Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at Community level of

Triflusulfuron-methyl; methyl 2-({[4-(dimethylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl]carbamoyl}sulfamoyl)-3-methylbenzoate

EC number: N/A
CAS number: 126535-15-7

CLH-O-0000001709-67-02/A1

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

5 December 2013

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: TRIFLUSULFURON-METHYL

EC Number: **not allocated**

CAS Number: 126535-15-7

Index Number: **not allocated**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance (The evaluated variant is the triflusulfuron-methyl)

Table 1. Substance identity:

Substance name:	***Triflusulfuron-methyl***
EC number:	***Not allocated***
CAS number:	126535-15-7
Annex VI Index number:	***Not allocated***
Degree of purity:	***≥960 g/kg***
Impurities:	See confidential annex

1.2 Harmonised classification and labelling proposal

Table 2. The current Annex VI entry and the proposed harmonised classification: triflusulfuron-methyl

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	-	-
Current proposal for consideration by RAC	**Carc. 2-H351** Acute category 1 – H400 Chronic category 1 – H410	**Carc. Cat.3 R40** N R50/53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	**Carc. 2-H351** Acute category 1 – H400 Chronic category 1 – H410	**Carc. Cat. 3; R40** N R50/53

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3. Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None		None	No classification warranted
2.2.	Flammable gases	None		None	Not adequate
2.3.	Flammable aerosols	None		None	Not adequate
2.4.	Oxidising gases	None		None	Not adequate
2.5.	Gases under pressure	None		None	Not adequate
2.6.	Flammable liquids	None		None	Not adequate
2.7.	Flammable solids	None		None	No classification warranted
2.8.	Self-reactive substances and mixtures	None		None	No data
2.9.	Pyrophoric liquids	None		None	Not adequate
2.10.	Pyrophoric solids	None		None	No data
2.11.	Self-heating substances and mixtures	None		None	Not adequate
2.12.	Substances and mixtures which in contact with water emit flammable gases	None		None	No data
2.13.	Oxidising liquids	None		None	Not adequate
2.14.	Oxidising solids	None		None	No classification warranted
2.15.	Organic peroxides	None		None	Not adequate
2.16.	Substance and mixtures corrosive to metals	None		None	No data
3.1.	Acute toxicity - oral	None		None	Data conclusive but not sufficient for classification
	Acute toxicity - dermal	None		None	Data conclusive but not sufficient for classification
	Acute toxicity - inhalation	None		None	Data conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	None		None	Data conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	None		None	Not evaluated
3.4.	Respiratory sensitisation	None		None	Data lacking
3.4.	Skin sensitisation	None		None	Data conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	None		None	Data conclusive but not sufficient for classification
3.6.	Carcinogenicity	**Carc. 2-H351**		None	

3.7.	Reproductive toxicity	None		None	Data conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	None		None	Data conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	None		None	Data conclusive but not sufficient for classification
3.10.	Aspiration hazard			None	Not evaluated
4.1.	Hazardous to the aquatic environment	**Acute category 1 – H400** **Chronic category 1 – H410**	100	None	Not evaluated
5.1.	Hazardous to the ozone layer	-		None	No data

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Signal word: Warning
Hazard statements: H351 (Suspected of causing cancer); H410
Precautionary statements: not harmonised
Pictograms: GHS09, GHS08

Proposed notes assigned to an entry:

Table 4. Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	None		None	No classification warranted
Oxidising properties	None		None	No classification warranted
Flammability	None		None	No classification warranted
Other physico-chemical properties *[Add rows when relevant]*	None		None	No other physic-chemical properties tested
Thermal stability	None		None	No classification warranted
Acute toxicity	None		None	Data conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	None		None	Data conclusive but not sufficient for classification
Repeated dose toxicity	None		None	Data conclusive but not sufficient for classification
Irritation / Corrosion	None		None	Data conclusive but not sufficient for classification
Sensitisation	None		None	Data Lacking
Carcinogenicity	**Carc. Cat.3 R40**		None	
Mutagenicity – Genetic toxicity	None		None	Data conclusive but not sufficient for classification
Toxicity to reproduction – fertility	None		None	Data conclusive but not sufficient for classification
Toxicity to reproduction – development	None		None	Data conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation	None		None	Data conclusive but not sufficient for classification
Environment	N, R50/53	C≥0.25% N; R50-53 0.025%≤C<0.25% N; R51-53 0.0025%≤C<0.025% R52-53	None	

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:
Indication of danger: N, Xn
R-phrases: R40, R50-53
S-phrases: S60, S61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Trimethylsulfuron-methyl is not listed in the Annex I of the 67/548/EC Directive.

2.2 Short summary of the scientific justification for the CLH proposal

The data presented here, in particular Leydig cell hyperplasia and adenomas observed in male rats after Triflusulfuron-methyl treatment, which seems to act as a weak aromatase inhibitor, inducing a decrease in blood estradiol and a subsequent disruption of the hypothalamic-pituitary-testis axis, a relevant mechanism to human justify warranting a classification as a Cat 2 H351.
Toxicity studies for algae and aquatic plants EC50s at concentrations ≤ 1 mg/L were observed. In addition, triflusulfuron-methyl is not readily biodegradable although it is unlikely for the substance to bioaccumulate in aquatic organisms (log Kow < 3). As a consequence and according to the CLP Regulation, triflusulfuron-methyl should be classified as R50-53 (Aquatic Acute 1 – Aquatic Chronic 1). Based on the toxicity data for *Lemna gibba* (ErC50 = 0.0035 mg/L) an M-factor of 100 is also proposed.

2.3 Current harmonised classification and labelling

No current harmonised classification in Annex VI of CLP.

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

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2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

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2.4 Current self-classification and labelling

Triflusulfuron-methyl is currently classified with Xn Carc. Cat.3 R40 at the national level. Triflusulfuron-methyl is currently labelled at the national level with S2: keep out of the reach of children S36/37: wear suitable protective clothing and gloves and S46: if swallowed, seek medical advice immediately and show this container or label.

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Triflusulfuron-methyl is currently classified with Carc. 2-H351 at the national level.

2.4.2 Current self-classification and labelling based on DSD criteria

Triflusulfuron-methyl is currently classified with Xn Carc. Cat. 3 R40 at the national level. Triflusulfuron-methyl is currently labelled at the national level with S2: « keep out of the reach of children », S36/37 « wear suitable protective clothing and gloves » and S46: « if swallowed, seek medical advice immediately and show this container or label ».

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Triflusulfuron-methyl is currently not classified according to Annex VI of CLP.

Triflusulfuron-methyl is an active substance in the meaning of Directive 91/414/EEC. In accordance with Article 36(2) of the CLP Regulation, Triflusulfuron-methyl shall be subjected to harmonised classification and labelling. Therefore, this proposal considers all human health and environmental end points.

Part B.

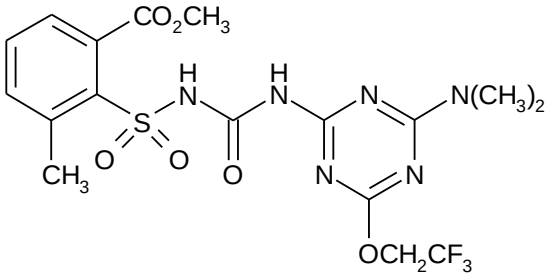
SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

The variant triflusulfuron-methyl is evaluated below

Table 5. Substance identity; triflusulfuron-methyl

EC number:	Not allocated
EC name:	Triflusulfuron-methyl
CAS number (EC inventory):	Not allocated
CAS number:	126535-15-7
CAS name:	methyl 2-[[[[[4-(dimethylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl]amino]carbonyl]amino]sulfonyl]-3-methylbenzoate
IUPAC name:	methyl 2-[4-dimethylamino-6-(2,2,2-trifluoroethoxy)–1,3,5-triazin-2-ylcarbamoylsulfamoyl]-*m*-toluate
CLP Annex VI Index number:	Not allocated
Molecular formula:	$C_{17}H_{19}F_3N_6O_6S$
Molecular weight range:	492.43
Structural formula:	

1.2 Composition of the substance

Table 6. Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Triflusulfuron-methyl		≥ 960 g/kg	
impurities		see confidential annex	

Current Annex VI entry:

No harmonised classification

Table 7. Impurities (non-confidential information)

Impurities are confidential. See confidential annex.

Table 8. Additives (non-confidential information)

none

Current Annex VI entry:

No harmonised classification

1.2.1 Composition of test material

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1.3 Physico-chemical properties

Table 9. Summary of physico - chemical properties of triflusulfuron-methyl

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance	White crystalline solid. (PGAI 98.9%) and white powdery crystalline solid (TGAI.)	Moore, 2002 Dupont 5776	observation
Melting/freezing point	159 °C – 162 °C (purity 98.9 %)	Moore, 2002 Dupont 5775	Measured
Boiling point	No boiling was measured (decomposition of active substance occurs at the temperature above melting point)	Moore, 2002 Dupont 5775	Measured
Relative density	*Density: 1.481 ± 0.001g/cm^3 at 20° ± 0.8 ° C (n=3)*	Huntley, 2001 Dupont 6280	Expressed as density. Measured
Vapour pressure	The vapour pressure at 20°C was 1.01 x 10^{-5} Pa	Ravi, 2010 Dupont-27588 revision 1	Measured using a > 95 % purity test item.
Henry's law	*At pH 5 H=1.31 10^{-3} Pa.m^3.mol^{-1}* *At pH 7 H=1.91 10^{-5} Pa.m^3.mol^{-1}* At pH 9 H=4.52 10^{-7} Pa.m^3.mol^{-1}	*Hirata, 2009* Dupont-28975	calculation
Surface tension	67.92 mN/m at 4.465 mg/L at 20°C Purity : 98.9%	Hammond 1999 Dupont-2280	measured
Water solubility	Purity 98.6% PH 3: 0.0011 g/L at 25 °C PH 5: 0.0038 g/L at 25 °C PH 7: 0.26 g/L at 25 C PH 9: 11 g/L at 25 °C	Moore, Schmuckler, 1997 AMR 4571-97	Measured
Partition coefficient n-octanol/water	pH 5: 2.3 at 25 °C pH 7: 0.96 at 25 °C pH 9: -0.066 at 25 °C purity : 95.6%	Rhodes, and Cooke, 1992 AMR 1984-91	Measured
Flash point	No data available. Moreover, triflusulfuron-methyl is a solid	-	-
Flammability	The test material (95.6 % purity) failed to propagate a flame so the active substance can be considered as not flammable TGAI (95.6%)	Gravell, 1995 AMR 3028-94	measured
Explosive properties	No explosive properties (95.6%)	Gravell, 1995 AMR 3028-94	measured
Self-ignition temperature	not relevant as the active substance is not a liquid and does not have a melting point below 40°C		
Oxidising properties	Not oxidizing	Gravell, 1995 AMR 3028-94	Expert statement
Granulometry	no data	-	
Stability in organic solvents and identity of relevant degradation	No data on stability but solubility is given below		

products			
Dissociation constant	pKa: 4.4 at 25 °C	Rhodes, and Cooke, 1983 AMR 1983-91	measured
Viscosity	Not relevant. Moreover triflusulfuron is a solid	-	-
Solubility in organic solvent	Purity : 95.6%, at 25 °C Acetone : 120 g/L, Acetonitrile : 80 g/L, Chloroform : 160 g/L, Ethyl acetate : 27 g/L, n-hexane : <0.0016g/L, Methanol 7.0 g/L, Dichloromethane 580 g/L, Octan-1-ol : 0.026 g/L Toluene : 2.0 g/L	Rhodes, and Cooke, 1992 AMR 1981-91	measured
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	λ = 228 nm et 291 nm for acidic solution λ = 235 nm et 291 nm for neutral et basic solutions at 291 nm ε □□$mol^{-1}.cm^{-1}$ □□for acidic is 9.81 10^2, for neutral is 4.74.10^2, for basic is 4.81 10^2 purity : 98.9%	Moore, 1999 Dupont 2560	measured
Storage stability at 25°C and 5°C	no data		

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant in this dossier

2.2 Identified uses

Triflusulfuron-methyl (variant of triflusulfuron) is an herbicide to be used in agriculture under field conditions. In the EU dossier, deposited representative uses are on Sugar and fodder beets

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10. Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
EEC A10 (flammability)	negative		Gravell, 1995 AMR 3028-94
UN-Bowes-Cameron-Cage test Q (auto-flammability)	negative		Gravell, 1995 AMR 3028-94
EEC A14 (explosivity)	negative		Gravell, 1995 AMR 3028-94
Structural interpretation (oxidizing properties)	negative		Gravell, 1995 AMR 3028-94

3.1 Explosive properties

Triflusulfuron-methyl is a stable organic substance. None of these components or grouping are associated with explosive hazards. All are stable groupings in high oxidation states. Moreover, a study from Gravell, 1995 (AMR 3028-94) using EEC A14 method has been performed indicating no explosive properties for triflusulfuron-methyl test item.

3.2 Flammability

Triflusulfuron-methyl is an organic compound. This material is not likely to undergo self heating under bulk storage conditions and is unlikely to auto-ignite. Moreover, in the Gravell's study (1995), triflusulfuron-methyl was shown not to be highly flammable using EEC A10 method. In the same study, auto-ignition has not been observed (see Table 9)

The determination of flash point is not relevant because the active substance is a solid.

Triflusulfuron-methyl can be given as not flammable.

3.3 Oxidising potential

Oxidising compounds are materials that can easily transfer oxygen to other compounds i.e. they contain weakly bound oxygen, for example NO3 and peroxides. Bound oxygen must also become available through a low energy degradation route with a low energy of activation. The oxygen in Triflusulfuron-methyl is bound in stable structural groupings with strong oxygen bonds. The decomposition temperature of Triflusulfuron-methyl is around 160°C. Triflusulfuron-methyl can therefore be considered stable under the conditions of oxidation.

RAC evaluation of physical hazards

Summary of the Dossier submitter's proposal

The dossier submitter (DS) addressed explosive properties, flammability and oxidising potential. The chemical structure indicated that there is no cause for concern for any of these endpoints. Furthermore, tests have been performed for explosive properties and flammability with negative results. The DS concluded that classification for explosive

properties, flammability or oxidising potential is not needed.

Comments received during public consultation
No comments were received during public consultation.

Assessment and comparison with the classification criteria
RAC agreed that the substance did not fulfil the criteria for classification as explosive, flammable or oxidising.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

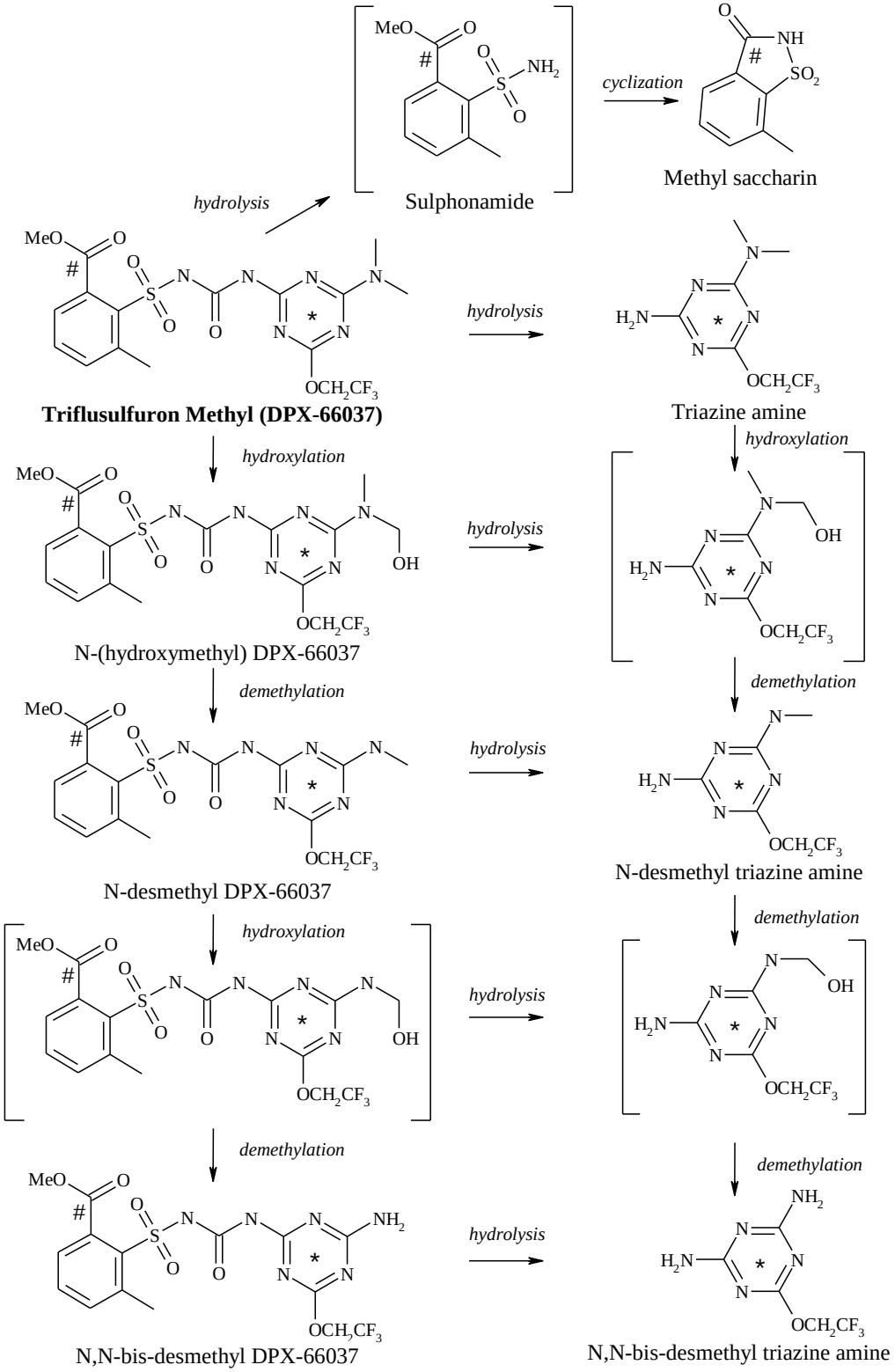
See Draft Assessment Report and corrigenda.

Following oral dosing in rats, [^{14}C]-Triflusulfuron-methyl was rapidly absorbed and excreted both in urine and faeces (> 80% and > 90% of the administered dose was excreted respectively in 48 and 72 hours in urine and faeces). Female rats appeared to excrete slightly more residues in urine than male rats. The difference in urine was offset by a greater excretion of residues in the faeces of male rats than female rats.

The oral absorption of the low dose of Triflusulfuron-methyl in the rat was estimated to be 63.5 and 79.5% of the dose, in males and females respectively, based on the radioactivity recovered in the urine and the carcass (table 6.1.2). The notifier has estimated that the mean absorption of Triflusulfuron-methyl in the rat was 87% (84-92%) of the administered low dose, based on the sum of ^{14}C metabolites in the liver, urine and faeces (assuming all faeces metabolites were derived from liver metabolism).
Although the biliary elimination of the radioactivity was not measured and the possible metabolism of Triflusulfuron-methyl in the gastrointestinal tract was not studied, the high similarity between the metabolite profiles in the faeces and in the urine or liver was consistent with the notifier's proposal.

Tissue clearance was rapid with less than 2.5% remaining in all tissues at 120 hours. Clearance was slower from liver and blood than from other tissues. There was no evidence of alteration in the pattern of excretion or tissue distribution of radioactivity after several daily administrations of the compound.

Triflusulfuron-methyl was extensively metabolised especially when administered at low doses in the rat. The major biotransformation pathways for Triflusulfuron-methyl were hydroxylation/demethylation on the triazine ring and cleavage of the sulphonylurea bridge. No qualitative difference was noticed in the metabolism of the compound in the male and female rats. Considering the percentage of the metabolites identified and the metabolic pathway proposed, it can be concluded that the metabolism of Triflusulfuron-methyl in rats was well understood.



4.1.2 Human information

No data available.

4.1.3 Summary and discussion on toxicokinetics

Following oral administration in rats, Triflusulfuron-methyl is rapidly absorbed and excreted in urine and faeces. Triflusulfuron-methyl did not accumulate in the body and was extensively metabolised, especially when administered at low doses in the rat. The major biotransformation pathways for Triflusulfuron-methyl were hydroxylation/demethylation of the triazine ring and cleavage of the sulphonylurea bridge.

4.2 Acute toxicity

Table 11. Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Oral, rat EEC Method B.1	LD_{50} administered in methylcellulose > 5000 mg/kg b.w.	Purity: 98.7% "cyanate process"	Clouzeau J. (1992)
Oral, rat OECD 401	LD_{50} administered in corn oil > 5000 mg/kg b.w.	Purity: 95.6% "carbamate process"	Sarver J.W. (1991a)
Oral, rabbit OECD 401	LD_{50} administered in methylcellulose > 5000 mg/kg b.w.	Purity: 95.6% "carbamate process"	Sarver J.W. (1991b)
Percutaneous, rat EEC Method B.3	LD_{50} administered > 2000 mg/kg b.w.	Purity: 98.7% "cyanate process"	Clouzeau J. (1992)
Percutaneous, rabbit OECD 402	LD_{50} administered > 2000 mg/kg b.w.	Purity: 95.6% "carbamate process"	Sarver J.W. (1991)
Inhalation, rat OECD 403	4-h LC_{50} > 5.1 mg/L (nose only)	Purity: 95.6% "carbamate process"	Panepinto A.S. (1991)

4.2.1 Non-human information

4.2.1.1 *Acute toxicity: oral*

See Draft Assessment Report and corrigenda.

The oral LD_{50} of Triflusulfuron-methyl (cyanate or carbamate process), administered in methylcellulose or corn oil was greater than 5000 mg/kg b.w in rat and rabbit.

4.2.1.2 *Acute toxicity: inhalation*

See Draft Assessment Report and corrigenda.

The acute inhalation LC_{50} for Triflusulfuron-methyl (carbamate process) was greater than 5.1 mg/L of air for 4 hours (nose only) for both male and female rats.

4.2.1.3 *Acute toxicity: dermal*

See Draft Assessment Report and corrigenda.

The dermal LD_{50} of Triflusulfuron-methyl (cyanate or carbamate process) was greater than 2000 mg/kg b.w for both male and female rats and rabbits.

4.2.1.4 *Acute toxicity: other routes*

Not data available

4.2.2 Human information

No data available

4.2.3 Summary and discussion of acute toxicity

Triflusulfuron-methyl (cyanate or carbamate process) has low acute toxicity via the oral, dermal or inhalation routes.

4.2.4 Comparison with criteria

-

4.2.5 Conclusions on classification and labelling

These data indicate that no classification is required under either Directive 67/548/EEC or the CLP Regulation.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Six studies on acute toxicity were provided in the CLH report, three on oral, one on inhalation and two on the dermal route. No substance related mortalities were seen and only minor clinical signs observed. LD_{50} oral was determined to be >5000 mg/kg/d, dermal >2000 mg/kg/d and inhalation > 5.1 mg/L. No classification was proposed.

Comments received during public consultation

No comments were received during public consultation

Assessment and comparison with the classification criteria

Acute toxicity: oral

The LD_{50} of triflusulfuron-methyl in rat and rabbit is >5000 mg/kg bw, and thus above the cut-off value of 2000 mg/kg bw for classification for acute toxicity by the oral route according to both CLP and DSD.

Acute toxicity: inhalation

No mortalities were observed in a study where rats were exposed to a concentration of 5.1 mg/L/4hr, i.e. a concentration above the cut-off value of 5.0 mg/L/hr for dusts and mists (CLP), and aerosols and particulates DSD.

Acute toxicity: dermal

The LD_{50} of triflusulfuron-methyl in rat and rabbit is>2000 mg/kg bw, and thus above the cut-off value of 2000 mg/kg bw for classification for acute toxicity by the dermal route according to both CLP and DSD.

RAC therefore supported no classification for acute toxicity as proposed by the DS.

4.3 Specific target organ toxicity – single exposure (STOT SE)

No specific target organ toxicity identified after single exposure.

These data indicate that no classification is required under either Directive 67/548/EEC or the CLP Regulation.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal

The DS stated that no effects relevant for this hazard class were observed in the acute toxicity studies and concluded that no classification was warranted.

Comments received during public consultation

No comments were received during public consultation

Assessment and comparison with the classification criteria

According to CLP, classification as STOT-SE should be considered when there is clear evidence of toxicity to a specific organ, especially when it is observed in the absence of lethality. As no specific target organ toxicity was observed after a single dose/exposure concentration of triflusulfuron-methyl, no classification was demed necessary.

RAC supported no classification for STOT-SE as proposed by the DS.

4.4 Irritation

4.4.1 Skin irritation

Table 12. Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
Skin irritation, rabbit EEC Method B.4.	Not irritating	Purity: 98.7% "cyanate process"	Clouzeau J. (1992)
Skin irritation, rabbit, OECD 404	Not irritating	Purity: 95.6% "carbamate process"	Sarver J.W. (1992)

4.4.1.1 *Non-human information*

See Draft Assessment Report and corrigenda.

After a 4-hour skin exposure of Triflusulfuron-methyl (cyanate or carbamate process) to New Zealand rabbits under semi-occlusive dressing, no skin irritation was observed in any rabbit

4.4.1.2 *Human information*

No data available

4.4.1.3 *Summary and discussion of skin irritation*

Triflusulfuron-methyl is not a skin irritant.

These data indicate that no classification is required under either Directive 67/548/EEC or the CLP Regulation.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

Two studies performed in rabbits (conducted in accordance with EEC method B.4. and OECD test guideline (TG) 404, respectively) were presented in the report. Score 1 erythema was seen in one animal in one of the studies. The effect was reversed after 48 h. The DS concluded that the criteria for classification were not fulfilled.

Comments received during public consultation

No comments were received during public consultation

Assessment and comparison with the classification criteria

In two skin irritation studies in rabbit, triflusulfuron-methyl was applied under a semi-occlusive dressing. Reversible erythema was observed in 1 of 3 animals in one study. In the other study no dermal irritation was observed. Since no irreversible damage to the skin was observed, classification as corrosive to skin is not warranted.

According to CLP, a reaction is normally needed in 2 out of 3 animals for classification as a skin irritant. However very definite positive reaction in only one animal may be sufficient for classification. In this case with triflusulfuron-methyl the reaction in one animal was so weak (erythema, score of 1) that no classification is considered justified. No classification is required for skin irritation according to DSD, as the criteria for significant inflammation of the skin in two or more animals is not fulfilled.

RAC supported no classification for skin corrosion/irritation as proposed by the DS.

4.4.2 Eye irritation

Table 13. Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Eye irritation, rabbit EEC Method B.5.	Not irritating	Purity: 98.7% "cyanate process"	Clouzeau J. (1992)
Skin irritation, rabbit, EEC Method B.5.	Not irritating	Purity: 95.6% "carbamate process"	Sarver J.W. (1991)

4.4.2.1 *Non-human information*

See Draft Assessment Report and corrigenda.

After application Triflusulfuron-methyl (cyanate or carbamate processs) in the eyes of male and female New Zealand rabbits, transient and slight ocular reactions were observed, including

conjunctival redness, conjunctival chemosis and discharge. At 48 hours, no signs of irritation were observed in any rabbit.

4.4.2.2 *Human information*

No data available

4.4.2.3 *Summary and discussion of eye irritation*

Triflusulfuron-methyl is not an eye irritant.

4.4.2.4 *Comparison with criteria*

-

4.4.2.5 *Conclusions on classification and labelling*

These data indicate that no classification is required under either Directive 67/548/EEC or the CLP Regulation.

RAC evaluation of eye corrosion/irritation
Summary of the Dossier submitter's proposal Two studies performed in rabbits (both according to EEC method B.5.) were presented in the CLH report, one with three and one with six animals. Conjunctival redness (scores 1 or 2) was seen in all animals. Conjunctival chemosis, discharge and corneal opacity (score 1 in one rabbit) were also reported. All effects were reversed after 48 h. The DS concluded that the results did not fulfil the criteria for classification. **Comments received during public consultation** No comments were received during public consultation **Assessment and comparison with the classification criteria** In two eye irritation studies in rabbit, mean scores for corneal opacity, iritis, conjunctival redness and conjunctival oedema at 24 to 72 hours were below the criteria for classification and labelling in CLP and DSD. According to CLP, Irritating to eyes (Category 2) is applied to substances that produce, a positive response at least in 2 of 3 tested animals, of: – corneal opacity ≥ 1 and/or – iritis ≥ 1, and/or – conjunctival redness ≥ 2 and/or – conjunctival oedema (chemosis) ≥ 2 – calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days. Irreversible eye effects should be assigned to Category 1. No signs of irritation were present at 48 hours in either test. Signs observed after 24 hours were below the cut-off values for classification, both when compared to criteria in CLP and DSD. RAC supported no classification for eye corrosion/irritation as proposed by the DS.

4.4.3 Respiratory tract irritation

4.4.3.1 *Non-human information*

No data available

4.4.3.2 *Human information*

No data available

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4.5 Corrosivity

Triflusulfuron-methyl is not a corrosive substance.

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4.6 Sensitisation

4.6.1 Skin sensitisation

Table 14. Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
Skin sensitization, guinea-pigs OECD 406	Not skin sensitizer	Purity: 98.7% "cyanate process" The study was only found indicative as no concurrent control was used.	Clouzeau J. (1992)
Skin sensitization, guinea-pigs OECD 406	Not skin sensitizer	Purity: 95.6% "carbamate process" The study was only found indicative as no concurrent control was used.	Armondi S. (1991/1994)

4.6.1.1 *Non-human information*

See Draft Assessment Report and corrigenda.

Under the conditions of the two M & K tests, Triflusulfuron-methyl did not induce any positive response in guinea pigs.

4.6.1.2 *Human information*

No data available

4.6.1.3 *Summary and discussion of skin sensitisation*

Triflusulfuron-methyl is not a skin sensitizer.

4.6.1.4 *Comparison with criteria*

-

4.6.1.5 *Conclusions on classification and labelling*

These data indicate that no classification is required under either Directive 67/548/EEC or the CLP Regulation.

RAC evaluation of skin sensitisation
Summary of the Dossier submitter's proposal Two Magnusson and Kligman maximisation tests (OECD 406) were described in the report. Both were considered by the DS not to justify classification. **Comments received during public consultation** No comments were received during public consultation **Assessment and comparison with the classification criteria** Two Magnusson and Kligman Guinea Pig Maximisation Tests (GPMT) are available, i.e. adjuvant tests in which sensitisation was potentiated by the injection of Freunds Complete Adjuvant (FCA). In one test, intradermal induction consisted of 0.1 ml of 1% solution of the test substance. In the other test the corresponding intradermal dose was 0.1 ml of 1.5 %. For cutaneous induction, 500 mg of the test substance (purity 98.7%) was used in the first test, and 0.2 ml of the test preparation (25% w/v) was applied in the second. No cutaneous reactions were observed following the exposure in either test. The DS considered the first study to be only indicative, as no positive control was used. In the other test 2,4-Dinitrochlorobenzene was used as a positive control. RAC agreed with the DS that the first test provided only indicative results, and supported no classification according to CLP (including its 2nd ATP) or DSD for skin sensitisation, as no cutaneous reactions from exposure to triflusulfuron-methyl were observed.

4.6.2 Respiratory sensitisation

No data available

4.7 Repeated dose toxicity

Table 15. Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks	Reference
90-day feeding study in Sprague Dawley rats 0, 100, 2000, 10000 and 15000 ppm corresponding to 0, 6.2, 127, 646 and 965 mg/kg b.w. in males and 0, 7.54, 150, 774 and 1070 mg/kg b.w. in females OECD 408	At 2000ppm in M and F: ↓ body weights, ↓ body weight gains, ↓ food efficiency, ↑ mean relative liver weights (without histological changes), and regenerative anemia. At 15000 ppm: renal tubular atrophy in M and F (marked only in F), testicular atrophy/degeneration and oligospermia, ↓ testicular weights. NOAEL for Triflusulfuron-methyl (synthetized via the carbamate process) was 100 ppm (6.2 mg/kg b.w.) for M and (7.54 mg/kg b.w) for F	Purity: 95.8% "carbamate process"	Biegel L.B. (1993)
90-day feeding study in Sprague Dawley rats 0, 100, 2000, 10000 and 15000 ppm corresponding to 0, 6.56, 133, 658 and 1036 mg/kg b.w. in males and 0, 7.71, 153, 783 and 1124 mg/kg b.w. in females OECD 408	At 2000 ppm in M and F: ↓ body weighs, ↓ body weight gains, ↓ food efficiency, ↑ mean relative liver weights (without histological changes), and haemolytic anemia. At 10000 ppm, in both sexes, renal hemosiderosis was correlated to the haemolytic process of red blood cells. NOAEL for Triflusulfuron-methyl (synthetized via the cyanate process) was 100 ppm (6.56 mg/kg b.w.) for M and (7.71 mg/kg b.w) for F	Purity: 98.7% "cyanate process"	Biegel L.B. (1992)
90-day feeding study in CD1 mice 0, 50, 750, 3750 and 7500 ppm corresponding to 0, 7.13, 116, 569 and 1164 mg/kg b.w. in males and 0, 11.8, 166, 817 and 1799 mg/kg b.w. in females (based material purity of 98.2%) OECD 408	No test substance related effects on the incidence of clinical signs of toxicity or mortality, body weights, food consumption or food efficiency for M or F at any dietary concentration. There were no test substance related effects on haematology parameters. ↑ mean absolute and relative liver weights in 3750 and 7500 ppm in M and F and at 750 ppm in M with ↑ incidence of centrilobular hepatocellular hypertrophy. NOAEL for Triflusulfuron-methyl (synthetized via the carbamate process) was 50 ppm (7.13 mg/kg b.w.) for M and 750 ppm (166 mg/kg b.w) for F	Purity: 91.9% "carbamate process" (the purity decreased between the beginning (94%) and the completion (81%) of the study. The actual intake of Triflusulfuron-methyl by mice might be lower due to the degradation of the active substance during the study and to the instability of the test material in food at the lowest concentration. Then, the correspondence between ppm and mg/kg b.w could not	Mebus C.A. (1991)

Method	Results	Remarks	Reference
		be accurately determined.	
90-day feeding study in Beagle dogs 0, 100, 4000 and 8000 ppm corresponding to 0, 3.9, 146 and 268 mg/kg b.w. in males and 0, 3.7, 160 and 261 mg/kg b.w. in females OECD 409	At 4000 and 8000 ppm: - enlargement of the liver in M and F with an ↑ incidences of pigmented sinusoidal macrophages, bile stasis only in F, -testicular atrophy characterized by aspermatogenesis (aspermia in epididymis), decrease in thickness of the seminiferous tubules and cytoplasmic vacuolation of the germinal epithelium. - at 8000 ppm in M and F: hypercellularity of bone marrow consistent with the regenerative nature of the haematological effects NOAEL for Triflusulfuron-methyl (synthetized via the carbamate process) was 100 ppm (3.9 mg/kg b.w.) for M and (3.7 mg/kg b.w) for F	Purity: 95.6% "carbamate process"	Atkinson J.E. (1991)
1-year feeding study in Beagle dogs 0, 35, 875, and 3500 ppm corresponding to 0, 0.99, 26.9 and 111.8 mg/kg b.w. in males and 0, 1.2, 27.7 and 93.9 mg/kg b.w. in females OECD 452	At 3500 ppm : ↓ red blood cells, haematoglobin and haematocrit in M and F, ↑liver weight (+36% in M and +35% in F) with minimal centrilobular hepatocellular hypertrophy ↑ alkaline phosphatase only in M NOAEL = 875 ppm in M (26.9 mg/kg b.w) and F (27.7 mg/kg b.w)	Purity: 95.6% "carbamate process	Auletta C.S. (1993)

4.7.1 Non-human information

4.7.1.1 *Repeated dose toxicity: oral*

See Draft Assessment Report and corrigenda.

The short-term toxicity of Triflusulfuron-methyl was evaluated in rats (90-day), mice (90-day), dogs (90-day and 1-year), after oral exposure. All of the studies were considered acceptable.
The targets organs of orally administered Triflusulfuron-methyl were primarily liver and red blood cells in rats and dogs, and liver in mice., rat and dog. Mice were relatively less sensitive than rats or dogs to Triflusulfuron-induced toxicity, as effects were limited to liver in this species.
Body weight gains were particularly impaired at the highest dose levels in rats (10000 and 15000 ppm) and in dogs (8000 ppm). Food efficiency was reduced at the same dose levels in the rats.

Liver weight was increased in all species, without any histological modification in rats, with centrilobular hypertrophy in mice and with some indication of moderate hepatotoxicity in dogs at 8000 ppm (elevated blood enzymes). Increased liver weight and corresponding microscopic liver hypertrophy were also present at 3500 ppm in the 1-year dog study.
The haematological changes in rats and dogs were consistent with a compound relative moderate to slight haemolytic anaemia at 10000-15000 ppm in rats and 3500-8000 ppm in dogs. Anaemia was occasionally accompanied by liver or kidney hemosiderosis.
Additionally, testicular atrophy/degeneration accompanied by oligospermia and decrease in the thickness of seminiferous tubules was observed in one 90-day rat study and the 90-day dog study. They were not recorded in the other 90-day rat study and in the 1-year dog study. It should be noticed that the testicular effects were observed at doses that significantly impaired the growth rate and were likely secondary to marked effects on body weight gain of treated animals. In a 90-day rat study statistically decreased testicular weights, and increased incidence of testicular atrophy/degeneration and oligospermia were observed in rats fed 15000 ppm Triflusulfuron-methyl. The mean body weight for this group of male rats was decreased by 40% when compared to the control group. This type of testicular effect has previously been reported to be caused by poor nutrition in the rat. Therefore, in light of the marked decrease in body weight, body weight gain, as well as the statistically significant decrease in food consumption, it was concluded that the observed testicular effects in this study were attributed to general toxicity and not a direct compound-related effect In another 90-day rat study, in male rats fed 15000 ppm Triflusulfuron-methyl, only a 20% decrease in body weight and no testicular effects were observed, supporting the conclusion that the testicular effects were primarily due to general toxicity. In the 90-day study in dogs with Triflusulfuron-methyl, the testicular effects noted at 8000 ppm could be most likely the result of significantly decreased body weight gains in sexually immature animals. Testicular changes at 4000 ppm were equivocal at best, and the absence of testicular effects in dogs administered 3500 ppm for one year strongly suggests that the findings noted at 4000 ppm in the 90 day study could be not compound-related. Thus, based on consideration of the results of both the 90-day and 1-year studies, Triflusulfuron-methyl should not be considered a primary testicular toxin in dogs. "The report also concludes that, based on testicular weights and histology, compound-related effects were also present at 4000 ppm. However, there were no statistically significant effects on testes weights and with the exception of one animal (which had bilateral testicular atrophy, see below), the testicular weights of individual animals in the 4000 ppm were similar to-controls. Microscopically, bilateral testicular atrophy was present in 1 dog. The weight of evidence strongly suggests that this change is unrelated to compound exposure since only 1 of 4 dogs was affected, testicular atrophy is known to occur spontaneously in beagle dogs, and, perhaps most importantly, no testicular changes were present in dogs fed diets containing 3500 ppm of Triflusulfuron-methyl for 1 year. In the epididymis, minimal accumulation of cell debris in the epididymis was present in all dogs in the 4000 ppm group. However, this change was not dose-related, was associated with corroborative testicular changes in only one dog, and is a common finding in immature animals. Thus, this epididymal change is most likely attributable to the immaturity of the test species."
As already mentioned, two different methods have been used to produce the technical test compound. Similar target organs were observed in 90-day feeding studies in rats with Triflusulfuron-methyl synthesised by the carbamate or cyanate coupling processes. However, body weight and food consumption decrements were less severe in the study using the cyanate-derived technical material, particularly at high dose levels, and effects likely to be linked to general toxicity (testicular effects) were not reproduced.

4.7.1.2 *Repeated dose toxicity: inhalation*

No data available

4.7.1.3 *Repeated dose toxicity: dermal*

Method	Results	Remarks	Reference
21-day dermal study in New Zealand White Rabbits 0, 50, 300 or 1000 mg/kg b.w/day OECD 410	No evidence of systemic toxicity. NOAEL = 1000 mg/kg b.w/day in M and F	Purity: 95.6% "carbamate process" EU guidelines requires 28 days. This study was conducted for only 21 days	MacKenzie S.A. (1993)

Triflusulfuron-methyl was not toxic by the dermal route in the rabbits at doses of up to 1000 mg/kg/day.

4.7.1.4 *Repeated dose toxicity: other routes*

No data available

4.7.1.5 *Human information*

No data available.

4.7.1.6 *Other relevant information*

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4.7.1.7 *Summary and discussion of repeated dose toxicity*

The short-term toxicity of Triflusulfuron-methyl was evaluated in rats (90-days), mice (90-day), dogs (90-day and 1-year) and rabbits (21-day), after oral and dermal (rabbits) exposure. Triflusulfuron-methyl caused a decrease in body weight gain, food intake and food efficiency, as well as increased liver enzymes and anaemia when administered to rats and dogs. Mice were less sensitive than rats or dogs as effects were limited to the liver. Liver weight was increased in all species, without any histological modifications in rats, with centrilobular hypertrophy in mice and with elevated blood enzymes in dogs. Testicular atrophy/degeneration accompanied by oligospermia and a decrease in thickness of seminiferous tubules was observed in one 90-day rat study and in the 90-day dog study. These findings were not confirmed in a second 90-day rat study and in the 1-year dog study. Triflusulfuron-methyl was not toxic by the dermal route in the rabbits at doses up to 1000 mg/kg b.w/day.

4.7.1.8 *Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD*

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4.7.1.9 *Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD*

Rationale for classification as R48/22 (Danger of serious damage to health by prolonged exposure):

The 67/548/EEC criteria for classification as R48/22 are as follow:
Substances are classified as R48/22 when significant serious damage (clear functional disturbance or morphological change which has toxicological significance), is likely to be caused by repeated or prolonged exposure by an appropriate route, in a 90-day repeated-dose study conducted in experimental animals at a

dose ≤ 50 mg/kg/d. When interpreting the results of a sub-acute (28-days) toxicity test, this value should be increased approximately three fold.

Consequently, as the observed changes of liver and red blood cells in rats and dogs and liver in mice are observed at the highest doses (> 50 mg/kg b.w/d), Triflusulfuron-methyl does not require classification for sub-chronic toxicity.

4.7.1.10 *Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD*

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4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

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

Rationale for classification as STOT-RE:

The CLP criteria for classification as STOT-RE are as follow:
"Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were observed in a 90-day repeated-dose study conducted in experimental animals within the guidance value ranges of 10-100 mg/kg/d.

Consequently, as the observed changes of liver and red blood cells in rats and dogs and liver in mice are observed at the highest doses (> 100 mg/kg b.w/d), Triflusulfuron-methyl does not require classification for sub-chronic toxicity.

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

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4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

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RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)
Summary of the Dossier submitter's proposal Three 90 day OECD 408 studies (two in rats, one in mice), one 90 day OECD 409 study in dog and one 1 year OECD 452 study in dog conducted by the oral route, were included in the CLH report. The main target organs were liver and blood in rat and dog and liver in mice. In the 1 year dog study, mortalities were also seen. All effects occurred above the guidance value of 100 mg/kg/d or, in case of the 1 year study effects (mortality) were seen at 90 mg/kg/d. The DS conclude that classification was not warranted. **Comments received during public consultation** No comments were received during public consultation

Assessment and comparison with the classification criteria

In the 90 days oral studies in rats, mice and dogs the NOAELs were > 100 mg/kg bw for changes in the liver and red blood cells in rats and dogs and in the liver in mice. Thus the NOAELs were above the cut-off values of 100 mg/kg bw for classification in STOT RE 2 and above the cut-off value of 50 mg/kg bw for repeated dose toxicity (R48) in DSD. Findings in a 1 year oral dog study at 94 mg/kg bw in females and 112 mg/kg bw in males were not sufficient for classification after the use of Haber´s rule adjusting the guidance values to 100/4 for the guidance values in CLP, and 50/4 according to Directive 67/548.

RAC supported no classification for repeated dose toxicity, as proposed by the DS.

4.9 Germ cell mutagenicity (Mutagenicity)

Table 16. Summary table of relevant in vitro and in vivo mutagenicity studies

Method	Results	Remarks	Reference
Gene mutation Ames test *S typhimurium* (TA97 TA98, TA100, TA1535) OECD 471	Negative	Purity 91.9% "carbamate process"	Reynolds V.L. (1991)
Gene mutation Ames test *S typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) OECD 471	Negative	Purity : 98.7% "cyanate process"	Molinier B. (1992)
Gene mutation CHO/HPRT assay OECD 476	Negative	Purity : 95.6% "carbamate process"	Rickard L.B. (1991)
DNA damage and repair *In vitro UDS assay* OECD 482	Negative	Purity : 95.6% "carbamate process"	Bentley K.S. (1991)
Chromosome aberration *In vitro* Mammalian Chromosomal Aberration (human lymphocytes) OECD 473	Negative without metabolic activation (3h exposure) Positive with metabolic activation (≥ 1700 µg/mL)	Purity : 95.6% "carbamate process"	Bentley K.S. (1991)
Chromosome aberration *In vitro* Mammalian Chromosomal Aberration (human lymphocytes) OECD 473	Negative without metabolic activation (3h exposure) Positive with metabolic activation (≥ 1850 µg/mL)	Purity : 98.7% "cyanate process"	Bentley K.S. (1992)
Chromosome aberration *In vitro* Mammalian Chromosomal Aberration (human lymphocytes) OECD 473	Negative (24 to 48 h exposure without metabolic activation). Negative with metabolic activation	Purity : 98.7% "cyanate process"	Molinier B. (1992)
Chromosome aberration *In vivo* mouse micronucleus test (oral route) OECD 474	Negative	Purity : 95.6% "carbamate process"	Gerber K.M. (1991)
Chromosome aberration *In vivo* mouse micronucleus test (oral route) OECD 474	Negative	Purity : 98.7% "cyanate process"	Molinier B. (1992)
Chromosome aberration *In vivo* spermatogonial chromosome aberration OECD 486	Negative	Purity : 98.7% "cyanate process"	Gudi R. (1997)

4.9.1 Non-human information

See Draft Assessment Report and corrigenda.

4.9.1.1 *In vitro data*

Triflusulfuron-methyl was negative for mutagenicity and/or genotoxic potential in bacterial cultures, cultured mammalian cells (CHO cells), and primary rat hepatocytes (unscheduled DNA synthesis). Triflusulfuron-methyl was positive for chromosome aberration in 2 out of 3 *in vitro* assays in human lymphocytes. These positive responses occurred only at high *in vitro* concentrations (≥ 1700 µg/mL), in the presence of a metabolic activation system.

4.9.1.2 *In vivo data*

Three *in vivo* assays for chromosome aberrations (2 mouse micronucleus assays and a mouse spermatogonial assay) were all negative.

4.9.2 Human information

No data available.

4.9.3 Other relevant information

No data available.

4.9.4 Summary and discussion of mutagenicity

Mutagenicity data are presented for information as they may provide relevant data for assessment of long term toxicity and carcinogenicity, no classification is discussed and proposed for this endpoint.

The weight of evidence from the complete battery of *in vitro* and *in vivo* genetic toxicology studies conducted with Triflusulfuron-methyl indicates no genotoxic potential.

4.9.5 Comparison with criteria

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4.9.6 Conclusions on classification and labelling

No classification is required.

RAC evaluation of germ cell mutagenicity
Summary of the Dossier submitter's proposal The CLH report included seven *in vitro* (bacteria and mammalian cells) and three *in vivo* genetic toxicity tests (all in mice). All the tests were negative. The DS concluded that classification was not warranted. **Comments received during public consultation** A comment was received from one MSCA, agreeing with the proposal not to classify the substance for this hazard class. **Assessment and comparison with the classification criteria** The mutagenicity data base for triflusulfuron-methyl is extensive and consists of Ames tests in bacteria as well as tests *in vitro* and *in vivo* both in human and non-human mammalian cells. All tests had a negative outcome both with and without metabolic

activation, except two *in vitro* chromosome aberration tests of human lymphocytes. As these were conducted with high (cytotoxic) concentrations (≥ 1700 µg/ml) and the three *in vivo* chromosome aberration tests were all negative, analysis of the weight of evidence indicates that triflusulfuron-methyl has no genotoxic potential, and should not be classified according to CLP. According to the DSD, substances showing positive results only in one or more in vitro mutagenicity assays should normally not be classified.

RAC therefore supported no classification for germ cell mutagenicity (CLP) / mutagenicity (DSD) as proposed by the DS.

4.10 Carcinogenicity

Table 17. Summary table of relevant carcinogenicity studies

Method	Results	Remarks	Reference
2-year dietary carcinogenicity study in Sprague Dawley rat (0, 10, 100, 750 or 1500 ppm corresponding to 0, 0.406, 4.06, 30.6 and 64.5 mg/kg b.w for males and 0, 0.546, 5.47, 41.5 and 87.7 mg/kg b.w. for females OECD 453	At 750 and 1500 ppm :decreases in body weight, food consumption and circulating erythrocyte mass and increased incidences of interstitial cell (Leydig cells) hyperplasia and adenoma in male rats. In female rats, no neoplastic lesions were observed.	Purity: 95.6% "carbamate process" Due to poor survival in this study, it was necessary to terminate after 22 months, as opposed to the normal 24 months.	Biegel L.B. (1993)
18-month dietary long term/carcinogenicity study in CD-1 mouse 0, 10, 150, 2500 or 7000 ppm corresponding to 0, 1.37, 20.9, 349 or 1024 mg/kg b.w. for males and 0, 1.86, 27.7, 488 or 1360 mg/kg b.w. for females OECD 451	At 2500 and 7000 ppm: decreases in mean body weight gain and elevated liver weights and hepatic cytochrome P-450 content in both males and females, as well as microscopic findings: increased hepatic foci of cellular alteration and the presence of intrahepatocellular erythrocytes. Slightly increased incidences of hepatocellular adenomas were also present in males.	Purity: 95.6% "carbamate process"	Initial report: Biegel L.B. (1993) Supplement to intial report Makovec G.T. (1995)

4.10.1 Non-human information

No data available.

4.10.1.1 *Carcinogenicity: oral*

- Rat study

The long term toxicity and carcinogenicity of Triflusulfuron-methyl were evaluated in Sprague Dawley rats and in CD-1 mice. Based on the findings in the rat study, a series of mechanistic *in vivo* and *in vitro* studies were undertaken to define the mechanism of interstitial cell tumour genesis.

In the rat study, Triflusulfuron-methyl (66037-24, carbamate process, purity 95.6%) was administered to groups of 62 male and 62 female Sprague Dawley rats. The substance was incorporated in the diet at 0, 10, 100, 750 and 1500 ppm for 22 months (24 months at the beginning). The doses were based on a previous 90-day feeding study in the rat. The corresponding mean daily intake in function of body weight was 0, 0.406, 4.06, 30.6 and 64.5 mg/kg in males and 0, 0.546, 5.47, 41.5 and 87.7 mg/kg b.w. for females.
Due to the poor survival in this study, it was necessary to terminate the study after 22 months, as opposed to the normal 24 months. The percent survival of male rats was 44, 42, 31, 41, and 54% for the 0, 10, 100, 750, and 1500 ppm groups, respectively, after being fed Triflusulfuron-methyl for 670 days. The female rats had percent survival rates of 38, 44, 37, 35, and 46% for the 0, 10, 100, 750, and 1500 ppm groups, respectively, after being fed Triflusulfuron-methyl for 670 days. This poor survival rate was considered to be not compound-related.

A decreased body weight (up to – 16%) in the 750 (transiently) and 1500 ppm dose groups was observed.
A moderate (up to -17%), compound-related decrease in circulating erythrocyte mass was observed in male rats fed dietary concentrations of 750 and 1500 ppm Triflusulfuron-methyl. These changes were evident at the 3, 6, 12 and 18-month sampling times. No compound-related haematological alterations were observed in female rats.
A compound-related statistically significant increase (+13%) in mean liver weight occurred in the 1500 ppm female rats in the 12-month interim sacrifice. There were no microscopic findings associated with this change.
A slight increase (+ 5-6%, not statistically significant) in mean absolute testes weight occurred in the 1500 ppm males at the final sacrifice. Additionally, mean relative testes weight of the 1500 ppm males was statistically increased (+ 23-28%). Mean relative testes weight of the 750 ppm males was not statistically increased (1-year treatment, + 14%). The increase in absolute testes weight may have been the result of compound-related interstitial cell hyperplasia. However, the increase in relative testes weights was primarily due to the decrease in mean final body weight of the 1500 ppm males.
There were no compound-related gross or microscopic effects noted at the 12-month interim sacrifice. Compound-related microscopic effects were observed in the testes of male rats fed 750 and 1500 ppm Triflusulfuron-methyl and in the sciatic nerve of both male and female rats fed 1500 ppm for 22 months (table 4.10.1.1-1).

Table 4.10.1.1-1 - Two-Year feeding study in rats: Triflusulfuron-methyl-induced microscopic effects

Triflusulfuron-methyl (ppm):	**0**	**10**	**100**	**750**	**1500**
Males:					
Testes					
Number examined	*51*	*46*	*47*	*50*	*51*
Adenoma, interstitial cell	*0*	*2*	*1*	*7**	*7**
Hyperplasia, interstitial cell	*10*	*7*	*11*	*18**	*27**
Sciatic nerve					
Number examined	*51*	*45*	*47*	*50*	*51*
Myelin/axon degeneration	*42 (40min, 2mil)*	*38 (38min)*	*40 (38min, 1mil, 1mod)*	*40 (36min, 3mil, 1mod)*	*46 (35min, 9mil, 2mod)*

Table 4.10.1.1-1- Two-Year feeding study in rats: Triflusulfuron-methyl-induced microscopic effects (continued)

Triflusulfuron-methyl (ppm):	**0**	**10**	**100**	**750**	**1500**
Females:					
Sciatic nerve					
Number examined	*48*	*51*	*48*	*48*	*49*

Myelin/axon degeneration	*25 (25min)*	*31 (31min)*	*32 (32min)*	*33 (32min, 1mil)*	*42* (30min, 12mil)*

*Statistically significant ($p \leq 0.05$). Grade of lesions: min=minimal, mil=mild, mod=moderate.

In the testes, there was an elevated incidence of both interstitial cell (Leydig cell) adenoma and hyperplasia in male rats fed 750 and 1500 ppm Triflusulfuron-methyl. Most Leydig cell lesions were not observed until late in the study. The incidence of Leydig cell hyperplasia for male rats being fed 0, 10, 100, 750, and 1500 ppm was 19.6, 15.2, 23.4, 36.0, and 52.9%, respectively, and the incidence of Leydig cell adenomas was 0, 4.3, 2.1, 14.0, and 13.7%, respectively, with adenomas being defined as a lesion greater in size than three cross sections of seminiferous tubules.

A statistically significant increase in the incidence of myelin/axon degeneration of the sciatic nerve was observed in 1500 ppm females. Although an increased incidence in this lesion was not apparent in males, there was an increase in lesion severity in 1500 ppm males. The effect in both males and females was primarily an increase in lesions graded as mild (table 4.10.1.1-1). Furthermore, almost all of the lesions graded as mild occurred in rats examined at the final sacrifice.

The sciatic nerve lesions noted in this study are likely due to an exacerbation, by some unknown mechanism, of the spontaneous lesion seen commonly in the aging rat. The mild nature of this observation, the significantly high background incidence among ageing control rats, its absence in other species tested for chronic toxicity, and the absence of neurological effects in the long term study suggest that Triflusulfuron-methyl is not a neurotoxin. Moreover, most substances toxic to the peripheral nervous system have a diffuse effect and lead to symmetrical polyneuropathy. However, in the present study, lesions occurred only in the sciatic nerve. Sections of optic nerve, present with the eye, were free of lesions as were sections of the spinal cord. Rear limb skeletal muscle innervated by the sciatic nerve was also unaffected, and there was no clinical evidence of a peripheral neuropathy at any time during the study. Further, one would expect that lesions caused by substances that are directly toxic to the nerve would appear sooner than at the end of a two-year feeding study.

The NOAEL for Triflusulfuron-methyl in the 2-year feeding study in rats was 100 ppm (4.06 mg/kg/day) for males and 750 ppm (41.5 mg/kg/day) for females. In male rats, this NOAEL was based on decreases in circulating erythrocyte mass and increased incidences of interstitial cell (Leydig cells) hyperplasia and adenoma in groups fed at 750 or 1500 ppm. In female rats, triflusulfuron was not carcinogenic, and the NOAEL was based on body weight effects and increased incidence of sciatic nerve degeneration at 1500 ppm.

- Mice

In the 18-month long term/carcinogenicity study in mouse, Triflusulfuron-methyl (66037-24, carbamate process, purity 95.6%) was administered to groups of 110 male and 110 female CD-1 mice. The substance was incorporated in the diet at 0, 10, 150, 2500 or 7000 ppm for 18 months. The calculated mean daily intake of Triflusulfuron-methyl was 0, 1.37, 20.9, 349 or 1024 mg/kg body weight for males and 0, 1.86, 27.7, 488 or 1360 mg/kg body weight for females. After approximately 2 weeks and 3 and 12 months of feeding, cell proliferation was evaluated in the livers of five mice from each group. At these time points, additional mice from each group were sacrificed and evaluated for hepatic peroxisomal beta-oxidation activity and hepatic cytochrome P-450 content.

A slight decrease of body weight gain was seen at 7000 ppm in both sexes (-11 to –13%).
The liver cell proliferation indices of the 7000 ppm male and female mice were not affected by test substance administration at any of the time points evaluated (2 weeks and 3 and 12 months). There were statistically significant elevations (+46 to +81%) in the total hepatic microsomal cytochrome P-450 content in 7000 ppm males and females at two weeks and in 7000 ppm females at 3 months. Although not statistically significant, the hepatic cytochrome P-450 content was also elevated in 7000 ppm males at 3 months. There were no

effects on cytochrome P-450 at the 12-month time point. There were no test substance-related changes in hepatic beta oxidation activity at any of the time points evaluated.
Absolute and relative liver weights were increased relative to controls in the 2500 (+8 to +10%) and 7000 ppm (+26 to +30%) male and female groups. The increases in liver weight correlated with the elevated hepatic cytochrome P-450 activity in the 7000 ppm mice. Other organ weights for both males and females were comparable to controls. Compound-related non-neoplastic changes occurred in the liver of male mice fed 2500 ppm and in male and female mice fed 7000 ppm. Increased incidences of hepatic foci of cellular alteration were present in 2500 and 7000 ppm males and females, although this increase was statistically significant only in the female groups. Additionally, there was an increased incidence of intra-hepatocellular erythrocytes in 2500 ppm males and in 7000 ppm males and females (males: 2500 ppm, 5/80; 7000 ppm, 21/80; and females: 7000 ppm, 9/81). This lesion consisted of randomly distributed hepatocytes containing intact erythrocytes. Affected hepatocytes varied in size from normal to three or four times normal. Erythrocytes appeared to be free in the hepatocellular cytoplasm and varied in number from a few to too-numerous-to-count. The hepatocyte nucleus was often displaced to the cell periphery but appeared intact. Lesion severity was graded minimal in all affected livers except for three graded mild and one graded moderate in the 7000 ppm males. The pathogenesis and toxicological significance of this change is unclear. All other microscopic changes occurred in the liver of male mice fed 7000 ppm and included necrosis of individual hepatocytes and increased pigment accumulation in Kupffer cells (Table 4.10.1.1-2).

Slightly increased incidences of hepatocellular adenomas were present in 2500 and 7000 ppm males (Table 4.10.1.1-2). These increases were statistically significantly relative to controls by the Cochran-Armitage trend test. This increase in adenomas also resulted in an increase in the combined incidence of adenomas and carcinomas in the 7000 ppm male group, even though incidences of carcinomas in this group were actually less than in controls. Background incidences of hepatocellular tumours are high in male mice of this strain in chronic studies. The increases in hepatocellular adenomas in 2500 and 7000 ppm males were within laboratory historical control ranges, were not statistically significant by the Fishers exact test, and were not associated with increased incidences of hepatocellular carcinomas. Similarly, a small increase in hepatocellular adenomas (and thus combined adenomas and carcinomas) was present in females fed 2500 ppm. This increase was not dose-related as only one hepatocellular tumour occurred in the 7000 ppm female group.

Table 4.10.1.1-2**– 18-month feeding study in mice: Triflusulfuron-methyl-induced microscopic effects**
MALES

Triflusulfuron-methyl (ppm): **Number of mice/group:**	**0** **81**	**10** **80**	**150** **81**	**2500** **81**	**7000** **80**
Liver					
Adenoma, hepatocellular[a]	*10*	*4*	*5*	*13**	*15**
Carcinoma, hepatocellular	*3*	*3*	*0*	*0*	*1*
Adenoma and/or Carcinoma[b]	*12*	*7*	*5*	*13*	*16**
Focus of hepatocellular alteration	*9*	*11*	*9*	*14*	*15*
Intracellular pigment accumulation, Kupffer cell/macrophage	*16*	*8*	*10*	*12*	*37#*
Intrahepatocellular erythrocytes	*0*	*0*	*0*	*5#*	*21#*
Necrosis, individual hepatocellular, increased	*0*	*1*	*2*	*2*	*14#*

FEMALES

Triflusulfuron-methyl (ppm): **Number of mice/group:**	**0** **78**	**10** **81**	**150** **79**	**2500** **83**	**7000** **81**
Liver					
Adenoma, hepatocellular[a]	*0*	*0*	*0*	*4*	*1*
Carcinoma, hepatocellular	*0*	*0*	*0*	*1*	*0*
Adenoma and/or Carcinoma[b]	*0*	*0*	*0*	*5#*	*1*
Focus of cellular alteration	*2*	*1*	*3*	*6*	*7**
Intracellular pigment accumulation, Kupffer cell/macrophage	*24*	*34*	*27*	*22*	*26*
Intrahepatocellular erythrocytes	*0*	*0*	*0*	*0*	*9#*
Necrosis, individual hepatocellular, increased	*1*	*0*	*0*	*0*	*1*

a Includes single or multiple adenomas (there were no multiple adenomas in females)

b Total incidence of mice with hepatocellular tumours (adenoma, carcinoma, or both)

* Statistically significant by the Cochran-Armitage trend test ($p \leq 0.05$)

\# Statistically significant by Fisher's exact test ($p \leq 0.05$)

In conclusion, the NOAEL for Triflusulfuron-methyl was 150 ppm (20.9 mg/kg b.w in males and 27.7 mg/kg b.w in females), this is based on the decrease in mean body weight gain and elevated liver weights and hepatic cytochrome P-450 content in both males and females fed 7000 ppm test article, as well as microscopic findings: increased hepatic foci of cellular alteration and the presence of intrahepatocellular erythrocytes in the mice fed 2500 and 7000 ppm. Slightly increased incidences of hepatocellular adenomas were also present in the 2500 and 7000 ppm male groups.

4.10.1.2 *Carcinogenicity: inhalation*

No studies are available

4.10.1.3 *Carcinogenicity: dermal*

No studies are available

4.10.2 Human information

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4.10.3 Other relevant information

Mechanistic studies with triflusulfuron-methyl in relation to the increase incidences of Leydig cells hyperplasia and adenoma recorded in the 2-year feeding study in rats were assessed.

Hormone analysis in the serum of male rats fed with Triflusulfuron-methyl for 1 year.

Serum had been collected from rats from the chronic 2-year study of Triflusulfuron-methyl, at the 1-year interim sacrifice. Hormone levels (testosterone, estradiol, LH, FSH, and prolactin) were measured in the serum of 10 male rats per treatment group. Radio-immunoassays utilising commercially available kits were used for these hormonal measurements. The results were statistically analysed using (i) an ANOVA, Dunnett's test (assuming normality and homogeneity of variances) and the test for linear trend over groups,

and (ii) normality and homogeneity of variances were verified (Shapiro-Wilk and Leveae test) and when the requirement was not satisfied, Kruskal-Wallis and Dunn's multiple comparisons were done. A one-sided Jonckheere's trend test was also used.
Using statistical analysis (i), in rats fed 750 and 1500 ppm Triflusulfuron-methyl (table 4.10.3-1) there were statistically significant trends of increasing testosterone levels (165 and 189% of control, respectively} and FSH levels (113 and 134% of control, respectively) and a statistically significant trend of decreasing estradiol levels in rats fed 750 and 1500 ppm to 32 and 53% of control, respectively. There were no statistically significant effects on. serum LH or prolactin levels. Using statistical analysis (ii), an additional statistically significant trend of increasing LH concentration was observed in rats fed 1500 ppm Triflusulfuron-methyl. There were no alterations in hormonal levels in rats fed 10 and 100 ppm Triflusulfuron-methyl for 1 year (both statistical analysis).

Table 4.10.3-1 - Summary of hormone levels from male rats fed Triflusulfuron-methyl for 1-year

Conc. (ppm)	Testosterone ng/mL	Estradiol pg/mL	Prolactin ng/mL	LH ng/mL	FSH ng/mL
0	*0.888*	*4.852*	*1.741*	*0.182*	*6.742*
10	*0.810*	*4.183*	*2.766*	*0.155*	*6.197*
100	*0.966*	*3.179*	*1.831*	*0.178*	*7.279*
750	*1.467*	*1.534**	*1.362*	*0.179*	*7.594*
1500	*1.677**	*2.574**	*1.602*	*0.210**	*9.028**

*Statistically significant trend (Jonckheere's trend test) $p < 0.05$

The results of the hormone (estradiol, testosterone, FSH, LH, prolactine) analysis in the serum of rats fed triflusulfuron for 1 year (study HLR 3-93) might support the following mechanism for the test compound, found elsewhere to be an aromatase inhibitor: Triflusulfuron-methyl reduces the serum estradiol levels; this reduction in estradiol results in a perturbation of the negative feedback control of LH and FSH leading ultimately to the observed Leydig cell hyperplasia and increase in adenoma formation (in the 750 and 1500 ppm treated groups). Moreover, there were no alterations in hormonal levels in rats fed 10 and 100 ppm Triflusulfuron-methyl for 1 year and these concentrations did not produce Leydig cell lesions when fed to rats for 2 years.

Two-week oral study in the rat with high doses of Triflusulfuron-methyl.

Male Sprague Dawley rats (10/group) were administered doses of 0, 1000, 1500, and 2000 mg/kg/day of Triflusulfuron-methyl (66037-24, carbamate process, purity 95.6%). A control group, which was pair-fed to the 2000 mg/kg/day group, was included in addition to the *ad libitum* control group. This study also included 10 additional rats in the *ad libitum* control and 2000 mg/kg/day groups; these rats were injected with human chronic gonadotrophin (hCG) 1 hour prior to sacrifice. All rats were weighed daily and the weights were used to adjust the dose volume for each day of dosing. At the termination of the study, livers, accessory sex glands (weighed together), and testes were weighed and serum and testicular interstitial fluid were collected for hormonal measurements (testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin). Hepatic peroxisomes were prepared for beta-oxidation activity measurements, and hepatic microsomes were prepared for measurement of total cytochrome P450 content and aromatase activity. Radio-immunoassays utilising commercially available kits were used for the hormonal measurements. Data were analysed by ANOVA, Dunnett's test, Cochran Armitage test for trend or nonparametric procedure where necessary.

Oral doses of 1000, 1500, and 2000 mg/kg/day caused statistically significant decreases in body weight (11 to 13%), body weight gain (74 to 96%), food consumption (15 to 25%), and food efficiency (71 to 96%) when compared to *ad libitum* control. Test substance-related, statistically significant decreases in absolute

and relative accessory sex gland weights (androgen- and body weight- dependent) were observed in all dose groups. Relative testis weight was slightly increased as well as relative liver weight (Table 4.10.3-2).

Table 4.10.3-2 – Effect of a 2-week administration of Triflusulfuron-methyl on body and organ weights

	Pair fed control	1000 mg/kg	1500 mg/kg	2000 mg/kg
Final body weight	↓1(13)*	↓(11)*	↓(13)*	↓(13)*
Liver weight Absolute relative	 ↓(19)* ↓(7)	 ↓(6) ↑(6)	 ↓(5) ↑(10)*	 ↓(4)# ↑(10)*#
Testis weight Absolute Relative	 - ↑(10)	 - ↑(15)*	 - ↑(9)	 - ↑(14)*
Accessory sex glands Absolute Relative	 ↓(6)* ↓(2)	 ↓(26)* ↓(17)*	 ↓(35)* ↓(25)*	 ↓(30)*# ↓(20)*#

↓: decrease, ↑: increase, -: no statistically significant change, ( ): % from *ad libitum* control, *: statistically significant from *ad libitum* control, #: statistically significant from per fed control

Hormone analysis revealed no alterations in serum or interstitial fluid testosterone concentrations. Serum estradiol levels were statistically decreased to 31.9, 13.6, and 13.4% (13.6%, of pair-fed control) of *ad libitum* control in the 1000, 1500, and 2000 mg/kg/day dose groups, respectively. Interstitial fluid estradiol levels were unremarkable. Although not statistically significant in the 1000, 1500 and 2000 mg/kg/day groups, LH levels were slightly elevated to 133, 113, and 160% of control, respectively, FSH levels were elevated to 141, 141, and 122% of control, respectively, and prolactin levels were elevated to 128, 137, and 150% (250, pair fed) of control, respectively. Inter-individual variations were high. In hCG-stimulated rats dosed with 2000 mg/kg/day, serum testosterone level of the treated rats was statistically elevated to 192% of control and the serum estradiol level was statistically decreased to 24% of control. The serum LH, FSH, and prolactin and interstitial fluid testosterone and estradiol levels of hCG-stimulated rats were not statistically different from that of the control group. Measurements of hepatic beta-oxidation (peroxisome proliferation) and total cytochrome P450 content were unremarkable. Hepatic microsomal aromatase activity (cytochrome P450 isoenzyme responsible for the conversion of testosterone to estradiol) was not statistically significantly altered by administration of the test substance. Inter-individual variations were high, particularly in the control groups.

In a short-term study (2 weeks) in which high doses of Triflusulfuron-methyl were administered to rats, a significant decrease in serum estradiol levels was the most prominent effect of the test substance on hormonal levels. Serum testosterone concentrations were only increased after hCG challenge suggesting that the test compound enhances testosterone synthesis when the biosynthesis pathway is stimulated. LH, FSH and prolactin concentrations in serum were only slightly elevated (not statistically significant) after treatment. The decreased serum estradiol levels in the absence of altered testosterone levels in non-stimulated rats suggest that the test substance might acts to inhibit activity of the cytochrome P450 enzyme, aromatase, responsible for the transformation of testosterone to estradiol. However the activity of aromatase in the liver was not found modified after a short-term exposure to Triflusulfuron-methyl.

***In vitro* biochemical studies with Triflusulfuron-methyl**

In the *in vitro* biochemical studies, the following parameters were evaluated

- The cytochrome P450 spectra characteristics produced by the test substance were observed spectrophotometrically after incubation with hepatic microsomes from phenobarbital-induced rats;
- The ability of the test substance (at concentrations from 0.01 to 0.5 mM) to inhibit ammonium perfluorooctanoate (C8)-induced hepatic microsomal aromatase activity was measured. This assay measured the release of tritiated-water from androstan-4-ene-3,17-dione [1-beta-^{3}H] as an indicator of aromatase activity;

- The direct effect of the test substance, at concentrations from 0.1 to 1,000 μM, on isolated and cultured Leydig cells was assessed. The ability of the Leydig cells to produce testosterone, estradiol, and progesterone was measured in the presence and absence of hCG.

The test substance produced a Type II binding spectra with a peak at 435 nm and a trough at 415 nm. Ligands producing type II binding spectra are known to inhibit cytochrome P450 isozymes (for example, aminoglutethimide, which inhibits the cholesterol side chain cleavage and aromatase by interacting with cytochrome P450 isozymes, produce a type II binding spectra);
Triflusulfuron-methyl inhibited C8-induced aromatase activity in a dose-dependent manner. The estimated value for aromatase inhibition in C8-induced rat liver microsomes was, IC_{50} of 173.6 μM. Compared to other aromatase inhibitors, this value demonstrates a weak inhibitory response by Triflusulfuron-methyl *in vitro* (table 4.10.3-3).
Statistically significant decreases in estradiol synthesis (from – 31 to – 67%) by isolated Leydig cells were present at the two highest *in vitro* concentrations tested (100 and 1000 μM.). This decrease occurred in both hCG-stimulated and non-stimulated Leydig cells. A statistically significant increase in testosterone production (+ 99%) by non-hCG-stimulated Leydig cells was present at 1000 μM. Progesterone production was not affected. These data indicate that the compound does not inhibit testosterone biosynthesis but suggest that it inhibits the ability of Leydig cells to aromatize testosterone to estradiol.

Table 4.10.3-3 - Effect of Triflusulfuron-methyl on hepatic microsomal aromatase activity *in vitro*

Concentration (mM)	**Aromatase activity (fmol/min)**
0	*14025.54*
0.01	*12595.05**
0.02	*12093.99**
0.05	*10981.64**
0.1	*9325.72**
0.2	*7695.15**
0.5	*5463.81**

* Statistically significant difference from control by Dunnett's test, $p < 0.05$.

The *in vitro* studies (cytochrome P450 binding spectrum, hepatic aromatase activity and *in vitro* synthesis of testosterone, estradiol and progesterone by isolated Leydig cells) conducted with Triflusulfuron-methyl indicate that the compound is a likely aromatase inhibitor via a type II binding to cytochrome P450 and then inhibits the transformation of androgens to oestrogens.

To determine if oral gavage administration of low levels of Triflusulfuron-methyl (66037-24, carbamate process, purity 95.6%) would induce biologically significant hormonal alterations in male rats, male Sprague Dawley rats (15 per group) were dosed daily by oral gavage with 0, 0.1, 0.5, or 5.0 mg Triflusulfuron-methyl/kg body weight/day in a methyl cellulose/Tween 80 vehicle for 28 days. Doses were selected based on results from the 2-year study in rats. Serum was prepared from the collected blood and frozen until analysed for serum hormone concentrations (estradiol, testosterone, LH, FSH, and prolactin).
Since homogeneity of the test substance in gavage suspensions were found questionable at the beginning of the study, the vehicle was modified during the study. No clinical signs of toxicity were observed over the course of the study. There were no test substance-related effects on body weights, food consumption, or food efficiency. There were no statistically significant effects on any organ weights measured. There were no test substance related effects on serum testosterone, LH, FSH, or prolactin over the course of the study. In addition, administration of Triflusulfuron-methyl was not associated with a decrease in serum estradiol, the expected response to an aromatase inhibitor, at any concentration or time point evaluated. Serum estradiol

concentrations increased over the dosing period in all groups including controls except in the 5.0 mg/kg/day group (the biological meaning of these results is however not clear, table 4.10.3-4).

Table 4.10.3-4 – Effects of Triflusulfuron-methyl on serum estradiol concentrations (pg/mL) in rats

	Control	0.1 mg/kg	0.5 mg/kg	5.0 mg/kg
Pre-study	5.905 ± 0.462	5.122 ± 0.577	4.802 ± 0.581	5.043 ± 0.340
Week 2	8.483 ± 0.426	7.218 ± 0.701	7.267 ± 0.682	6.348 ± 0.492
Week 4	10.005 ± 0.665	9.477 ± 0.884	8.160 ± 0.620	7.365 ± 0.487
Recovery	6.859 ± 0.999	-	-	6.541 ± 0.727

The NOAEL of Triflusulfuron-methyl in this study was 5.0 mg/kg/day based on the absence of biologically significant effects on serum hormone concentrations at any time point evaluated.

4.10.4 Summary and discussion of carcinogenicity

The long term toxicity and carcinogenicity of Triflusulfuron-methyl were evaluated in rats and mice. They were completed with appropriate mechanistic *in vivo* and *in vitro* studies. All studies were found acceptable and suitable to assess the oncogenic potential in rodents.

In the rat study, Triflusulfuron-methyl (66037-24, carbamate process, purity 95.6%) was incorporated in the diet at 0, 10, 100, 750 and 1500 ppm for 22 months. The NOAEL for Triflusulfuron-methyl in this long-term feeding study in rats was 100 ppm (4.06 mg/kg/day) for males and 750 ppm (41.5 mg/kg/day) for females. In male rats, this NOAEL was based on decreases in body weight, food consumption and circulating erythrocyte mass and increased incidences of interstitial cell (Leydig cells) hyperplasia and adenoma in groups fed at 750 or 1500 ppm. In female rats, Triflusulfuron-methyl was not carcinogenic, and the NOAEL was based on body weight effects and increased incidence of sciatic nerve degeneration at 1500 ppm (this effect was also observed in the male rat at the same dose level but was not statistically significant).

Oncogenic effects of Triflusulfuron-methyl in rats were limited to the males and consisted of increased incidence of interstitial (Leydig) cell adenomas at dietary concentrations of 750 ppm and above. Because Triflusulfuron-methyl has been shown to be non-genotoxic in a battery of genotoxicity tests, a series of *in vitro* and *in vivo* mechanistic studies were undertaken to define the mechanism of interstitial cell tumour genesis. These studies suggested that Triflusulfuron-methyl is a weak aromatase inhibitor *in vitro* (hepatic microsomes and cultured Leydig cells) via a type II binding to cytochrome P450. Although, hepatic aromatase activity was not significantly decreased *in vivo* for doses up to 2000 mg/kg b.w. administered to rats for 14 days, a significant decrease in serum estradiol levels was the most prominent effect of the test substance on hormonal levels in short-term or long term rat studies. A trend to increasing LH, FSH and testosterone levels was also observed in rat blood in the 1-year study, for dietary concentrations of Triflusulfuron-methyl inducing increased incidences of interstitial (Leydig) cell adenomas. The following possible mechanism of oncogenicity of Triflusulfuron-methyl in rat can be proposed from experimental *in vitro* and *in vivo* findings: the decrease in serum estradiol after treatment with Triflusulfuron-methyl results in a perturbation of the negative feedback control of LH and FSH. This perturbation is manifested as elevated levels of serum LH and FSH and results in an increase in serum testosterone. The long-term hypersecretion of LH is ultimately responsible for the observed increases in Leydig cell hyperplasia and adenoma formation. Disruption of the hypothalamic-pituitary-testis axis is a well known mechanism of Leydig cell hyperplasia and adenoma formation in the rat by non-genotoxic compounds. Exposure to Triflusulfuron-methyl at levels which do not inhibit estradiol synthesis should not increase the incidence of Leydig cell tumours. The experimental results support a threshold for the Triflusulfuron-methyl-induced Leydig cell tumours in the rat lying within the range of 100 and 750 ppm.

In the mouse, Triflusulfuron-methyl (66037-24, carbamate process, purity 95.6%) was incorporated in the diet at 0, 10, 150, 2500 or 7000 ppm for 18 months. The NOAEL for Triflusulfuron-methyl was 150 ppm (20.9 mg/kg b.w in males and 27.7 mg/kg b.w in females), based on decrease in mean body weight gain and elevated liver weights and hepatic cytochrome P-450 content in both males and females fed 7000 ppm test article, as well as on the following microscopic findings: increased hepatic foci of cellular alteration and the presence of intra-hepatocellular erythrocytes in the mice fed 2500 and 7000 ppm. Slightly increased incidences of hepatocellular adenomas were also present in the 2500 and 7000 ppm male groups.
The pathogenesis and toxicological significance of the presence of erythrocytes in hepatocytes is unclear. As indicated in the dossier, a similar hepatic lesion was seen in mice from a 18 month feeding study with Bromacil. Atypical hepatocytes were also described in treated male mice from a chronic feeding study with doxylamine succinate, an antihistaminic compound. The lesion significance or aetiology was not determined.

To conclude, the target organs of Triflusulfuron-methyl in long term studies were the testis in rat and the liver in mouse. In the rat, the test compound might be considered a weak aromatase inhibitor, inducing a decrease in blood estradiol and a subsequent disruption of the hypothalamic-pituitary-testis axis, a well recognised mechanism of Leydig cell hyperplasia and adenoma formation in the rat by non-genotoxic compounds. In the mouse, Triflusulfuron-methyl slightly increased the incidence of hepatocellular adenomas in the high dose male groups.

4.10.5 Comparison with criteria

Rationale for classification as a Carcinogen:

The CLP criteria for classification as a category 2 Carcinogen (category 3 carcinogen according to Directive 67/548/EEC) are as follow :
"Substances are classified as a category 2 Carcinogen when evidence is obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies."
In the mouse, Triflusulfuron-methyl slightly increased the incidence of hepatocellular adenomas at the higher dose. The increase in hepatocellular adenoma in the 2500 and 7000 ppm male mice groups was not considered relevant for human risk assessment for the following reasons: (i) the compound did not induce an increase in the formation of hepatic tumours in female mice at any dietary concentration, (ii) the occurrence of hepatic tumours was predominantly benign and the overall tumour incidence (of any type) was not increased in male or female treated mice when compared to the control, (iii) hepatic cell proliferation indices were similar between the control and the high dose group, (iv) Triflusulfuron-methyl was negative in a spectrum of short-term tests for mutagenicity and (v) it did not induce hepatic tumour formation in rats.
This does not fulfil the criteria for Cat 2 H351 classification.

In male rats, Triflusulfuron-methyl induced increased incidence of Leydig cell hyperplasia and adenomas at 750 or 1500 ppm. Mechanistic studies suggested that Triflusulfuron-methyl is a weak aromatase inhibitor, inducing a decrease in blood estradiol and a subsequent disruption of the hypothalamic-pituitary-testis axis, as well recognised mechanism of Leydig cell hyperplasia and adenoma formation in the rat by non-genotoxic compounds. This mechanism is considered relevant to humans. The notifier considers that the relevance of these tumours to human risk assessment is questionable mainly because (i) they are extremely rare in humans, (ii) the rat is more sensitive than human to disruption of the hypothalamus-pituitary-testis axis for physiological reasons (LH half-life, number of LH receptors on Leydig cells, qualitative and quantitative difference in hormonal stimulation effects) and (iii) of the results of some epidemiological studies. However, according to a specialized expert working group (see the Draft summary record of the meeting of Ispra, January 22_23 2004, ECBI/08/04 Rev 2, April 2004), substances causing Leydig cell tumours in rats by perturbating the HPT axis should be classified in Carcinogen Category 3, unless the mechanism can be proven not to be relevant for human Leydig cell carcinogenesis. Among the currently identified non-genotoxic mechanisms of rodent Leydig cell tumorigenesis (see review in Cook et al., *Critical Reviews in Toxicology*, 1999, 29(2), 169-261), only dopamine and GnRH agonist mediated-effects are not considered

relevant for humans. Therefore, as the mechanism of action of Triflusulfuron-methyl on Leydig cells was likely mediated by aromatase inhibition, the compound should be classified as a Cat 2 H351 classification.

4.10.6 Conclusions on classification and labelling

Based on the fact that evidence of carcinogenicity is restricted to a single experiment/specie, on the lack of genotoxicity potential and on the additional studies showing that disruption of the hypothalamic-pituitary-testis axis lead to the Leydig cell tumours, triflusulfuron-methyl can be considered as a non-genotoxic carcinogen and should not be classified as category 1B Carcinogen (category 2 carcinogen according to Directive 67/548/EEC).

In accordance with the criteria in Directive 67/548/EEC, classification in category 1 for carcinogenicity is not justified given that there is no evidence of Triflusulfuron-methyl having caused cancer in humans.

Based on the increased incidence of Leydig cell hyperplasia and adenomas at high doses in one specie which was considered as relevant to humans , a classification **Carc. Cat. 3; R40** is proposed.
Because evidence of carcinogenicity in rats is obtained from a single study, it is considered that there is a "limited evidence of carcinogenicity effects" which deserves a **classification Category 2– H351** according to CLP criteria.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

One two-year cancer bioassay in Sprague Dawley rats and one 18-month cancer bioassay in CD-1 mouse were described in the CLH report, as well as mechanistic studies related to hormone levels and aromatase effects. In mice a slight increase in hepatocellular adenomas was seen at the high dose. The DS concluded that this effect was not sufficient for classification.

In rats, Leydig cell hyperplasia and adenomas were seen at the two highest doses. Although arguments questioning the relevance for humans were discussed in the CLH report, the DS concluded that this effect was considered to be relevant to humans. Summary tables of the main results in the carcinogenicity studies presented by the DS are given below.

Table 1 - Two-year feeding study in rats: Triflusulfuron-methyl-induced microscopic effects in testes

Triflusulfuron-methyl (ppm):	**0**	**10**	**100**	**750**	**1500**
Number examined	*51*	*46*	*47*	*50*	*51*
Adenoma, interstitial cell	*0*	*2*	*1*	*7**	*7**
Hyperplasia, interstitial cell	*10*	*7*	*11*	*18**	*27**

*Statistically significant ($p \leq 0.05$).

Table 2– 18-month feeding study in mice: Triflusulfuron-methyl-induced microscopic

effects

MALES

Triflusulfuron-methyl (ppm): Number of mice/group:	**0 81**	**10 80**	**150 81**	**2500 81**	**7000 80**
Liver					
Adenoma, hepatocellular[a]	*10*	*4*	*5*	*13**	*15**
Carcinoma, hepatocellular	*3*	*3*	*0*	*0*	*1*
Adenoma and/or Carcinoma[b]	*12*	*7*	*5*	*13*	*16**
Focus of hepatocellular alteration	*9*	*11*	*9*	*14*	*15*
Intracellular pigment accumulation, Kupffer cell/macrophage	*16*	*8*	*10*	*12*	*37#*
Intrahepatocellular erythrocytes	*0*	*0*	*0*	*5#*	*21#*
Necrosis, individual hepatocellular, increased	*0*	*1*	*2*	*2*	*14#*

FEMALES

Triflusulfuron-methyl (ppm): Number of mice/group:	**0 78**	**10 81**	**150 79**	**2500 83**	**7000 81**
Liver					
Adenoma, hepatocellular[a]	*0*	*0*	*0*	*4*	*1*
Carcinoma, hepatocellular	*0*	*0*	*0*	*1*	*0*
Adenoma and/or Carcinoma[b]	*0*	*0*	*0*	*5#*	*1*
Focus of cellular alteration	*2*	*1*	*3*	*6*	*7**
Intracellular pigment accumulation, Kupffer cell/macrophage	*24*	*34*	*27*	*22*	*26*
Intrahepatocellular erythrocytes	*0*	*0*	*0*	*0*	*9#*
Necrosis, individual hepatocellular, increased	*1*	*0*	*0*	*0*	*1*

a Includes single or multiple adenomas (there were no multiple adenomas in females)

b Total incidence of mice with hepatocellular tumours (adenoma, carcinoma, or both)

* Statistically significant by the Cochran-Armitage trend test ($p \leq 0.05$)

\# Statistically significant by Fisher's exact test ($p \leq 0.05$)

Several mechanistic studies were presented by the DS in relation to the increased incidences of Leydig cells hyperplasia and adenomas:

Hormone levels in serum of male rats fed with triflusulfuron-methyl for 1 year were analysed. Doses were 0, 10, 100, 750 and 1500 ppm. Testosterone, estradiol, Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) levels were affected at the higher doses (750 and 1500 ppm) while prolactin remained constant. The DS suggest that the reduction seen in estradiol (possibly caused by aromatase inhibition, see below) would lead to increased FSH and LH levels, in turn leading to the observed Leydig cell hyperplasia and increase in adenoma formation. At lower doses (10 and 100 ppm) where no effects on hormone levels were seen, no tumours were observed.

In a two-week oral study in the rat with high doses (0, 1000, 1500, 2000 mg/kg/day) of triflusulfuron-methyl, the relative and absolute weight of accessory sex glands was significantly reduced in comparison with pair-fed controls. Levels of estradiol were again

decreased accompanied by a small increase in LH and FSH.

A number of *in vitro* studies were reported. It was shown that triflusulfuron-methyl acted as an aromatase inhibitor at all doses tested and that synthesis of estradiol was inhibited in cultured Leydig cells. However, in a 28 day oral Sprague-Dawley rat study dosed daily with low levels of triflusulfuron-methyl (up to 5 mg/kg bw/day), no decrease in estradiol or other hormone levels was seen.

The DS proposed classification as CLP Category 2 with H351.

Comments received during public consultation

Three Member States agree to the proposal. One industrial organisation disagreed with the classification and questioned the relevance of the animal data to humans.

During public consultation Industry stated that the tumours in male rats occurred in aged rats known to be especially susceptible to this tumour type. They further questioned the human relevance of the findings from a mechanistic point of view.

According to the Commission Working Group of Specialised Experts on carcinogenicity, mutagenicity and reprotoxicity (COM WG), studies on Fischer rats or other strains having a comparably high spontaneous Leydig cell tumour rate are normally not informative with regard to Leydig cell tumours (ECBI/08/04 Rev.2). However, the two-year study considered here was carried out with Sprague-Dawley (SD)-rats.

SD rats are reported not to be as susceptible as Fischer rats to the development of Leydig cell tumours in aged animals, even if such tumours in the case of triflusulfuron-methyl were not observed until late in the study. Thus RAC considers SD-rats to be a relevant species for findings on Leydig cell tumours leading to classification. Industry also questioned the human relevance of the mode of action of triflusulfuron-methyl on the Leydig cells. However RAC agreed with the DS and the COM WG that Leydig cell tumours in rats are relevant to humans if the mode of action is not through the perturbation of the hypothalamus-pituitary-testis (HPT) axis as a dopamine agonist or a gonadotropine releasing hormone (GnRH) agonist do. In the case of triflusulfuron-methyl the mode of action is probably mediated by aromatase inhibition, and considered relevant to humans.

<u>Comments received shortly before the RAC plenary</u>

Industry submitted a document entitled "Response to Opinion Development Document", with comments to the RAC draft opinion. In this document Industry expressed their disagreement with the draft opinion in relation to the conclusions contained in ECBI/08/04 Rev.2 regarding the possible human relevance of Leydig cell tumors (LCT). . In Industry's view, new information (published after 2004) on humans with mutations in the aromatase encoding gene (CYP-19) and new information from aromatase knock-out mice (CYP-19 knock out) supports an alternative mode of action. Industry summarised studies with 9 adult men aged 25-30 with aromatase deficiency where no instances of testicular neoplasia were reported from the clinical examination. Industry also stated that neither were any Leydig Cells Tomours seen in the aromatase knock-out mice, which in Industry's opinion is a better model than the rat for predicting LCT in humans.

Industry challenged the proposed mode of action from the COM WG and also described human cases as well as mice studies with the *opposite* MoA, where LCT is induced after increased aromatase expression, and not after inhibition.

These comments were received less than 10 calendar days prior to the RAC plenary meeting and the Committee was unable to take them fully into account. It was pointed out that considering the DS proposal for Repr. 2 under CLP which had been open for public consultation, this information could more appropriately have been submitted at

that point in time. None of the supporting studies were new and the late introduction of these comments in the context of an opinion tabled for discussion/adoption was not explained to the Committee.

Additional key elements

Historical control values for Leydig cell tumours in SD rats were not reported by the DS, but are available in previous RAC opinions (and Annexes) on PFOA and APFO published by ECHA in 2011:

The historical control incidence of Leydig cell adenomas was 0.82% (from 1 340 Sprague-Dawley rats used in 17 carcinogenicity studies. The spontaneous incidence of Leydig cell tumours in 2-year old Sprague-Dawley rats is reported to be approximately 5% (Clegg et al., 1997).

The DuPont Haskell Laboratory report on the rat carcinogenicity study of triflusulfuron-methyl is dated 1993, so the mentioned historical control values are probably reasonable to use in this case. The incidence of Leydig cell adenoma in the two highest dose groups in the rat study of triflusulfuron-methyl was 14.0 and 13.7%, respectively, and exceeded the historical control incidences reported in the papers cited above.

Assessment and comparison with the classification criteria

The carcinogenicity data for triflusulfuron-methyl consists of a 2-year carcinogenicity study in rats and an 18 month combined chronic toxicity/carcinogenicity study in mice. No information in humans was available. Thus classification in CLP Category 1A and Category 1 in DSD is not warranted.

In SD rats there was a statistically significant increase in incidences of interstitial cells hyperplasia (Leydig cells, testes) and adenomas at the two highest dose levels. No neoplastic lesions were observed in female rats. In mice, triflusulfuron-methyl slightly increased the incidence of hepatocellular adenomas in males at the two highest dose levels. There was no increase of tumours in female mice.

The slight increase of hepatocellular adenomas in male mice in the two highest dose groups and in female mice in the 2500 ppm dose group are not considered relevant for classification because they were within laboratory historical control ranges, only statistically significant in male mice, predominantly benign, and only observed in a single species. Also no effect was observed in mice on hepatic cell proliferation.

According to CLP a substance should be classified in Category 1B if a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of a combination of benign and malignant neoplasms in at least two species or in two independent studies in one species. Substances may also be classified in Category 1B according to CLP if they produce an increased incidence of tumours in both sexes of a single species in a well-conducted study or if the substance leads to an unusual degree of malignant of neoplasms in one species and sex.

In this case the findings are not sufficient to justify classification in CLP Category 1B.

According to the DSD, classification in Category 2 requires either positive results in two animal species or clear positive evidence in one species, together with supporting evidence. For triflusulfuron-methyl classification in Category 2 according to DSD is not required.

CLP states that substances should be classified as Category 2 carcinogens when evidence is obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited evidence of

carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies. In the case of triflusulfuron-methyl, there is limited evidence of carcinogenicity in rats and mice manifested as benign tumours in different organs, i.e. testes (rats) and liver (male mice). The findings in mice are not considered relevant for classification for the reasons given above. There is no clear dose-response for the tumour findings in rats, as 7 testis adenomas were found in each of the two highest dose groups and none in the other dose groups. For interstitial cell hyperplasia a dose-response was present in male rats. Studies of a possible mode of action (MoA) in rats indicate that the carcinogenic effect from triflusulfuron-methyl on Leydig cells stems from a perturbation of the hypothalamus-pituitary-testis (HPT) axis mediated by aromatase inhibition. This MoA is considered to be relevant to humans.

RAC agreed with the DS that classification in CLP Category 2 with H351 was justified. In parallel, the DS proposal for classification in Category 3 with R40 according to DSD was also justified, as there was some evidence from appropriate animal studies.

4.11 Toxicity for reproduction

Table 18. Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
Two generation feeding in the Sprague Dawley rats 0, 10, 100, 750 or 1500 ppm corresponding to 0, 0.588, 5.81, 44.0 and 89.5 mg/kg b.w for F0 males and 0, 0.764, 7.75, 58.0 and 115.0 mg/kg b.w. for F0 females 0, 0.785, 7.84, 59.6 and 123.0 for F1 males 0, 0.881, 8.96, 67.2 and 137.0 mg/kg b.w for F1 females OECD 416	No reproductive and developmental effects at 1500 ppm. NOAEL for reproductive effects ≥ 1500 ppm in M (89.5 – 123 mk/kg b.w/day) and F (115.0-137.0 mg/kg b.w/day) At doses ≥ 750 ppm: ↓ in body weight and nutritional parameters in parental rats and a slight ↓ of body weights in pups NOAEL for overall toxicity in adults and offspring = 100 ppm (5.81-7.75 mg/kg b.w. /day in males and 7.84-8.96 mg/kg b.w./day in females)	Purity: 95.6% "carbamate process"	Hurtt M.E., Kreckman K.H. (1993)
Teratogenicity oral (gavage) study in Sprague Dawley rats 0, 30, 120, 350 or 1000 mg/kg b.w/day OECD 414	↓body weight and food consumption at doses ≥ 350 mg/kg b.w NOAEL for maternal toxicity = 120 mg/kg b.w. ↓of the incidence of malformations at 1000 mg/kg and visceral and skeletal variations in foetuses at doses ≥ 350 mg/kg. The developmental effects occurred at maternal toxic doses, were of low incidences and were in the historical control limits. Then a teratogenic effect of the test compound is questionable. NOAEL for developmental toxicity and teratogenicity = 120 mg/kg b.w.	Purity: 95.6% "carbamate process"	Mebus C.A. (1991), Mylchreest E. (2002)
Teratogenicity oral (gavage) study in (NZW)SPF rabbits 0, 15, 90, 270 or 800 mg/kg b.w/day OECD 414	↓body weight and nutritional changes at doses ≥ 90 mg/kg/day and ↑mortality and abortions in animals administered doses ≥ 270 mg/kg/day NOAEL for maternal toxicity = 15 mg/kg No teratogenic activity, absence of relevant adverse effects on the foetuses NOAEL for developmental toxicity ≥ 800 mg/kg	Purity: 95.6% "carbamate process"	Murray S.M. (1991)

4.11.1 Effects on fertility

4.11.1.1 *Non-human information*

See Draft Assessment Report and corrigenda.

The reproductive toxicity of Triflusulfuron-methyl was evaluated in rats.
No adverse effects on reproduction were observed with the highest (1500 ppm) dose of Triflusulfuron-methyl, in a two generation study in rats. Then, the reproductive NOAEL for Triflusulfuron-methyl was ≥ 1500 ppm (89.5-123.0 mg/kg b.w./day and 115.0-137.0 mg/kg b.w./day in males and females, respectively). The overall NOAEL (general toxicity) for the test compound in adults and offspring was 100 ppm (5.81-7.75 mg/kg b.w./day and 7.84-8.96 mg/kg b.w./day in males and females, respectively) based on decreases in body weight and nutritional parameters in parental rats and on slightly decreased body weights in pups at doses ≥ 750 ppm.

4.11.1.2 *Human information*

No data available

4.11.2 Developmental toxicity

4.11.2.1 *Non-human information*

See Draft Assessment Report and corrigenda.

Developmental toxicity studies were conducted with Triflusulfuron-methyl in rats and rabbits.
In the developmental study conducted in rabbits, the maternal NOAEL was 15 mg/kg based on compound-related body weight/nutritional effects at 90 mg/kg b.w./day and greater, and increased mortality and abortions in groups administered 270 mg/kg/day and above. The NOAEL for foetal toxicity in rabbits was 800 mg/kg/day, the highest dose tested, based on absence of foetal effects.
In rats, both the maternal and foetal NOAEL were 120 mg/kg/day. In maternal animals, this NOAEL was based on body weight effects, including body weight loss, in groups administered 350 mg/kg/day and above. These effects were most severe during gestation days 7-11, which coincide with the beginning of organogenesis. The foetal NOAEL was based on a slight increase in the mean percent of foetuses per litter with variations due to retarded development in groups administered 350 mg/kg/day and above. A slight increase in the number of malformed foetuses was also present at 1000 mg/kg/day. A direct effect of the compound in these foetal malformations and variations is questionable since foetal effects were likely secondary to maternal toxicity noted in early gestation, were of low incidences and were in the historical control data limits.

4.11.2.2 *Human information*

No data available

4.11.3 Other relevant information

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4.11.4 Summary and discussion of reproductive toxicity

No adverse effects on reproduction were observed with the highest (1500 ppm) dose of Triflusulfuron-methyl, in a two generation study in rats. Classification is thus not necessary.

In the developmental study in rabbits, Triflusulfuron-methyl did not show any teratogenic potential at 800 mg/kg, the highest tested dose.

In the developmental study in rats, a slight increase in the mean percent of foetuses per litter with variations due to retarded development in groups administered 350 mg/kg/day and above. A slight increase in the number of malformed foetuses was also present at 1000 mg/kg/day. These effects of low incidences and in the historical control data limits were observed at a dose that also caused maternal toxicity and therefore probably due to the maternal toxicity. Classification is thus not necessary.

4.11.5 Comparison with criteria

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4.11.6 Conclusions on classification and labelling

Overall reproductive studies in rats and rabbits suggested that Triflusulfuron-methyl is not toxic for the reproduction and the development. In the rat, it was demonstrated that Triflusulfuron-methyl is a weak aromatase inhibitor leading to Leydig cell hyperplasia and adenoma formation. Since no related effect to this mechanism of action has been observed in the reproductive and developmental *in vivo* toxicity studies, no classification is required.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

One two-generation study in rats (OECD 416) and two prenatal development studies (OECD 414) in rat and rabbit where included in the report. No treatment related adverse effects were seen in the two generation study in rats or the prenatal development study in rabbits. In the rat prenatal development study four pups with malformation were seen in four litters and there was an increase in variants. The DS concludes that the number of malformations were low and within the historical control and where probably caused by maternal toxicity; they considered that classification was not warranted.

Comments received during public consultation

Two comments from MSCAs agree with not classifying the substance for this hazard class.

Assessment and comparison with the classification criteria

Triflusulfuron-methyl was tested in a two-generation toxicity study in SD-rats and in prenatal development toxicity studies in SD-rats and (NZW) SPF-rabbits. No fertility or developmental effects were seen in the two-generation study. No malformations were observed in the prenatal development toxicity study in rabbits. In rats some malformations were seen at the top dose. This was not statistically significant. In rats receiving 350 mg/kg bw/d some variations due to retarded development were seen in the prenatal development toxicity study, in four fetuses from four different litters in the top dose group. No consistent pattern of malformations was seen, as the malformations were found in various anatomical sites.

Some effects were seen on testes in rats and dogs in subchronic studies but the effects were not consistently found across these studies or in the chronic study in dogs. Testes seemed to be the target organ in rats and dogs in studies of subchronic toxicity, manifested as testicular atrophy and reduced testicular weights in the top dose group in

one of the two 90-days rat studies (accompanied with high general toxicity and poor nutritional status), and as testicular atrophy and reduced testicular weights in dogs in the medium and high dose group in a 90-day study. This effect was however not seen in the 1 year dog study where the doses were lower. In the carcinogenicity study in rats testis was the target organ, see section on carcinogenicity.

RAC supported no classification for reproductive toxicity as proposed by the DS.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 *Neurotoxicity*

Method	Results	Remarks	Reference
Acute oral neurotoxicity in Crl:CD BR VAF/Plus rats 0, 500, 1000 or 2000 mg/kg b.w US EPA 81-8	Lack of any specific evidence of neurotoxicity NOAEL for acute neurotoxicity > 2000 mg/kg b.w At doses ≥ 1000 mg/kg b.w and at least 2000 mg/kg b.w for F: ↓ body weight gain and food consumption NOAEL for systemic toxicity = 500 mg/kg b.w	Purity: 95.6% "carbamate process"	Foss J.A. (1994)
90-day feeding neurotoxicity in BR VAF/Plus rats 0, 100, 750, 1500 or 3000 ppm corresponding to 0, 6.1, 46.1, 92.7 and 186.2 mg/kg b.w/day in males and 0, 7.1, 51.6, 104.1 and 205.2 mg/kg b.w/day in females US EPA 82-7	No evidence of subchronic neurotoxicity NOAEL for subchronic neurotoxicity = 3000 ppm in M (186.2 mg/kg b.w/day) and F (205.2 mg/kg b.w/day) At doses 750 ppm in F: ↓ body weight and food consumption At 3000 ppm: ↓ body weight in M, ↓food consumption in M NOAEL for systemic toxicity = 1500 ppm in M (92.7 mg/kg b.w/day) and 100 ppm in F (7.1 mg/kg b.w/day)	Purity: 95.6% "carbamate process"	Foss J.A. (1994)

Acute (single dose gavage) and subchronic (90-day feeding) neurotoxicity studies were conducted in rats with Triflusulfuron-methyl. In both studies, no clinical or morphological evidence of neurotoxicity was present in male or female rats at any dose tested (up to 2000 mg/kg/day in the acute gavage study and up to 3000 ppm in the subchronic feeding study). In a 2-year feeding study in rats an increased incidence and/or severity of axonal degeneration of the sciatic nerve was observed in male and female rats fed 1500 ppm, the highest concentration tested. These findings were explained by an exacerbation, by some unknown indirect mechanism, of the spontaneous lesion seen commonly in the aging rat.

4.12.1.2 *Immunotoxicity*

No data available

4.12.1.3 *Specific investigations: other studies*

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4.12.1.4 *Human information*

No data available

4.12.2 Summary and discussion

The results of the acute and short-term neurotoxicity studies confirmed that interpretation and strongly suggested that Triflusulfuron-methyl is not a neurotoxicant.

4.12.3 Comparison with criteria

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4.12.4 Conclusions on classification and labelling

No classification is required.

5 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental fate properties assessment for triflusulfuron-methyl is based on the Draft Assessment Report (EC, 2007), the Addendum to the Draft Assessment Report (EC, 2008) and the EFSA Scientific Report on the peer review of triflusulfuron (EFSA, 2010).

All the studies on the fate and behaviour of triflusulfuron-methyl in the environment were performed on GLP and according to EPA or OECD guidelines. Then, the reliability factor would be indicated in the summary only when different of 1.

5.1 Degradation

Table 19. Summary of relevant information on degradation

Method	Results	Remarks	Reference
OECD 301 D	Not readily biodegradable	None	Aldred D. (1992)

5.1.1 Stability

5.1.1.1 *Hydrolysis*

A hydrolysis study of triflusulfuron-methyl is available.

Hawkins D.R. et al. (1992a):
This study is performed according to EPA guidelines and is GLP.
Purified ^{14}C-ester carbonyl triflusulfuron-methyl (purity 95.8-98.9%) or ^{14}C-triazine triflusulfuron-methyl (purity > 97.0%) in acetonitrile was dissolved at about 1 mg/L in buffers at pH 5, 7 and 9 (solvent was < 1.1% in the final solutions). Solutions were kept at 25° C for 30 d. At each sampling time, radioactivity in solutions was measured by LSC and analysed by HPLC.
Hydrolysis of triflusulfuron-methyl involves cleavage of the sulfonylurea bridge to give IN-W6725 (methyl saccharin, 99.4%, 46.4% and 44.1% after 30 d at pH 5, 7 and 9, respectively) and IN-D8526 (triazine amine, 98.4%, 47.4% and 43.0% after 30 d at pH 5, 7 and 9, respectively).
DT_{50} is 3.7 d at pH 5, 32 d at pH 7 and 36 d at pH 9 (linear 1st order).

5.1.1.2 *Photolysis*

In water
Two studies of the photolysis of triflusulfuron-methyl in water are available.

Hawkins D.R. et al. (1992b):
This study is performed according to EPA guidelines and is GLP.
Purified ^{14}C-triazine or -ester carbonyl triflusulfuron-methyl in acetonitrile was dissolved at about 1 mg/L in sterile buffers at pH 5, 7 and 9 (solvent was < 1.1%). Solutions were exposed to Xenon arc light source (> 290 nm) for 15 d at 25°C (equivalent to 68-81 d of natural summer sunlight at latitude 52° N assuming that the average daily radiation intensity from the sun is about 75% of the peak intensity over a 12 h period). Radioactivity in solution was measured by LSC and analysed by HPLC and TLC. A preparative scale experiment was carried out for identification of photolysis products by MS. The dark controls were those from the hydrolysis study.
As compared to the dark conditions (hydrolysis), light slightly enhances degradation of triflusulfuron-methyl in aqueous solutions at pH 7 and 9 (in the light DT_{50} are 3.8 d at pH 5, 13.9 d at pH 7 and 24.6 d at pH 9) and a different degradation pathway is observed. At all pH, cleavage of the sulfonylurea bridge still occurs in the light and the metabolites IN-W6725 = methyl saccharin (max. 71.2% at pH 5, 18.1% at pH 7 and 18.9% at

pH 9) and IN-D8526 = triazine amine (max. 46.8% at pH 5, 18.2% at pH 7 and 12.1% at pH 9) are formed in significant amounts. However, light favours oxidation of triazine amine at pH 5 to give formyl N-desmethyl triazine amine = IN-E0Q47 = IN-JY947 (max. 20.1% at pH 5, < 1.5% at pH 7 and < 0.9% at pH 9) and N-demethylation of the AS (Active Substance) at pH 7 and 9 to give IN-66036 = N-desmethyl triflusulfuron-methyl (max. 4.0% at pH 5, 14.7% at pH 7 and 9.5% at pH 9). Formation in low amounts of IN-JL000 = triazine urea (< 1.3-3.8%) suggests that light could also favour another cleavage of the sulfonylurea bridge. An unknown photodegradation product (T9) derived from the triazine moiety is detected in significant amounts at all pH (max. 24.0% at pH 5, 13.5% at pH 7 and 16.2% at pH 9). Despite further investigations, the chemical structure of T9 has not been elucidated but it was shown to release triazine urea. IN-E7710 is formed in low amounts (< 6.9%) at all pH. With regard to the light intensity (15 d continuous artificial light would correspond to 68-81 d equivalent natural summer sunlight at latitude 52° N) photodegradation is expected to be not significant under real conditions at least in Northern Europe.

Singles S.K. (2001):
This study is performed according to EPA guidelines.
The quantum yield for direct photolysis of triflusulfuron-methyl was obtained by iterative calculations using the US EPA photolysis model GCSOLAR. When the calculated instantaneous photolysis rate at mid-day in summer at 50° latitude equaled the photolysis rate constant (half life 127 d natural sunlight equivalent at pH 7) observed in the light-irradiated experiment (Hawkins D.R., Kirkpatrick D., Dean G.M., Mellor S. , 1992, report HRC/DPT 218/91535 DuPont AMR-1629-90; summarised above) the calculations were concluded. The quantum efficiency that gave agreement between the model calculations and experiment was 0.0000685.
The quantum efficiency for photodegradation of triflusulfuron-methyl in water has been estimated to be 0.0000685 by iterative calculations using the US EPA model GCSOLAR and comparison between the model calculations at mid-day in summer at 50° latitude and the measured photodegradation at pH 7. Based on model calculation, photodegradation half lives at mid-day in summer are expected to decrease from 127 d to 112 d as latitude decreases from 50° to 30° and thus no significant photodegradation of triflusulfuron-methyl in water is expected even for Southern Europe.

On soil (informative data only)
A study of the photolysis of triflusulfuron-methyl on soil is available.

Hawkins D.R. et al. (1992):
This study is performed according to EPA guidelines and is GLP.
Purified ^{14}C-ester carbonyl or ^{14}C-triazine triflusulfuron-methyl (purity 95-97%) in acetonitrile was applied at 1 µg/cm^2 to thin layer (1 mm) of air dried Somersham soil. Soil layers (2.5 x 4.0 cm units) were kept at 25° C in darkness or continuously exposed to xenon arc light source (> 290 nm) using a Suntest apparatus for up to 15 d (equivalent to about 75 d of natural summer sunlight at latitude 52° N assuming that the average daily radiation intensity from the sun is about 75% of the peak intensity over a 12 h period). Volatiles were trapped. Soil samples were periodically removed and analysed for triflusulfuron-methyl and metabolites by HPLC and TLC as described in the aerobic studies (see DAR) except that acetonitrile : 0.1 M ammonium carbonate (9:1) was used as the first extraction solvent and extracts were concentrated to dryness and dissolved in 1 mL 0.1 M ammonium carbonate : acetonitrile (9:1) for analysis.
In the dark, triflusulfuron-methyl is rapidly degraded on dry soil (DT_{50} about 13 d) by cleavage of the sulfonylurea bridge to give IN-D8526 = triazine amine (max. 47.5% after 15 d) and IN-W6725 = methyl saccharin (max. 62.4% after 15 d). In the light (continuous artificial irradiation), degradation occurs at the same rate but a different pathway is observed. As compared to the dark conditions, the metabolites IN-D8526 and IN-W6725 are formed in lower amounts (11.8% and 11.7% respectively, after 15 d). Light favours N-demethylation of triflusulfuron-methyl to give IN-66036 = N-desmethyl triflusulfuron-methyl (max. 12.2% after 2 d, decline observed) which could be further degraded to IN-W6725 and IN-E7710 = N-desmethyl triazine amine (max. 6.9% after 15 d) by cleavage of the sulfonylurea bridge (IN-E7710 could be also formed by N-demethylation of IN-D8526). Light also favours another cleavage of the sulfonylurea bridge to give two triazine urea degradates IN-JL000 = triazine urea (max. 7.1% after 15 d) and IN-JM000 = N-desmethyl triazine urea (max. 13.5%, after 15 d) which could be derived from triflusulfuron-methyl and N-desmethyl triflusulfuron-methyl, respectively. These urea metabolites are derived from the triazine moiety

and the corresponding degradation products from the ester carbonyl moiety could be minor unknowns (< 6.8%). The urea metabolites could be further degraded to the corresponding triazine amine and N-desmethyl triazine amine. Small amounts of IN-M7222 = N,N-bis-desmethyl triazine amine (max. 4.2% at 15 d) are formed. Volatiles (< 10.2%) and bound residue (< 5.0%) are not significant. With regard to the light intensity (15 d continuous artificial light would correspond to about 75 d of natural summer sunlight at latitude 52° N), soil photolysis is not expected to play a significant role under real conditions as compared to biological degradation and even chemical degradation, at least in Northern Europe. Because latitude (30° - 50°) has been shown to have little effect on the rate of photodegradation in water, photodegradation on soil is expected to be not significant throughout Europe.

5.1.2 Biodegradation

5.1.2.1 *Biodegradation estimation*

No data.

5.1.2.2 *Screening tests*

A study on the ready biodegration of triflusulfuron-methyl is available.

Aldred D. (1992):

This study is a closed bottle test performed according to OECD 301 D guideline. This study is GLP.
Triflusulfuron-methyl (purity 91.2%) was dissolved at 2 mg/L in a mineral medium (pH 7.2) inoculated with a low level of micro-organisms obtained from a secondary effluent plant. Incubation was at 20°C for 28 d. Dissolved O_2 concentration was determined by the modified Winkler titrimetric method (combination of O_2 with manganous hydroxide, acidification in presence of iodide and titration of the released iodine). The oxygen depletion was used to calculate the percent biodegradation of the test substance against its theoretical oxygen demand. Sodium acetate was used as the reference standard (6 mg/L). Percents of biodegradation of triflusulfuron-methyl at day 5, day 15 and day 28 were 2.8%, 11.1% and 25%, respectively. For the reference standard, the corresponding figures were 71.2%, 74.7% and 100%.
Since the biodegradation of triflusulfuron-methyl after 28 days was determined to be 25%, triflusulfuron-methyl is not readily biodegradable.

5.1.2.3 *Simulation tests*

Water

In the two water sediment systems available (pHwater = 7.5 both) triflusulfuron-methyl degrades with a half-life of DT_{50} whole system = 22 – 40 d. In these systems, triflusulfuron-methyl partition to the sediment (max. 22% AR) and degrades by cleavage of the sulfonylurea urea bridge to methyl saccharin (IN-W6725, max. 38.4% AR (Applied Radioactivity) in water and 12% AR in sediment after 100 d) and triazineamine (IN-D8526, max. 23.2% AR in water and 18.9% AR sediment after 61 d) which subsequently degrades to *N*-desmethyl triazine amine (max. 10.7% AR in water after 61 d). In an alternative pathway triflusulfuron (JK-55517; max. 28.6% AR in water after 100 d and 19.7% AR in sediment after 61 d) is formed. A meeting of experts agreed that the half-life in water may only be considered a dissipation half-life and not a degradation half-life.

Soil

The aerobic route of degradation study, the rate of degradation of triflusulfuron-methyl was investigated in four soils (pH 5.2-8.1; OC 0.72-1.96%; clay 5-13%; 40% MWHC (Maximum Water Holding Capacity)) under dark aerobic conditions at 20°C using triazine ^{14}C-labelled triflusulfuron-methyl. For one of the soils,

incubation was carried out at a lower concentration of triflusulfuron-methyl (one tenth), 10°C and 21% MWHC. Triflusulfuron-methyl exhibits low to moderate persistence in soil under dark aerobic conditions at 20°C (DT 50 lab aerobic = 5.3 – 15 d) or 25°C (DT 50 lab aerobic = 5.7 d [geometrical mean of the two labels]).

Under dark anaerobic conditions at 25°C, degradation of triflusulfuron-methyl is slower than under aerobic conditions (DT_{50} anaerobic = 21 d).

In the photolysis study, triflusulfuron-methyl was degraded at the same rate in the irradiated and the dark control (DT_{50} light = 11.6 d; DT_{50} dark = 12.6 d). The Rapporteur Member State considered that soil photolysis does not play a significant role in the environmental degradation of triflusulfuron-methyl.

5.1.3 Summary and discussion of degradation

Hydrolysis of triflusulfuron-methyl involves the cleavage of the sulfonylurea bridge to produce methyl saccharine (IN-W6725) and triazine amine (IN-D8526). Hydrolysis half-lives for triflusulfuron-methyl were DT_{50} = 3.7 d (pH 5), DT_{50} = 32 d (pH 7) and DT_{50} = 36 d (pH 9). According the available photolysis study, aqueous photolysis has no effect on the degradation of triflusulfuron-methyl at pH 5 and would increase the rate of degradation by a factor of 2.2 (pH 7) and 1.4 (pH 9) with respect to aqueous hydrolysis under dark conditions. Based on an aqueous photolysis study and model calculations photodegradation is not expected to play a significant role in the degradation of triflusulfuron-methyl in the environment and assessment of exposure to photolysis metabolites was not deemed necessary. This conclusion was confirmed by the meeting of experts. Metabolites methyl saccharine (IN-W6725) and triazine amine (IN-D8526) are stable to hydrolysis and to aqueous photolysis. Triflusulfuron-methyl is not readily biodegradable according the available study.

Based on these available studies, we can conclude that triflusulfuron-methyl is not rapidly degradable in the environment according to the CLP Regulation.

In the two water sediment systems available (pHwater = 7.5 both) triflusulfuron-methyl degrades with a half-life of DT_{50} whole system = 22 – 40 d. In these systems, triflusulfuron-methyl partition to the sediment (max. 22% AR) and degrades by cleavage of the sulfonylurea urea bridge to methyl saccharin (IN-W6725, max. 38.4% AR in water and 12% AR in sediment after 100 d) and triazineamine (IN-D8526, max. 23.2% AR in water and 18.9% AR sediment after 61 d) which subsequently degrades to *N*-desmethyl triazine amine (max. 10.7% AR in water after 61 d). In an alternative pathway triflusulfuron (JK-55517; max. 28.6% AR in water after 100 d and 19.7% AR in sediment after 61 d) is formed. A meeting of experts agreed that the half-life in water may only be considered a dissipation half-life and not a degradation half-life.

Fate and behaviour on soil

Triflusulfuron-methyl exhibits low to moderate persistence in soil under dark aerobic conditions at 20°C (DT 50 lab aerobic = 5.3 – 15 d) or 25°C (DT 50 lab aerobic = 5.7 d [geometrical mean of the two labels]).

Under dark anaerobic conditions at 25°C, degradation of triflusulfuron-methyl is slower than under aerobic conditions (DT_{50} anaerobic = 21 d).

In the photolysis study, triflusulfuron-methyl was degraded at the same rate in the irradiated and the dark control (DT_{50} light = 11.6 d; DT_{50} dark = 12.6 d).

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

From the available studies (see DAR), triflusulfuron-methyl may be considered to exhibit high to very high mobility (Kfoc = 25 – 52 mL/g).

5.2.2 Volatilisation

Based on the low vapour pressure (1.01 x 10^{-5} Pa at 20°C), triflusulfuron-methyl is not considered as a volatile substance.

5.2.3 Distribution modelling

Not relevant for this report.

5.3 Aquatic Bioaccumulation

Based on its log Kow values of 2.3 (pH 5 at 25°C), 0.96 (pH 7 at 25°C) and -0.066 (pH 9 at 25°C), no concern over any potential for bioaccumulation could be concluded for triflusulfuron-methyl.

5.3.1 Aquatic bioaccumulation

Measured data on bioaccumulation of triflusulfuron-methyl are not available. Triflusulfuron-methyl has high water solubility and a low log Kow (0.96 at pH 7), it is therefore not predicted to bioconcentrate in aquatic organisms.

5.3.2 Summary and discussion of aquatic bioaccumulation

Based on a log Kow value of 0.96 (pH 7 at 25°C) for triflusulfuron-methyl, the cut-off value of log Kow ≥ 4 (as the experimental BCF measure is not available) set out in the CLP Regulation is not exceeded.

5.4 Aquatic toxicity

Only validated ecotoxicity tests accepted for risk assessment from Draft Assessment Reports were used.

All the aquatic toxicity studies of triflusulfuron-methyl were performed on GLP and according to EPA or OECD guidelines. Then, the reliability factor would be indicated in the summary only when different of 1. The reliability factors of the aquatic toxicity studies are reported in the Table 20, which summarised the available data on the toxicity for aquatic organisms. Algae and aquatic plants are the most sensitive species (see section "5.4.3. Algae and aquatic plants").

5.4.1 Fish

5.4.1.1 *Short-term toxicity to fish*

Three short-term toxicity studies to fish are available for triflusulfuron-methyl.

Baer K.N. (1991a):

This test was GLP and performed according to OECD guideline no 203 (1992). The tested species was *Oncorhynchus mykiss* (rainbow trout).
The acute toxicity of triflusulfuron-methyl (technical substance, purity 95.6% w/w) was assessed in unfed juvenile rainbow trout exposed for 4 days under static conditions. Fish ranged from 3.3 to 4.3 cm in standard length (mean 3.7 cm) at the start of the study. Test solutions were maintained between 10.6 and 12.4°C. Exposure was performed in 20 L containers containing a pH (8.0) adjusted control and test water (respectively 0 and 130, 216, 360, 600, or 1000 mg/L, nominal). Ten fish were allocated randomly per container (loading rate: 0.45 g/L). Mortality and abnormal responses of fish were recorded at 24 h intervals throughout the exposure period.
Mean measured concentrations of triflusulfuron-methyl were 120, 210, 320, 660, and 1000 mg a.s./L. The LC50 was based on mean measured concentrations of triflusulfuron-methyl in the test media.
One of the surviving fish in the water control and one in the 600 mg/L group were observed to be upside down at the bottom of the test chamber after 24 h. The No Observable Effect measured Concentration was 210 mg/L.
LC50 – 96 h =730 mg a.s./L.

Baer K.N. (1991b):

This test was GLP and performed according to OECD guideline no 203 (1992). The tested species was *Lepomis macrochirus* (bluegill sunfish).
The acute toxicity of triflusulfuron-methyl (technical substance, purity 95.6% w/w) was assessed in bluegill sunfish exposed for 4 days under static, unaerated conditions. Fish ranged from 2.3 to 3.6 cm in standard length (mean 2.6 cm) at the start of the study. Test solutions were maintained between 22.5 and 22.7°C. Exposure was performed in 15 L containers containing a water control, a pH (8.0) adjusted control and test water (respectively 130, 216, 360, 600, or 1000 mg/L, nominal). Ten fish were allocated randomly per container (loading rate: 0.31 g/L). Mortality and abnormal responses of fish were recorded at 24 h intervals throughout the exposure period.
The dissolved oxygen was above the theoretical saturation value at 0 and 24 h in all test conditions. This high dissolved oxygen was not biologically significant based on the lack of mortality at 24 h.
Mean measured concentrations of triflusulfuron-methyl were 120, 180, 370, 590, and 1100 mg a.s./L. The LC50 was based on mean measured concentrations of triflusulfuron-methyl in the test media.
No mortality and no abnormal behaviour were recorded in control fish. The highest test concentration causing no mortality was 370 mg/L. Two surviving fish at 600 mg/L and one surviving fish at 1100 mg/L exhibited dark coloration and were at the surface.
LC50 – 96 h = 760 mg a.s./L.

Baer K.N. (1993a):

This test was GLP and performed according to OECD guideline no 203 (1992). The tested species was *Cyprinus carpio* (carp).
The acute toxicity of triflusulfuron-methyl (technical substance, purity 95.6% w/w, batch 66037-24) was assessed in unfed juvenile carp exposed for 4 days under static, unaerated conditions. Fish ranged from 2.3 to 2.8 cm in standard length (mean 2.4 cm) at the start of the study. Test solutions were maintained between 21.6 and 22.1°C. Exposure was performed in 20 L containers containing a water control, a pH (8.0) adjusted control and test water (respectively 130, 216, 360, 600, or 1000 mg/L, nominal). Ten fish were allocated randomly per container (loading rate: 0.23 g/L). Mortality and abnormal responses of fish were recorded at 24 h intervals throughout the exposure period.
Mean measured concentrations of triflusulfuron-methyl were 100, 210, 350, 550, and 830 mg a.s./L. The LC50 was based on mean measured concentrations of triflusulfuron-methyl in the test media.
There was no mortality observed. Some fish in the 830 mg a.s./L group were observed at the surface at 24, 48, and 96 hours. Because of the absence of mortality over the range of concentrations tested, no concentration-effect relationship, and therefore no LC50, could be established.
LC50 – 96 h > 830 mg a.s./L.

5.4.1.2 *Long-term toxicity to fish*

Two long-term toxicity studies to fish are available for triflusulfuron-methyl.

Baer K.N. (1992):

This test was GLP and performed according to OECD guideline no 204 (1984). The tested species was *Oncorhynchus mykiss* (rainbow trout).
The effects of triflusulfuron-methyl, technical substance (purity 95.6% w/w) on survival and growth of fingerling rainbow trout was assessed in an unaerated flow-through system over a 21-day exposure period. A dilution water control, and nominal test substance concentrations 6.0, 12, 25, 50, 100, and 200 mg/L were used during the study. Test solutions were delivered intermittently (about every 21 min.) to replicate 7-liter glass exposure chambers. The volume of each replicate was exchanged five times daily. A total of 10 embryos were exposed per concentration (5 embryos per replicate, 2 replicates per concentration) at test start. Mortality and abnormalities were recorded daily throughout the study and standard length and blotted wet weight of surviving fingerlings were calculated at the end of the test.
Analytical verification of triflusulfuron-methyl concentrations was made on test solutions sampled on Day 0, once weekly, and at test end (Day 21). Mean, measured concentrations of triflusulfuron-methyl were 0, 5.2, 12, 28, 56, 110, and 210 mg/L.
No mortality and no intoxication symptoms were observed in fish exposed to triflusulfuron-methyl over the exposure period. There was a statistically significant downward linear trend in fish length and weight with increasing test concentration. Due to the variability of these parameters, within each concentration, no single concentration was statistically significantly different from the control.
NOEC 21-d = 210 mg a.s./L.

Boeri R.L. et al. (1996):

This test was GLP and performed according to OECD guideline no 210 (1992). The tested species was *Oncorhynchus mykiss* (rainbow trout).
The effects of triflusulfuron-methyl, technical substance (purity 95.72% w/w) on the early life stage of rainbow trout was assessed in an unaerated, flow-through system for 97 days (61 days post-hatch). A dilution water control, and nominal test substance concentrations of 4.5, 8.8, 18, 35, 70, and 140 mg/L were used during the study. A total of 40 embryos were exposed per concentration (20 embryos per replicate, 2 replicates per concentration). Test solutions were maintained between 9.3 and 11.0°C.
Embryos and alevins were held in relative darkness until 1 week after hatching, and then held under a photoperiod of 16 hours light and 8 hours darkness for the remainder of the study. On Day 55, after swim-up had begun in the controls, the fingerlings were thinned to a total of 30 fish per concentration Following swim up, fish were fed commercial dry starter chow and live, newly hatched *Artermia salina* nauplii, *ad libitum,* 3 times per day except during the final 23 hours of the test. Daily observations were made for assessment of number of dead eggs, first and last day of hatching, first day of swim-up, survival and abnormalities from hatching to thinning, and survival and abnormalities from thinning to test end. Standard length and blotted wet weight of surviving fingerlings were determined at test end.
Analytical verification of triflusulfuron-methyl concentrations was made on test solutions sampled on Day 0, once weekly, and at test end (Day 90). Mean measured concentrations of triflusulfuron-methyl were 0, 2.41, 6.03, 11.8, 29.4, 57.7, and 136 mg/L.
Survival in the control averaged 73.8% at hatch, 72.5% at thinning, and 100% (after thinning) at the end of the study. The survival of test organisms at thinning was significantly decreased when compared to the controls at 136 mg/L. The time to hatch (start and end), time to swim up, and survival of test organism were not significantly different from the control at any concentration. In surviving fish exposed to triflusulfuron-methyl at 136 mg/L, the mean total length (43.1 cm) and mean wet weight (0.94 g) were significantly decreased when compared to control (48.3 cm and 1.21 g, respectively).

The 97-day NOEC of triflusulfuron-methyl was 57.7 mg/L, based on mean measured concentrations of triflusulfuron-methyl and survival of test organisms at thinning and total length and wet weight of surviving fish after 97 days of exposure.
NOEC 97-d = 57.7 mg a.s./L.

5.4.2 Aquatic invertebrates

5.4.2.1 *Short-term toxicity to aquatic invertebrates*

A single short-term toxicity study to aquatic invertebrates is available for triflusulfuron-methyl.

Baer K.N. (1991c):

This test was GLP and performed according to OECD guideline no 202 (1984). The tested species was *Daphnia magna*.
The acute toxicity of triflusulfuron-methyl (technical substance, purity 95.6% w/w) was assessed in neonate (less than 24 h old) waterfleas exposed for 2 days under unaerated static conditions. Exposure was performed in 250 mL beakers containing 200 mL of test water with 0 (water control or pH adjusted control) or 130, 216, 360, 600, or 1000 mg/L (nominal) test substance. Dilution water originated from laboratory well and flowed through aquaria containing fathead minnows, prior to use in the daphnid test. Each replicate (four per concentration) contained 5 daphnids added randomly. Test solutions were held between 20.2°C to 20.4°C. Oxygen values were close to 100% saturation. Immobilisation of daphnids was recorded at 24h intervals throughout the exposure period.
Mean measured concentrations of the active substance were 130, 170, 310, 490, and 960 mg a.s./L.
No effects on mobility were recorded at any of the concentrations tested. Because of the absence of mortality over the range of concentrations tested, no concentration-effect relationship, and therefore no LC50, could be established.
EC50 48 h > 960 mg a.s./L.

Comments (RMS): the origin of dilution water used is questionable. The notifier stated that dilution water used for some early daphnid studies was conditioned prior to use to ensure adequate growth and survival of daphnid cultures. Considering that this dilution water fulfill all validity criteria, including good analytical recovery, it may be concluded that the dilution water did not affect the outcome of the study. The study may be considered as acceptable.

5.4.2.2 *Long-term toxicity to aquatic invertebrates*

A single long-term toxicity study to aquatic invertebrates is available for triflusulfuron-methyl.

Baer K.N. (1993b):

This test was GLP and performed according to OECD guideline no 202 (1984). The tested species was *Daphnia magna*.
Effects of chronic exposure to triflusulfuron-methyl (technical substance, purity = 95.6% w/w) on *Daphnia magna* neonates was determined under semi-static conditions with test solution renewal 3 times a week for 21 d. Effects on survival and growth were assessed in tests vessels containing 200 mL test water with 0 (control), 0.33, 0.82, 2.0, 5.1, 13, 32, 80, 200, or 500 mg test substance/L. Each replicate (ten per concentration) contained four daphnids randomly assigned. Observations were made daily.
Mean measured concentrations of triflusulfuron-methyl were 0.28, 0.68, 1.7, 4.6, 11, 25, 67, 160, and 300 mg/L.

The first day of reproduction and the total number of young produced in 21 days were statistically different from controls at 11 mg/L and above. The variation at 11 mg/L was not considered biologically significant based on the lack of statistically significant effects in the total number of live young produced per surviving adult in 21 days. The total number of live young produced per surviving adult in 21 days was significantly reduced at 25 mg/L and above. There was no statistically significant effect on adult length at any test concentration where daphnids survived to day 21. The number of adults surviving to day 21 was significantly decreased at 160 mg/L and above.
NOEC 21-d = 11 mg a.s./L.

5.4.3 Algae and aquatic plants

Three toxicity studies to algae are available for triflusulfuron-methyl.

Douglas, M.T., Halls, R.W.S. (1991):

This test was GLP and performed according to OECD guideline no 201 (1984). The tested species was *Pseudokirchneriella subcapitata*.
The toxicity of triflusulfuron-methyl (technical substance, purity >97%, batch AGO216-11) to the green algae species Pseudokirchneriella subcapitata was determined under static conditions, continuous illumination over an exposure period of 120 h. The test was conducted in 250 mL flasks filled with 100 mL test water, containing 0 (control or solvent -acetone- control), 0.125, 0.250, 0.5, 1.0 and 2.0 mg test substance/L. The cell density was 9.69 x 10^4 cells/mL at the start of the test. Each concentration was repeated three times. Growth was monitored daily.
To assess recovery after the initial 120 hours exposure period, algae from the 2.0 mg/L concentration were placed in nutrient medium without triflusulfuron-methyl. Cell growth (absorbance at 665 nm) was assessed for up to 7 days following transfer to triflusulfuron-methyl-free medium.
Results based on nominal concentrations:
ErC50 24-48 h = 1.0 mg/L

EbC50 72 h = 0.50 mg/L; EbC50 120 h = 0.62 mg/L;

NOEC = 0.125 mg/L

Regrowth occurred in both the control and test culture (2.0 mg/L) within 7 days
Comments (RMS): analytical measurements were not performed. The results of this study should be considered with caution (reliability 2) and it is recommended to rely on the next study.

Hughes, J.S., Williams, T.L. (1993a):

This test was GLP and performed according to US-EPA Pesticide Assessment Guidelines, Subdivision J, §123-2 (1982). The tested species was *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*).
The toxicity of triflusulfuron-methyl (technical substance, purity 98.7%) to the green algae species *Pseudokirchneriella subcapitata* was determined under static conditions, continuous illumination over an exposure period of 120 h. Test treatments were control (medium only), solvent control (0.1 mL N,N-dimethylformamide (DMF)/L), and 4.50, 9.00, 18.0, 36.0, 71.9 µg triflusulfuron-methyl/L. Each treatment and control was replicated 3 times. The test concentrations were measured at test initiation and at the end of the study. The cell density was 3000 cells/mL at the start of the test. Each concentration was repeated three times. Treatments were incubated at 24±2°C for 120 hours and cell counts were made on days 3, 4, and 5.
Results based on nominal concentrations:
EbC50 120 h = 0.046 mg triflusulfuron-methyl/L [95% confidence limits 0.038 – 0.057 mg/L]

NOEC = 0.036 mg triflusulfuron-methyl/L

Comments (RMS): The cell density at the beginning of the test was 3000 cells/mL (consistent with the US-EPA test guideline used to conduct the test) (OECD recommendation: 10^4 cells/mL). Continuous illumination of 4306 ± 646 lumens/m^2 (300 µE/m^2s) is higher than the recommended value of 120 µE/m^2s. Cell concentration increase over 3 days was satisfactory in the controls. The study is acceptable.

Sloman, T.L. (1999a):

This test was GLP and performed according to US-EPA 850.5400 (1996). The tested species was *Anabaena flos-aquae*.
The toxicity of triflusulfuron-methyl (purity = 98.7%) to the blue-green alga *Anabaena flos-aquae* was determined under static conditions and continuous illumination over an exposure period of 96 h. The test was conducted in 250 mL flasks filled with 50 mL test water, containing 0 (control), 1, 2, 3, 4, and 5 mg test substance/L. Algae from a logarithmically growing stock culture were inoculated to achieve the cell density of 10^4 cells/mL at the start of the test. Each concentration was replicated three times. Cell density was measured every 24 h until the end of the test.
To assess recovery after the initial 96 hours exposure period, algae from the 2, 3, 4, and 5 mg/L concentrations were placed in nutrient medium without triflusulfuron-methyl. Cell counts were made approximately 72 and 144 h from recovery test initiation.
Results based on nominal concentrations:
Cell density:

96-hour EC50 = 1.46 mg/L
96-hour NOEC = 1 mg/L

Area under the growth curve:

96-hour EbC50 = 1.31 mg/L
96-hour NOEC = < 1 mg/L

Growth rate:

96-hour ErC50 = 2.80 mg/L
96-hour NOEC = 1 mg/L

Cell growth resumed within 6 days from recovery test initiation at concentration less than or equal to 5 mg/L.

Two toxicity studies to aquatic plants are available for triflusulfuron-methyl.

Sloman, T.L. (1999b):

This test was GLP and performed according to ASTM "Standard guide for conducting static toxicity test with *Lemna gibba*" G3 1415-91 (1991). The tested species was *Lemna gibba*.
The effects of technical triflusulfuron-methyl (purity = 98.7%) on the growth and reproduction of the duckweed *Lemna gibba* were determined without test medium renewal over a 14 days period. Plants were exposed to the test substance in 250 mL flasks filled with 100 mL of test water, that contained 0 (control), 1, 1.5, 2, 3, and 4 µg triflusulfuron-methyl/L. A total of 15 fronds (5 plants each with 3 fronds per plant) were allocated per flask. Each concentration and the control were tested as 4 replicates. Frond counts were made on days 0, 2, 4, 7, 9, 12, and 14. Biomass was determined at the end of the test.
The ability of the organisms to recover was assessed for each treatment with 50% or greater growth inhibition based on healthy frond count relative to the blank control.
Initial, measured concentrations were 0.78, 1.1, 1.5, 2.2, and 2.9 µg triflusulfuron-methyl/L. Measured concentrations after 14 d were 0.8, 1.1, 1.5, 2.5, and 3.1 µg triflusulfuron-methyl/L. Based on nominal concentrations:
ErC50 (14 days) = 3.5 µg triflusulfuron-methyl/L, 95% CI = [3.4-3.5] µg/L. (healthy frond count)
NOErC (14 days) = 1.5 µg triflusulfuron-methyl/L
EbC50 (14 days) = 4.4 µg triflusulfuron-methyl/L, 95% CI = [4.0-5.1] µg/L.
NOEbC (14 days) = 2.0 µg triflusulfuron-methyl/L
The effects on growth and reproduction of *Lemna gibba* were found to be phytostatic, *i.e.* growth resumed, at concentration less than or equal to 4 µg/L within 14 days.

Hughes J.S., Williams T.L. (1993b):

This test was GLP and performed according to US-EPA Pesticide Assessment Guidelines, Subdivision J, §123-2 (1982). The tested species was *Lemna gibba*.
The effects of triflusulfuron-methyl (technical substance, purity = 98.7%) on the growth of the duckweed *Lemna gibba* were determined without test medium renewal over a 14 days period. Plants were exposed to the active substance at 0 (control, DMF control), 0.635, 1.27, 2.53, 5.05, and 10.1 µg triflusulfuron-methyl/L. A total of 12 fronds (3 plants each with 4 fronds per plant) were allocated per flask (temperature: 25 ± 2°C; mean light intensity: 4198-5813 lux or 293 – 405 µE/m^2s; photoperiod: 24 h). Each concentration and the control were repeated three times. Effects on growth rate were assessed through the number of fronds measured on days 2, 4, 7, 9, 11, and 14.
The measured concentration values yielded from 91% to 148% of the nominal concentration on day 0 and from 80% to 151 % on day 14. The 3 highest concentrations had appreciable inhibitory effects upon the population growth of *L. gibba*. Effects on frond shape were noted at concentrations of 2.53 µg/L and higher, and fronds appeared smaller at the 1.27 µg/L concentration, relative to the 0.635 µg/L concentration and the controls. Based on nominal concentrations:
EC50 (14-d) = 2.82 µg triflusulfuron-methyl/L, 95% CI =[2.34-3.39]µg/L
NOEC (14-d) = 1.27 µg triflusulfuron-methyl/L

5.4.4 Other aquatic organisms (including sediment)

No data.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Data are summarised in Table 20 below.

Table 20. Summary of acute and long term toxicity of triflusulfuron-methyl to the most sensitive species within different groups of aquatic organisms

Organism	Species	Test conditions	LC_{50}/ EC_{50} (mg/L)	NOEC (mg/L)	GLP (Y/N)	Reliability
Fish	*Oncorhynchus mykiss* (Rainbow trout)	96 h static	760 (mean measured)	210 (mean measured)	Y	1
	Oncorhynchus mykiss (Rainbow trout)	Early life stage, flow-through, 97 days	-	57.7 (mean measured)	Y	1
Invertebrates	*Daphnia magna* (waterflea)	48 h, static	> 960 (mean measured)	960 (mean measured)	Y	1
	Daphnia magna (waterflea)	Growth and reproduction, semi-static, 21 days	-	11 (mean measured)	Y	1
Algae	*Pseudokirchneriella subcapitata*	Static Biomass (120 h): Growth rate:	 0.62 (nominal) 1.0 (nominal)	0.125 (nominal) - -	Y	2
	Pseudokirchneriella subcapitata	Static, 120 h Biomass: Growth rate:	 0.0463 (nominal) -	 0.036 (nominal) -	Y	1
	Anabaena flos-aquae	Static, 96 h Biomass: Growth rate:	 1.31 (nominal) 2.80 (nominal)	 < 1 (nominal) 1 (nominal)	Y	1
Aquatic plants	*Lemna gibba*	Static, 14 days Healthy frond count (ErC50) Biomass	 0.0035 (nominal) 0.0044 (nominal)	 0.0015 (nominal) 0.002 (nominal)	Y	1
	Lemna gibba	Static, 14 days	0.00282 (nominal)	0.00127 (nominal)	Y	1

In toxicity studies for algae and aquatic plants EC50s at concentrations ≤ 1 mg/L were observed. In addition, triflusulfuron-methyl is not readily biodegradable although it is unlikely for the substance to bioaccumulate in aquatic organisms (log Kow < 3). As a consequence and according to the CLP Regulation, due to its acute effect on algae/aquatic plants at a concentration ≤ 1 mg/L and due to its low degradability, triflusulfuron-methyl should be classified as R50-53 (Aquatic Acute 1 – Aquatic Chronic 1).

Based on the toxicity data for *Lemna gibba* (ErC50 = 0.0035 mg/L) an M-factor of 100 is proposed. The same approach was applied to determine specific concentration limits according to Directive 67/548/EEC:

Concentration Classification

C≥0.25% N ; R50-53

0.025%≤C<0.25% N; R51-53

0.0025%≤C<0.025% R52-53

where C is the concentration of triflusulfuron-methyl in the preparation (expressed as weight/weight percentage).

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Proposed classification based on Directive 67/548/EEC criteria:

N; R50-53

Proposed specific concentration limits (if any):

Proposed classification of mixtures		
N; R50-53	N; R51-53	R52-53
C ≥ 0.25%	0.25% > C ≥ 0.025%	0.025% > C ≥ 0.0025%

The concentration limits are expressed as weight/weight percentage.

Proposed classification based on CLP criteria:

Aquatic Acute 1 – H400

Aquatic Chronic 1 – H410

M-factor: 100

RAC evaluation of environmental hazards
Summary of the Dossier submitter's proposal The DS proposed classification as Aquatic Acute 1, H400 (M=100) and Aquatic Chronic 1, H410 (M=10) according to CLP, and R 50/53 according to DSD with the following specific concentration limits: N; R50-53: Cn ≥ 0.25% N; R51-53: 0.025% ≤ Cn < 0.25% R52-53: 0.0025% ≤ Cn < 0.025%

The proposal is based on the acute toxicity from test results for all three trophic levels, three fish studies (for *Oncorhynchus mykiss*, *Lepomis macrochirus* and *Cyprinus carpio*), one study of crustaceans (*Daphnia magna*), three studies of algae (two *Pseudokirchneriella subcapitata* and one *Anabaena flos-aquae*) and two tests with the duckweed *Lemna gibba*. In addition, chronic test results are available for *Oncorhynchus mykiss (two studies)*, *Daphnia magna*, *Pseudokirchneriella subcapitata* (two studies), *Anabaena flos-aquae* and *Lemna gibba* (two studies), which allows setting a separate M-factor.
The proposed classification is based on short- and long-term toxicity results on *Lemna gibba* 14-d ErC_{50} of 0.0035 mg/l and 14-d NOEC of 0.00127 mg/l, respectively, together with the fact that the substance is not rapidly degradable (or readily biodegradable).

Comments received during public consultation

Six Member States (MS) submitted comments on environmental classification during public consultation, all in agreement with the proposed classification.
Four MS had specific comments, mainly on the evaluation and selection of the key studies (e.g. the following suggestions were made: calculation and use of 7-day values for acute classification (2 MS), correction of the mean measured concentrations of one key study to initial measured concentrations (1 MS) and the use of another key study for classification (2 MS)).

The re-evaluation of the relevant studies and values revealed the results to be in the same concentration range with no effect on the final classification or setting of the M-factors. One MS asked for specification of the metabolites formed by hydrolysis and clarifications concerning the water sediment simulation tests and soil photolysis study. The DS provided this information in the RCOM document.

Assessment and comparison with the classification criteria

Degradability: In one hydrolysis study on triflusulfuron-methyl two hydrolysis products and DT_{50} values of 3.7, 32 and 36 days were determined at 25°C and pH 5, 7 and 9, respectively.

According to an OECD 301 D screening test based on oxygen consumption only 25% of triflusulfuron-methyl was biodegraded within 28 days. Therefore the substance is considered as not readily biodegradable.

A water-sediment study with two aerobic water-sediment systems (pH water: 7.5) resulted in a half-life of 22-40 days for the whole system (measured with applied radioactivity) so that triflusulfuron-methyl also failed to achieve ultimate degradation within 16 days.

The aerobic route of degradation and degradation rate of triflusulfuron-methyl were analyzed in four soil types "Triflusulfuron-methyl exhibits low to moderate persistence in soil under dark aerobic conditions at 20°C (DT_{50} lab aerobic = 5.3 – 15 d) or 25°C (DT_{50} lab aerobic = 5.7 d [geometrical mean of the two labels]). Under dark anaerobic conditions at 25°C, degradation of triflusulfuron-methyl is slower than under aerobic conditions (DT_{50} anaerobic = 21 d)." Although not directly relevant for classification purposes, these results provide some further evidence for the lack of rapid degradability.

On this basis, triflusulfuron-methyl does not meet the criteria for being rapidly degradable or readily biodegradable in the environment.

Bioaccumulation: No measured data on bioaccumulation are available for triflusulfuron-methyl. However, with log Kow values of 2.3 (pH 5, 25°C), 0.96 (pH 7, 25°C) and -0.066 (pH 9, 25°C), the substance does not show a potential for bioaccumulation.

Ecotoxicity: Valid ecotoxicolgical data is available for all three trophic levels. The purity of triflusulfuron-methyl used in the key studies ranges from 95.6% – 98.7% and complies with the specified composition in Section 1 of the CLH report. The lowest results from all valid studies were as follows (the key study results proposed by the DS are highlighted in **bold**, RAC prefers however using for classification purposes the recalculated values highlighted in ***bold italics***):

Trophic level	**Species**	**Short-term result**	**Long-term result**
Fish	*Oncorhynchus myciss*	96-h LC_{50} = 730 mg a.s./L (m.m.)	21-day NOEC = 210 mg a.s./L (m.m.) 97-day NOEC = 57.7 a.s./L. (m.m.)
Aquatic invertebrates	*Daphnia magna*	48-h EC_{50} > 960 mg a.s./L. (m.m.)	21-day NOEC = 11 mg a.s./L. (m.m.)
Aquatic algae and	*Pseudokirchneriella subcapitata*	120-h EbC_{50} = 0.046 mg/L (nom.) --- <u>*Recalculated:*</u> 96-h ErC_{50} = 0.137 mg/L (nom.)	120-h NOEC = 0.036 mg/L (nom.) --- <u>*Recalculated:*</u> 96-h NOEC = 0.018 mg/L (nom.)
aquatic plants	*Lemna gibba*	**14-day ErC_{50} = 0.0035 mg/L (nom.)** --- <u>*Recalculated:*</u> 14-day ErC_{50} = 0.0025 mg/L (initial measured concentration) ***7-day ErC_{50} = 0.002 mg/L (initial measured concentration)***	14-day NOErC = 0.0015 mg/L (nom.) --- <u>*Recalculated:*</u> *14-day NOErC = 0.0011 mg/L (initial measured concentration)* ***7-day NOErC = 0.0011 mg/L (initial measured concentration)***
	Lemna gibba	14-day ErC_{50} = 0.00282 mg/L (nom.) --- <u>*Recalculated:*</u> 7-day ErC_{50} = 0.00269 mg/L (nom.)	**14-day NOErC = 0.00127 mg/L (nom.)** --- <u>*Recalculated:*</u> 7-day NOErC = 0.00127 mg/L (nom.)

m.m. = mean measured concentrations, nom = nominal concentrations

The toxicity values for fish and aquatic invertebrates are based on mean measured concentrations (m.m.), whereas the studies for aquatic algae and plants provide only nominal concentrations (nom.). The available ecotoxicological data for fish and aquatic invertebrates lie outside the classifiable range (for acute toxicity LC_{50} > 100 mg/L and for chronic toxicity NOEC > 1 mg/L); the test results for aquatic algae and plants show that *Lemna gibba* is the most sensitive aquatic species.

For one *Lemna gibba* study the initial (0 hours) measured test concentrations were only 73-78% of the nominal concentrations. One MS corrected the test results from nominal to initial measured concentrations. When the measured initial concentration falls below 80%,

OECD test guideline 221 recommends the use of a semi-static test regime. As the present study was conducted under static conditions, RAC supports the approach to use initial measured instead of nominal concentrations. These corrections do however not affect the resulting classification. The **corrected 14-day ErC_{50}** (initial measured concentration) is **0.0025 mg/L** instead of the originally presented 14-day ErC_{50} of 0.0035 mg/L (nominal concentration) **for acute toxicity** and the **14-day NOErC = 0.0011 mg/L** instead of 14-day NOErC = 0.0015 mg/L **for chronic classification**. All test results range within the same order of magnitude.

The *Lemna gibba* studies were carried out according to EPA - or ASTM-guidelines respectively and were run over a period of 14 days. The OECD test guideline 221 recommends a test duration of 7 days and during public consultation one MS recalculated the 7-day ErC_{50} values for the *Lemna* studies. As for classification of the acute effects based on aquatic plant toxicity tests, the use of the EC_{50} values on day 7 (if available) is generally preferred instead of the data at day 14, RAC supports the approach to recalculate the 7-day ErC_{50} values for the *Lemna* studies. These are 7-day ErC_{50} = 0.002 and 7-day ErC_{50} = 0.00269, respectively and in the same concentration range as the key study proposed by the DS, so that this does not affect the CLH classification or the M-factors. For consistency, the 14-day NOErCs presented by the DS were also corrected to 7-day NOErCs and included in the table. The values are the same and consequently neither influences the classification nor the M-factors.

However, based on the correction of the results from nominal to initial measured concentrations in combination with the generally preferred use of test results of day 7 for classification purposes, RAC accepted this as the key study also for classification of the chronic toxicity.

Regardless of any re-calculations, the available data reveals an acute aquatic toxicity in the range of $0.001 < L(E)C_{50} \leq 0.01$ and a chronic aquatic toxicity of $0.001 < NOEC \leq 0.01$, warranting a classification as Aquatic Acute 1, H400 (M=100) and Aquatic Chronic 1, H410 (M=10).

Classification according to CLP:

Acute aquatic hazard: Acute toxicity data is available for all three trophic levels. With toxicity values of ≥ 700 mg/L, fish and aquatic invertebrates are outside the classifiable range.

The most sensitive aquatic species is *Lemna gibba*. The lowest reliable short-term aquatic toxicity result is 7-day ErC_{50} = 0.002 mg/L (initial measured concentration) for *Lemna gibba*. While the result for the aquatic algae is one magnitude higher, it is still in the classifiable range. Triflusulfuron methyl is therefore classifiable as Aquatic Acute 1 (H400), with an M-factor of 100 ($0.001 < L(E)C_{50} \leq 0.01$).

Chronic aquatic hazard: Triflusulfuron-methyl is considered to be not rapidly degradable. Data is presented for all three trophic levels. The lowest long-term aquatic toxicity result is the 7-day NOErC = 0.0011 for *Lemna gibba*, leading to classification as Aquatic Chronic 1 (H410) with an M-factor of 10 ($0.001 < L(E)C_{50} \leq 0.01$ when not rapid degradable).

Classification according to DSD:

The lack of ready biodegradation together with an EC_{50} = 0.002 mg/L (initial measured concentration) for *Lemna gibba* mean that triflusulfuron-methyl fulfils the criteria for classification with N; R50-53. The following specific concentration limits are applicable:

Concentration of triflusulfuron methyl in the mixture; C (w/w)	Classification of the mixture
Cn ≥ 0.25%	N; R50-53

0.025% ≤ Cn < 0.25%	N; R51-53
0.0025% ≤ Cn < 0.025%	R52-53

In summary, RAC agrees with the original proposal of the DS to classify triflusulfuron methyl as **Aquatic Acute 1, H400 (M=100) and Aquatic Chronic 1, H410 (M=10)**.

6 OTHER INFORMATION

-DAR refers to triflusulfuron. However, all of the data evaluated refer to triflusulfuron-methyl. Therefore CLR Report & dossier is presented for triflusulfuron-methyl. No data allows to draw a conclusion on triflusulfuron.

7 REFERENCES

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8 ANNEXES

See appendix 1 for confidential data.