. Besides, the results in pups were far from consistent, with, often, discrepancies between the generations within a study and the absence of dose-response relationships. Background levels of the findings were sometimes rather high, with no information on the variation within groups. Furthermore, one would expect the incidence and severity of any toxicity to be higher in the first study, in which doses of up to 340 mg/kg/d were administered, than in the second, in which the maximum dose was only 17 mg/kg/d (the same strain of rat was used in each study); this was not the case. The incidence of small and misshapen kidneys in the first study was inconsistent between the F1 and the F2 generations, and, additionally, there was not always a clear dose-response relationship in either study. This finding of small/misshapen kidneys was not clearly defined and could be a subjective observation; no further information was available to RAC to enable a judgement of the severity or otherwise of these effects, and so their relevance is unclear. Overall, therefore, the uncertainties that surround the renal data from the two-generation studies are considerable.

It was clear that *in utero* exposure to sulcotrione had no effect on the numbers of live litters, live litter size or pup weight at birth. Pup deaths were increased during lactation in four cohorts (with statistical significance in three of these cohorts) of the first two-generation study and in both generations of the second two-generation study. However, it was recognised that the number of deaths even at the highest tested dose was not high (isolated incidences across litters) and that the dose-response was shallow; this observation was consistent with the results from the repeated dose studies. The cause of the increased pup deaths in these studies was not determined. Information on the time of their occurrence during the lactation period was not available in the dossier submitter's report nor in the draft assessment report, but was subsequently provided to the rapporteurs by industry. This information indicated that, generally, most of the deaths occurred between post-natal days 0 and 4. These deaths early in the post-natal period indicated that a classification for developmental toxicity rather than lactation was appropriate.

RAC concluded that, because of the uncertainty surrounding the early pup deaths, a classification for developmental toxicity in category 2 (Repr Cat 2 – H361d) was appropriate. (Repr Cat 3; R63 under DSD).

CLP: Repr. 2; H361d: Suspected of damaging the unborn child

DSD: Repr. Cat. 3; R63: Possible risk of harm to the unborn child

RAC opinion

Effects on or via lactation

The possibility of the kidney effects seen post-natally in pups in the two-generation studies being a consequence of exposure via the milk was not discussed in the original Dossier Submitter's classification rationale, but was raised during the public consultation. In response, the Dossier Submitter argued that the observations in the offsprings' kidneys were related to increased tyrosine concentrations in the milk, as a result of hypertyrosinaemia in the dams, and so were not relevant to humans, since the development of plasma tyrosine levels above the threshold for (ocular) toxicity is not likely after human exposure to HPPDase-inhibiting herbicides.

A classification for effects on or via lactation was discussed further by RAC. The effects on the pups' kidneys were consistent with the findings in repeated dose toxicity studies and appeared to indicate that sulcotrione was causing direct toxicity rather than a specific developmental effect. The absence of kidney effects and malformations in foetuses at term in developmental studies, in doses that resulted in maternal toxicity, supported this conclusion. Since the observed effects developed during the lactation period, it is possible that direct toxicity occurred via lactation. The adverse effects were first recorded on PND 4, and so direct dietary exposure by ingestion of the dams' food (which occurs from about post-natal day 14) could be excluded. Notwithstanding, opportunistic intake from the dosed food may have contributed to the effects seen at weaning. There appeared to be no evidence that the kidney findings were related to tyrosine concentrations, as postulated by the Dossier Submitter, and the repeated-dose section (section 5.6.5) included the Dossier Submitter's conclusion that the renal effects were at least partially the result of direct toxicity and/or excretion of the test substance. Therefore, the argument that the observed effects were not relevant to humans was not accepted.

However, as indicated in the above section on developmental toxicity, further evaluation of the renal effects in pups has led to doubt over their significance. In particular, there were inconsistencies within and between studies, and the far higher doses employed in the first study compared with the second did not result in higher incidences or increased severity of the findings. Overall, therefore, the relevance of these effects is unclear.

Additional information on the pup deaths observed in the two-generation studies, provided by industry during the RAC discussions, indicated that they mainly occurred early in the post-natal period (between days 0 and 4). RAC therefore considered it unlikely that the deaths were the result of an adverse effect on or via lactation but were more likely to have been a developmental toxicity effect. Furthermore, the very low log P of sulcotrione indicated that it was improbable that the substance would be present in milk in sufficient quantities to cause direct toxicity to the pups.

RAC is therefore of the opinion that the evidence does not support a classification for adverse effects on or via lactation.

5.9 Other effects

5.10 Neurotoxicity

In the 90-day dog study, neurological signs of toxicity were seen in parallel with systemic toxicity at 300 and 800 mg/kg bw/day, but these signs were not reproducible in the 1-year dog study. No specific neurotoxicity studies were required.

RAC opinion
No further classification is justified.

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

Sulcotrione (technical) is not explosive in the sense of EEC method A14.

6.2 Flammability

Sulcotrione (technical) not highly flammable in the sense of EEC method A10.

6.3 Oxidising potential

Sulcotrione (technical) has no oxidising properties in the sense of EEC method A17.

RAC assessment

No comments were received in relation to these endpoints, and RAC agreed fully with the conclusions presented by the Dossier Submitter: no classification was required for explosivity, flammability or oxidising potential.

7 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental fate properties assessment for sulcotrione is based on the Draft Assessment Report and Proposed Decision of Germany prepared in the context of the inclusion of sulcotrione in Annex I of Council Directive 91/414/EEC (DAR July 2006 + Final addendum June 2008, RMS Germany).

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

The acute toxicity of sulcotrione and its major metabolite CMBA to fish is summarised in Table 21.

Table 21: Acute toxicity of sulcotrione and its major metabolite CMBA to fish

Guideline/ Test method	**Species**	**Exposure**		**Results**		**Reference**
		Design	**Duration (h)**	**Endpoint**	**Value (mg/L)**	

Parent sulcotrione						
OECD 203	*Oncorhynchus mykiss*	static	96	LC_{50}	227 m.m.[1)]	Tapp, J.F. et al. (1989), Document No: BL/B/3560; WAT 94-00904
Test item: ICIA 0051 techn.; specification: Batch no. S264; Purity: 96 % Test conditions: pH-range: 3.8 – 8.2; Temp.-range: 14.4 – 14.7°C						
OECD 203	*Cyprinus carpio*	static	96	LC_{50}	240 m.m.[1)]	Tapp, J.F. et al. (1989), Document No: BL/B/3575; WAT 94-00903
Test item: ICIA 0051 techn.; specification: Batch no. S264; Purity: 96 % Test conditions: pH-range: 3.8 – 7.8; Temp.-range: 22.3 – 22.7°C						
Metabolite CMBA						
OECD 203	*Oncorhynchus mykiss*	static	96	LC_{50}	> 180 m.m.[1)]	Brown, D. (1991), Document No: BL4116/B; WAT 2004-1080
Test item: CMSBA; reference WRC/11498-27-24; code T996; Purity: not stated Test conditions: pH-range: 7.8 – 8.0; Temp.-range: 15±1°C						

[1)] m.m. … mean measured concentration

Long-term toxicity to fish

The long term toxicity of sulcotrione and its major metabolite CMBA to fish is summarised in Table 22.

Table 22: Long-term toxicity of sulcotrione and its major metabolite CMBA to fish

Guideline/ Test method	**Species**	**Exposure**		**Results**		**Reference**
		Design	**Duration (d)**	**Endpoint**	**Value (mg/L)**	
Parent sulcotrione						
OECD 204	*Oncorhynchus mykiss*	semi static	28	NOEC	3.2 nom	Sankey, S.A. et al. (1994), Document No: BL5290/B, WAT 95-00544
Test item: ICIA 0051 techn.; specification: Batch no. P21; Purity: 95.2 % Test conditions: pH-range: 6.7 – 7.6; Temp.-range: 14.3 – 15.6°C						
Metabolite CMBA						
OECD 204	*Oncorhynchus mykiss*	semi static	28	NOEC	> 120 nom	Kent, S.J. (1995), Document No: BL5470/B; WAT 2004-1081
Test item: CMSBA; reference Y06913/004; Batch no. 16708; Purity: 97.8 % Test conditions: pH-range: 4.7 – 7.6; Temp.-range: 14.9 – 15.3°C						

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

The acute toxicity of sulcotrione and its major metabolite CMBA to invertebrates is summarised in Table 23.

Table 23: Short-term toxicity of sulcotrione and its major metabolite CMBA to invertebrates

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (h)	Endpoint	Value (mg/L)	
Parent sulcotrione						
OECD 202, part 1	*Daphnia magna*	static	48	EC_{50}	> 848 m.m. [1)]	Farrelly, E. et al. (1992), Document No: RJ1166B, WAT 94-00900
Test item: ICIA 0051 techn.; specification: Batch no. P21; Purity: 94.0 % Test conditions: pH-range: 5.6 – 8.1; Temp.-range: 19.5 – 19.9°C						
Metabolite CMBA						
OECD 202, part 1	*Daphnia magna*	static	48	EC_{50}	233 m.m. [1)]	Brown, D. (1991), Document No: BL4117/B; WAT 2004-1084
Test item: CMSBA; reference Y06913/004; Batch no. 16708; Purity: 97.8 % Test conditions: pH-range: 4.7 – 7.6; Temp.-range: 14.9 – 15.3°C						

[1)] m.m. … mean measured concentration

Long-term toxicity to aquatic invertebrates

The long-term toxicity of sulcotrione and its major metabolite CMBA to invertebrates is summarized in Table 24.

Table 24: Long-term toxicity of sulcotrione and its major metabolite CMBA to invertebrates

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
Parent sulcotrione						
OECD 202, part 2 (1984); OECD 211	*Daphnia magna*	Static renewal	21	NOEC	75 nom	Dorgerloh, M. (2001), Document No: DOM 21048, WAT 2004-1085

(1998)						
Test item: ICIA 0051 techn.; specification: Batch no. P21; Purity: 94.0 % Test conditions: pH-range: 7.3 – 8.4; Temp.-range: 18.8 – 22.0°C						
Metabolite CMBA						
OECD 202, part 2	*Daphnia magna*	Static renewal	21	NOEC	≥ 120 nom	Kent, S.J. et al. (1995), Document No: BL5495/B; WAT 2004-1086
Test item: CMSBA; reference Y06913/004; Batch no. 16708; Purity: 97.8 % Test conditions: pH-range: 6.6 – 8.2; Temp.-range: 20.0 – 20.5°C						

7.1.1.3 Algae and aquatic plants

The toxicity of sulcotrione and its major metabolite CMBA to algae and aquatic plants is summarised in Table 25.

Table 25: Long-term toxicity of sulcotrione and its major metabolite CMBA to algae and aquatic plants

Guideline/ Test method	**Species**	**Exposure**		**Results**		**Reference**
		Design	**Duration (h)**	**Endpoint**	**Value (mg/L)**	
Parent sulcotrione						
OECD 201	*Selenastrum capricornutum*	static	96	E_rC_{50} NOEC	3.5 m.m.[1)] 0.19 m.m. [1)]	Smyth, D.V. et al. (1992), Document No: BL4575/B, WAT 94-00897
Test item: ICIA 0051 techn.; specification: Batch no. P21; Purity: 95.0 % Test conditions: pH-range: 7.1 – 10.0; Temp.-range: 23.6 – 23.9°C						
OECD 201	*Anabaena flos-aquae*	static	72	E_rC_{50} NOErC	54 nom 4.6 nom	Seyfried, B. (2002), Document No.: 816276, WAT 2004-1087
Test item: ICIA 0051 techn.; specification: Batch no. P22; Purity: 95.3 % Test conditions: pH-range: 7.6 – 8.8; Temp.-range: 23.0°C						
OECD 221 (Draft October 2000)	*Lemna gibba*	static	7 d	E_rC_{50} $E_{AUC}C_{50}$ E_bC_{50} NOEC	0.56 m.m.[1)] 0.0062 m.m.[1)] 0.051 m.m.[1)] 0.0062 m.m.[1)]	Bätscher, R. (2002), Document No.: 826007, WAT 2004-1088
Test item: sulcotrione; specification: Batch no. P22; Tox no. 05854-00; Purity: 95.3 % Test conditions: pH-range: 7.5 (adjusted) – 8.9; Temp.-range: 23.0°C						

Metabolite CMBA						
OECD 201	*Selenastrum capricornutum*	static	72	E_rC_{50} E_bC_{50} NOEC	33 nom 34 nom 32 nom	Smyth, D.V. et al. (1994), Document No: BL5176/B, WAT 94-01144
Test item: CMSBA; reference WRC-12702-28; WRC code 10573-21-1; Purity: 98 % Test conditions: pH-range: 3.7 – 10.0; Temp.-range: 23.9 – 24.2°C						
OECD 221 (Draft October 2000)	*Lemna gibba*	static	7 d	E_rC_{50} $E_{AUC}C_{50}$	≥ 100 nom ≥ 100 nom	Bätscher, R. (2002), Document No.: 843567, WAT 2004-1089
Test item: CMSBA; Batch no. M16837; Purity: 98.1 % Test conditions: pH-range: 7.4 (adjusted) – 8.8; Temp.-range: 23.0 – 24.0°C						

[1)] m.m. … mean measured

The study with the aquatic plant *Lemna gibba* can be regarded as the key study for the aquatic toxicity of sulcotrione and hence for classification and labelling. Therefore the study is presented in more detail below:

Author: Bätscher, R. (2002)
Report: Toxicity of sulcotrione to the aquatic higher plant *Lemna gibba* in a 7-day static growth inhibition test.
Source: RCC Ltd, Itingen, CH
Report No.: 826007; unpublished report
Document No.: WAT 2004-1088
Guidelines: OECD 221 (Draft October 2000).
Deviations: None
GLP: Yes (certified laboratory)
Validity: Acceptable

Material and methods:

Test item: sulcotrione; specification: Batch no. P22; Tox no. 05854-00; Purity: 95.3 %.

Lemna gibba was exposed under static conditions for 7 days. The following nominal test item concentrations were tested: 0.0032, 0.010, 0.032, 0.10, 0.32, 1.0, and 3.2 mg/L. Calculations are based on mean measured concentrations of 0.0037 mg/L (nominal 0.0032 mg/L), 0.0062 mg/L (nominal 0.010 mg/L), 0.015 mg/L (nominal 0.032 mg/L), 0.059 mg/L (nominal 0.10 mg/L), 0.25 mg/L (nominal 0.32 mg/L), 0.86 mg/L (nominal 1.0 mg/L), and 2.54 mg/L (nominal 3.2 mg/L).

Findings and observations:

Table 26: Effects on the growth rate after 7 days test duration (based on mean measured concentrations)

Test item	**Sulcotrione**
Test system	***Lemna gibba***
Exposure	**7 days, static**
E_rC_{50} (growth rate, day 0-7) [mg/L] 95 % confidence limits	0.56 0.14 - n.d.
$E_{AUC}C_{50}$ (area under the growth curve, day 0-7) [mg/L] 95 % confidence limits	0.062 0.017 - n.d.
E_bC_{50} (final biomass, day 0-7) [mg/L] 95 % confidence limits	0.051 0.018 - 0.18
Lowest observed effect concentration (0-7 day) [mg/L] LOE_rC, $LOE_{AUC}C$, LOE_bC	0.015
Highest tested concentration without effects (0-7 day) [mg/L] NOE_rC, $NOE_{AUC}C$, NOE_bC	0.0062

n.d.: could not be determined

Growth rate related values are preferred, because the validity criteria according to exponential growth are fulfilled.

Conclusion:

The E_rC_{50} for sulcotrione to *Lemna gibba* is 0.56 mg/L. The $E_{AUC}C_{50}$ was found to be 0.062 mg/L and the E_bC_{50} for final biomass was 0.051 mg/L. The NOEC was determined to be 0.0062 mg/L.

7.1.1.4 Sediment organisms

No data available.

7.1.1.5 Other aquatic organisms

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of dossier.

7.2 Terrestrial compartment

Not relevant for this type of dossier.

7.3 Atmospheric compartment

Not relevant for this type of dossier.

7.4 Microbiological activity in sewage treatment systems

Not relevant for this type of dossier.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

7.6 Conclusion on the environmental classification and labelling

Sulcotrione is hydrolytically stable. Sulcotrione was found to be not readily biodegradable in a water/sediment study.

The log Pow of sulcotrione has been determined as ≤ 0.2 (pH 4-9), therefore a bioconcentration in aquatic organisms is unlikely. A bioconcentration study is not available.

Sulcotrione shows a high toxicity to aquatic plants (ErC_{50} = 0.56 mg/L). The lowest endpoints in long- term studies were observed also with aquatic plants (7-d static study NOEC = 0.0062 mg/L). The acute toxicity of sulcotrione to fish and invertebrates is in the mg/L range with a toxicity of LC_{50} = 227 mg/L to fish and of EC_{50} > 848 mg/L to invertebrates. The toxicity to algae is ErC_{50} = 3.5 mg/L.

Conclusion of environmental classification according to Directive 67/548/EEC

In aquatic toxicity studies, ErC_{50} value for aquatic plants are obtained at sulcotrione concentrations < 1 mg/L. Sulcotrione is not readily biodegradable according to the water/sediment study. Considering the results of levels of mineralisation in the simulation studies, sulcotrione is considered not rapidly biodegradable (a degradation of >70% within 28 days) for purposes of classification and labeling. Sulcotrione has a log Kow of ≤ 0.2. Sulcotrione and its major metabolite CMBA do not fulfil the trigger of log Kow ≥ 3 (criterion for bioaccumulating potential conform Directive 67/548/EEC) for not readily biodegradable substances.

Sulcotrione therefore fulfils the criteria for classification with N; R50-53.

Based on ErC_{50} value of 0.56 mg/L obtained for the aquatic plant *Lemna gibba* in a 7-d static study the following specific concentration limits should be applied:

Concentration	Classification
C ≥ 25%	N; R50-53
2.5% ≤ C < 25%	N; R51-53
0.25% ≤ C < 2.5%	R52-53

Where C is the concentration of sulcotrione in the preparation.

Conclusion of environmental classification according to Regulation EC 1272/2008

In aquatic toxicity studies, ErC_{50} value for aquatic plants are obtained at sulcotrione concentrations < 1 mg/L. Sulcotrione is not readily biodegradable according to the water/sediment study. Considering the results of levels of mineralisation in the simulation studies, sulcotrione is considered not rapidly biodegradable (a degradation of >70% within 28 days) for purposes of classification and labeling. Sulcotrione and its major metabolite CMBA have log Kow of ≤ 0.2. Sulcotrione and its major metabolite CMBA do not fulfil the trigger of log Kow ≥ 4 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not rapidly biodegradable substances.

Sulcotrione therefore fulfils the criteria for classification as aquatic environmental hazard acute category 1, H400 and aquatic environmental hazard chronic category 1, H410.

The M-factor for sulcotrione is 1. This value is based on ErC_{50} value of 0.56 mg/L obtained for the aquatic plant *Lemna gibba* in a 7-d static study.

RAC opinion:

The proposal from the Dossier Submitter was to classify the substance as Aquatic acute 1 (H400) and Aquatic chronic 1 (H410) in accordance with CLP, with an M-factor of 1 for both. The corresponding classification according to the DSD is N; R50-53.

A small number of comments were made during the public consultation, none of which proposed a different environmental classification or provided additional data. The comments were mostly editorial with one exception, which concerned the argument for lack of rapid degradability. This is considered further below.

Degradability: Sulcotrione is hydrolytically stable under standard conditions at pH 5, 7 and 9. Aqueous photolysis is not expected to be significant (the experimental half-life was 100 days under natural summer sunlight conditions), and is not relevant to classification. A test for ready biodegradation is not available. Biological degradation of [phenyl-UL-^{14}C]sulcotrione was studied in two water-sediment systems with different organic carbon contents over 100 days at 20ºC in the dark (additional details of this study are available in the DAR and EFSA (2008)). Between 4 and 6 % of the applied radioactivity was attributed to carbon dioxide after 100 days, so mineralisation was negligible. Two processes were seen to occur: a relatively rapid partitioning of sulcotrione to sediment, and gradual transformation to 2-chloro-4-(methylsulfonyl)benzoic acid. One of the comments made during public consultation suggested that the rapid dissipation from water (with a DT_{50} between 6 and 15 days) was indicative of fast primary degradation in the aquatic environment (i.e. with a half-life <16 days). However, dissipation is not the same as degradation. Taking the whole system (water and sediment) into account, around 79% of the applied radioactivity was still present as parent substance after 30 days, and the overall primary degradation half-life of sulcotrione for the whole system was calculated to be 64 days (geometric mean).

Degradation was also investigated in simulation tests in soils under both laboratory and field conditions. Mineralisation to carbon dioxide took place under aerobic conditions, accounting for up to 74 % of applied radioactivity after 120 days.

Since ultimate degradation (mineralisation) in an aquatic water-sediment system and soil did not reach 70% within 28 days, sulcotrione does not meet the criteria for being rapidly degradable or readily biodegradable in the environment.

Bioaccumulation: The log *n*-octanol-water partition coefficient of sulcotrione is ≤ 0.2 at pH 4-9. It is therefore unlikely to bioconcentrate in aquatic organisms, and the criteria for being bioaccumulative are not met.

Ecotoxicity: The lowest reliable ecotoxicity results were as follows (the key study is highlighted in bold):

Trophic level	Species	Short-term result	Long-term result
Fish	*Oncorhynchus mykiss*	96-h LC_{50} = 227 mg/L	*
Aquatic invertebrates	*Daphnia magna*	48-h EC_{50} > 848 mg/L	21-d NOEC = 75 mg/l
Aquatic algae and plants	*Selenastrum capricornutum*	96-h E_rC_{50} = 3.5 mg/L	96-h NOEC = 0.19 mg/L
	Lemna gibba	**7-d E_rC_{50} = 0.56 mg/L**	**7-d NOEC = 0.0062 mg/L**

Note: *The CLP dossier presents a 28-d NOEC of 3.2 mg/L for fish (*Oncorhynchus mykiss*) as a long-term result. However, the test was conducted according to OECD Test Guideline 204, which is effectively a prolonged acute fish toxicity test, with mortality as the major endpoint. It is therefore not an appropriate method to assess long-term effects.

The water solubility of the substance changes significantly with pH, but this does not appear to have been an influence in any of the ecotoxicity studies. The relative sensitivity of aquatic plants reflects the intended function of the substance (a herbicide). The purity profile of the key study complies with the specified composition in Section 1. Although some of the other tests used a test substance of slightly lower purity (94.0% rather than ≥95% w/w), this is not considered important. The long-term invertebrate result is based on nominal concentrations only (the other reported values were based on mean measured concentrations). Since this study was performed under semi-static conditions, it is possible that the actual exposure concentrations (in terms of parent substance) might have been lower. There is also a data gap for long-term fish toxicity. However, given the much higher acute sensitivity of *L. gibba*, these factors are not considered likely to affect the classification.

Classification according to CLP

Acute aquatic hazard: The lowest reliable short-term aquatic toxicity result is a 7-d ErC50 of 0.56 mg/L for *L. gibba* based on mean measured concentrations. This concentration is below the threshold value of 1 mg/l. Sulcotrione is therefore classifiable as Aquatic acute 1 (H400). Since this toxicity value is in the range 0.1 – 1 mg/L, the M-factor (Acute) is 1.

Chronic aquatic hazard: Sulcotrione is considered to be neither rapidly degradable nor readily biodegradable. The lowest reliable long-term aquatic toxicity result is a 7-d NOEC of 0.0062 mg/L for *L. gibba* based on mean measured concentrations. This concentration is below the threshold value of 0.1 mg/L for non-rapidly degradable substances. Sulcotrione is therefore classifiable as Aquatic chronic 1 (H410). Since this toxicity value is in the range 0.001 – 0.01 mg/L, the M-factor (Chronic) is 10. [Note: the CLH dossier proposed an M-factor of 1, based on the surrogate approach using the acute toxicity result and environmental fate data, since the 2nd ATP had not been implemented at the time the dossier was submitted.]

Classification according to DSD

The lack of rapid degradation or ready biodegradation and 7-d E_rC50 of 0.56 mg/L mean that sulcotrione fulfils the criteria for classification with N; R50-53. The following specific concentration limits are applicable:

Concentration of sulcotrione in the mixture, C (w/w)	Classification of the mixture
$C \geq 25\%$	N; R50-53
$2.5\% \leq C < 25\%$	N; R51-53

0.25% ≤ C < 2.5%	R52-53

In summary, the RAC agrees with the original proposal of the dossier submitter, with one small modification relating to the M-factor for Aquatic Chronic classification, due to the change in legislation that has occurred since the dossier was originally produced.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Sulcotrione is an active substance in the meaning of Directive 91/414/EEC and therefore subject to harmonised classification and labelling (Regulation EC 1272/2008 article 36.2).

OTHER INFORMATION

This proposal for harmonised classification and labelling is based on the data provided for the registration of the active substance sulcotrione according to Directive 91/414/EEC. The summaries included in this proposal are partly copied from the DAR and the final addendum to the DAR. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR and its addendum.

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