

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: 1R-trans-Z-momfluorothrin

EC Number: Not available

CAS Number: 1065124-65-3

Index Number: Not available

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	<i>1R-trans-Z-momfluorothrin</i>
EC number:	<i>Not available</i>
CAS number:	<i>1065124-65-3</i>
Annex VI Index number:	<i>Not available</i>
Degree of purity:	<i>≥ 83.8 % (typically ≥ 86.0 %) (Total isomer content ≥ 91.7%)</i>
Impurities:	<i>The active substance contains a number of impurities. These have been taken into consideration in the CLH proposal and are not considered to be relevant for the classification and labelling. Further information is provided in the technical dossier.</i>

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

Current entry in Annex VI, CLP Regulation	Not currently listed
Current proposal for consideration by RAC	Acute Tox 4; H302- Harmful if swallowed STOT-SE 2; H371 – May cause damage to the CNS Aquatic Acute 1: H400 – Very toxic to aquatic life (M = 100) Aquatic Chronic 1: H410 – Very toxic to aquatic life with long lasting effects (M = 100)
Resulting harmonised classification (future entry in Annex VI, CLP)	Acute Tox 4; H302- Harmful if swallowed STOT-SE 2; H371 – May cause damage to CNS

Regulation)	Aquatic Acute 1: H400 – Very toxic to aquatic life (M = 100) Aquatic Chronic 1: H410 – Very toxic to aquatic life with long lasting effects (M = 100)
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1.3 Proposed harmonised classification and labelling

Table 3: Proposed classification

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	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.2.	Flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.3.	Flammable aerosols	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.4.	Oxidising gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.5.	Gases under pressure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.6.	Flammable liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.7.	Flammable solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.10.	Pyrophoric solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.13.	Oxidising liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.14.	Oxidising solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

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2.15.	Organic peroxides	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	Acute Tox 4; H302 – Harmful if swallowed	Not applicable	-	-
	Acute toxicity - dermal	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
	Acute toxicity - inhalation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	Not classified	Not applicable	Not classified	Data lacking
3.4.	Skin sensitisation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.6.	Carcinogenicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	STOT-SE 2; H371 – May cause damage to the CNS	Not applicable	-	-
3.9.	Specific target organ toxicity – repeated exposure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.10.	Aspiration hazard	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1: H400 Very toxic to aquatic	Acute M factor = 100	-	-

		life Aquatic Chronic 1: H410 Very toxic to aquatic life with long lasting effects	Chronic M factor = 100		
5.1.	Hazardous to the ozone layer	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

¹⁾ Including specific concentration limits (SCLs) and M-factors

²⁾ Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Pictogram(s): GHS07; GHS08, GHS09

Signal word: Warning

Hazard statements: H302: Harmful if swallowed.

H371: May cause damage to the CNS

H410; Very toxic to aquatic life with long lasting effects

Precautionary statements: Not included in Annex VI of CLP

Proposed notes assigned to an entry:

None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

1R-trans-Z-momfluorothrin is an active substance in scope of the Biocidal Product Regulation (528/2012). As such, it is subject to the harmonised classification and labelling process in accordance with Article 36 (2) of CLP. There is no current entry on Annex VI of CLP for the substance and the classification and labelling has not been discussed previously within the EU.

At the time of submission the substance is not registered under REACH.

2.2 Short summary of the scientific justification for the CLH proposal

In a standard acute oral toxicity study, an LD₅₀ value of 300 – 2000 mg/kg bw was observed in female rats. This value meets the criteria for classification with Acute Tox 4; H302 - Harmful if swallowed. In the standard acute oral and inhalation studies, and in an acute oral neurotoxicity study, signs of neurotoxicity were observed at doses of 2 mg/l and above. The substance is also a pyrethroid, a class of chemicals known to induce neurotoxic effects (Ray, 1991). Consequently, it is proposed to classify the substance with STOT-SE2; H371 – Causes damage to the central nervous system.

An increased incidence of hepatocyte adenomas and carcinomas was observed in males rats. However, there is clear evidence suggesting that CAR activation is a plausible mode of action for the formation of these tumours in this species. It has been demonstrated that the substance causes CYP2B induction, hepatocyte hypertrophy and cell replication *in vivo* and *in vitro* for rats by CAR activation. This is consistent with the potential to cause cell foci and tumours in long term studies. In contrast, available data suggest that the substance is capable of inducing CYP2B6 and hypertrophy but then does not increase cell replication in human hepatocytes, which is a prerequisite for tumour formation. Taking into account the supporting *in vivo* and *in vitro* mechanistic studies, it can be argued that 1R-trans-Z-momfluorothrin causes tumours in rats by a mechanism that is not relevant to humans. Therefore, no classification for carcinogenicity is proposed.

From the available aquatic acute toxicity data, fish and invertebrates are the most sensitive trophic group with L(E)C₅₀ values in the range 0.001 to 0.01 mg/l. The lowest value is a 96-h LC₅₀ of 0.0012 mg/l for fish. The substance should be classified as Aquatic Acute 1 with an M factor of 100.

Chronic toxicity data are available for fish, invertebrates, algae and aquatic plants. The lowest value is a 21-day NOEC for *Daphnia magna* of 0.0005 mg/l. Given this is the range 0.0001 to 0.001 mg/l, The substance should be classified as Aquatic Chronic 1 with an M factor of 100. However, it should be noted the species of fish used for the single chronic test did not reflect the most sensitive fish species (based on the acute data), resulting in a chronic NOEC greater than the LC₅₀ values for two fish species. On this basis, it is appropriate to consider the surrogate approach for chronic toxicity to fish. This also results in a classification of Aquatic Chronic 1 with an M factor of 100.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI of CLP

Not currently listed

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling

The substance is not currently listed in the classification and labelling inventory. The classification proposed by the applicant during the biocides review was as follows

Acute Tox 4; H302 – Harmful if swallowed

STOT SE 1; H370 - Causes damage to organs (central nervous system) if swallowed

STOT RE 2; H373 - May cause damage to organs (Central nervous system, Liver) through prolonged or repeated exposure if swallowed.

Aquatic Acute 1; H400 – Very toxic to aquatic life

Aquatic Chronic 1; H410 – Very toxic to aquatic life with long lasting effects

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

1R-trans-Z-momfluorothrin is an active substance in the scope of Biocidal Products Regulation (528/2012). As such it is subject to the harmonised classification and labelling process in accordance with Article 36 (2) of the CLP.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

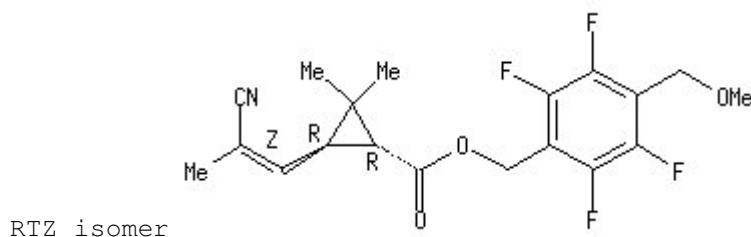
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	Not available
EC name:	Not listed
CAS number (EC inventory):	Not listed
CAS number:	1065124-65-3 [609346-29-4 (All isomers)]
CAS name:	Cyclopropanecarboxylic acid, 3-[(1Z)-2-cyano-1-propen-1-yl]-2,2-dimethyl-, [2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl]methyl ester, (1R,3R)-
IUPAC name:	2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate
CLP Annex VI Index number:	Not currently listed
Molecular formula:	C ₁₉ H ₁₉ F ₄ NO ₃
Molecular weight range:	385.35

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
1R-trans-Z-momfluorothrin 2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate	≥ 86.0 %	83.8% - 95.5%	Active substance

The ISO name Momfluorothrin is associated with the IUPAC name 2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (EZ)-(1RS,3RS;1SR,3SR)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate. In accordance with the guidance on the identification and naming of substances under REACH and CLP, this relates to a mixture of the 8 potential isomers.

However, whilst all isomers are present in the active substance, the major isomer is the RTZ isomer (2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate), which is individually present at > 80%. The other isomers are all individually present at concentrations > 0.1% but < 10%, with the total isomer content in the active substance ≥ 91.7%. As such, the active substance is identified as 1R-trans-Z-momfluorothrin (the RTZ isomer) with CAS number 1065124-65-3 in this CLH proposal.

Full information on the composition of the substance is considered to be confidential and further details are provided in the IUCLID.

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Refer to IUCLID			

There are a number process impurities in the substance. These have been taken into consideration and are not considered to impact on the classification proposed in this dossier. Further information on the impurities is considered to be confidential but full details are provided in the confidential section of the technical dossier.

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
None				

1.2.1 Composition of test material

During the review of the active substance under Reg 528/2012, the tested substance was considered to be equivalent to the material outlined above. The human health and environmental data were generated on the substance identified by the manufacturers code S-1563. The minimum purity of S-1563 given in the test reports is 95.2% (based on total isomer content). However, the RTZ isomer is present in S-1563 at a concentration >86%. The purity specified in the human health and environmental sections for S-1563 generally relates to the total momfluorothrin isomer content unless otherwise specified. In some cases, pure isomers (i.e. the RTZ or RTE isomers) were tested. Where this is the case it is specified in the dossier.

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Powdery white solid	Foster, B. (2012g)	GLP Purity 95.4 %
Melting/freezing point	63.95-73.3 °C (PAI) 73.26-79.07oC (RTZ)	Moseley, R. H. (2011a) Moseley, R. H. (2011b)	EC Method A1 (DSC) OECD 102 GLP Purity 99.9 % (PAI) and 100% (RTZ)
Boiling point	No boiling point observed. Decomposition onset at 326.21 °C (PAI) No boiling point observed. Decomposition onset at 327.48 °C (RTZ)	Moseley, R. H. (2011a) Moseley, R. H. (2011b)	EC Method A2 (DSC) OECD 103 GLP Purity 99.9 % (PAI) and 100% (RTZ)
Relative density	1.3432 at 19.7 °C (PAI)	Foster, B. (2012a)	EC Method A3 (gas pycnometer) OECD 109 GLP Purity 99.9 %
Vapour pressure	2.478 x 10 ⁻⁷ Pa at 20 °C 1.39 x 10 ⁻⁶ Pa at 25 °C (PAI) 4.702 x 10 ⁻⁷ Pa at 20 oC 1.378 x 10 ⁻⁸ Pa at 25 oC (RTZ)	Moseley, R. H.. (2011d) Leslie S (2012)	EC Method A4 (Effusion Method) OECD 104 GLP Purity 99.9 % (PAI) and 99.7% (RTZ)
Surface tension	62.9 mN/m at 19.9 °C (TGAI)	Foster, B. (2011b)	EC Method A5 (Ring Method) OECD 115 GLP Purity 95.4 %
Water solubility	0.933 mg/L at 20 °C (PAI) 0.607 mg/l at 20 oC (RTZ)	Leslie, S. (2010a) Leslie, S. (2010b)	EC Method A6 (column elution) OECD 105 GLP Purity 99.9 % (PAI and RTZ)
Partition coefficient n-octanol/water	LogPow = 2.99 at 25 °C (RTZ isomer) Log Pow = 2.88 at 25oC (RTE isomer)	Wright, D. (2011b) Wright D. (2001c)	EC Method A8 (Shake flask) OECD 107 GLP Purity 99.7 % (RTZ) and 99.7% (RTE)
Flash point	Not applicable as 1R-trans-Z-momfluorthrin is a solid with a melting point > 40 °C		

Flammability	Not highly flammable. The test substance did not ignite. Experience in handling and use indicate that the substance is stable in contact with air and water.	Foster, B. (2012j)	EC Method A10 GLP Purity 95.4 % (TGAI)
Explosive properties	Not explosive. The substance does not contain any groups that are indicative of explosive properties. The oxygen balance is – 184.76% and no exotherms were observed in the DSC.	Foster, B. (2012k)	EC Method A14 GLP Purity 95.4 % (TGAI)
Self-ignition temperature	No relative self ignition observed (up to a temperature of 400 °C)	Foster, B. (2012j)	EC Method A16 GLP Purity 95.4 % (TGAI)
Oxidising properties	Not oxidising. The substance does not contain any groups that are indicative of oxidising properties.	Foster, B. (2011c)	Structural assessment
Granulometry	No data		
Stability in organic solvents and identity of relevant degradation products	No data		
Dissociation constant	No dissociation observed (by spectrophotometric evaluation). (RTZ)_	Wright, D. R. (2011a)	OECD 102 GLP Purity 99.7 % (RTZ)
Viscosity	Not relevant, substance is a solid).		

RTZ = 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate CAS: 1065124-65-3 (RTZ isomer)

PAI = 2,3,5,6-tetrafluoro-4-(methoxymethyl)benzyl (EZ)-(1RS,3RS,1RS,3SR)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate with RTZ and RTE isomers (in the approximate ratio 9:1)

TGAI = 2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (EZ)-(1RS,3RS;1RS,3SR)-3-(2-cyanoprop-1-enyl)-2,2-Dimethylcyclopropanecarboxylate, isomer content unspecified.

2 MANUFACTURE AND USES

2.1 Manufacture

The substance is manufactured outside of the EU for use as biocidal active substance.

2.2 Identified uses

The substance is used as a biocidal active substance inside the EU.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 9: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Refer to table 8			

3.1 *Physical Hazards*

3.1.1 Summary and discussion of physical hazards

A standard flammability study (EEC A10) is available and the substance is not classified as a flammable solid. Experience in handling and use indicates it is not pyrophoric and does not react with water to liberate flammable gases. Further, a standard self ignition temperature study (EEC A16) is available and no spontaneous ignition was observed up to a temperature of 400 °C.

The substance does not contain any groups that are indicative of explosive or oxidising properties.

3.1.2 Conclusions on classification and labelling

Not classified, conclusive but not sufficient for classification

4 HUMAN HEALTH HAZARD ASSESSMENT

The technical material used for the generation of the majority of the human health data is referred to by the manufactures code S-1563 in the study reports. S-1563 is quoted as having a minimum purity of 95.2% (based on total momfluorothrin isomer content) in the study reports, but it is predominantly the RTZ isomer (>86% RTZ). The purity specified in the dossier generally relates to the total isomer content in S-1563 unless otherwise specified. In some cases the pure isomers (i.e. the RTZ or RTE isomers) were tested. Where this is the case it is specified in the dossier.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

The pure RTZ and RTE isomers have also been investigated in the toxicokinetic studies.

S-1563 is rapidly absorbed and extensively metabolised in the rat during single and repeat dose studies by the oral route. The main metabolic pathways include ester cleavage and hydroxylation followed by glucuronidation on available alcohol groups. The parent and metabolites did not accumulate in tissues and are rapidly excreted in urine and faeces (>80%). There are no marked differences across sexes in absorption, distribution, metabolism or excretion.

4.1.2 Human information

Only *in vitro* data with human liver microsomes was available on metabolism of the substance. Exposure of human microsomes resulted in ester cleavage of the parent compound which was consistent with the rat *in vitro* and *in vivo* data.

Dermal absorption of the RTZ:RTE isomers in a ratio of 95:5 was investigated in an *in vitro* study with human skin as a 1% solution in ethanol (10g/L). Absorption was low and under current guidance, 6% the RTZ:RTE was available systemically.

No additional data is available on the toxicokinetics in humans.

4.1.3 Summary and discussion on toxicokinetics

1R-trans-Z-momfluorothrin is rapidly absorbed with no bioaccumulation and excreted by the urinary and faecal routes.

4.2 Acute toxicity

The acute toxicity of 1R-trans-Z-momfluorothrin has been investigated in four studies.

Table 10: Summary table of relevant acute toxicity studies

Acute Oral			Reference
Method	LD ₅₀	Observations and remarks	
Rat (Sprague Dawley) 5/sex/dose 0, 50, 300, 2000 mg/kg bw in corn oil S-1563 Purity: 95.2% OECD 420 Study compliant with GLP.	> 2000 mg/kg bw males. 300 – 2000 mg/kg bw females.	<p>2000 mg/kg bw 2/5 male and 5/5 female rats died. Clinical signs observed at this dose level included urinary incontinence (2 males, 1 female), tremor (1 male, 3 females), salivation (4 males, 4 females), clonic convulsion (4 males, 4 females), ocular discharge (1 male) and fur staining of the perianal (2 males), perioral (1 male), perinasal areas (2 males) and abdomen (3 males) and tip toe gait (1 female).</p> <p>300 mg/kg No deaths in either sex, but tremor (1), urinary incontinence (2) and fur staining of the perianal area (4) in male rats.</p> <p>On necropsy no abnormal findings were seen in the animals that died. In animals that survived to the end of the study, scab and retention of a white substance in urinary bladder of males were observed. These were not considered to be treatment related as they are commonly observed in this strain of rats of the same age and were not dose-dependent.</p>	Deguchi (2010a)
Neurotoxicity (single dose with 14 day observation period) Rat, Sprague Dawley 10/sex/group 0, 30, 80, 200 mg/kg bw in corn oil S-1563 Purity: 95.7% OECD 424 Study compliant with GLP and OECD guidelines	NOAEL:80 mg/kg	<p>200 mg/kg bw: One female was found dead on the day after administration. Wetted fur and soiled fur in perianal region of two females at day one and one male at day 2 after the administration respectively. These signs were resolved by day 3. The incidence of tremors in 3 females and salivation in 3 males at 6 hours after administration was increased in detailed clinical observation. Straub tail observed in 1 male and 1 female at 6 hours after administration. There were no abnormal changes in functional tests, body weight, necropsy or histopathological findings.</p> <p>30 mg/kg bw and 80 mg/kg bw: No changes were observed in either sex during the 14 day observation period.</p>	Shutoh (2012)
Acute Inhalation			
Method	LC50	Observations and remarks	
Rat (Sprague Dawley) 5/sex/dose 500, 1000, 2000 mg/m ³ (Actual aerial concentration; 0, 583, 1110, 2030 mg/m ³) MMAD = 5.00, 3.73,	>2000 mg/m ³ (2 mg/l)/ 4 hr	<p>Animals in all groups exhibited wet fur and stains around eyes and snout from the end of exposure to 2 hours after exposure.</p> <p>2000 mg/m³ (2mg/l) One female animal died 4 hours after the start of exposure. Tremor of tail (2 females) and tremor (1 female) during exposure. Hypersensitivity (4 males, 1 female), muscular rigidity (1 male), urinary</p>	Deguchi (2011)

<p>4.86 µm S-1563 Purity: 95.7% OECD 403 Study compliant with GLP and OECD guidelines</p>		<p>incontinence (1 female), ataxic gait (1 male, 4 females) and tip toe gait (4 females) after exposure. These signs disappeared within 4 days after exposure.</p> <p>1000 mg/m³(1 mg/l) Ataxic gait in one female, which had disappeared on day 1 after exposure.</p> <p>500 mg/m³(0.5 mg/L) Ataxic gait (1 male), tremor (1 female), muscular rigidity (2 females) and urinary incontinence (1 female). These signs disappeared within two days after exposure. Animals in all groups exhibited wet fur and stains around eyes and snout from the end of exposure to 2 hours after exposure.</p> <p>On necropsy no treatment related findings were reported for any dose group.</p>	
Acute Dermal			
Method	LD50	Observations and remarks	
<p>Rat Sprague Dawley (5/sex) 2000 mg/kg bw moistened with injection water S-1563 Purity: 95.2% OECD 402 Study compliant with GLP and OECD guidelines</p>	<p>>2000 mg/kg bw</p>	<p>There were no mortalities and no evidence of systemic toxicity at the dose tested.</p>	<p>Deguchi (2010c)</p>

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Oral LD₅₀ values of >2000 and 300-2000 mg/kg bw were derived for male and female rats respectively.

4.2.1.2 Acute toxicity: inhalation

In an acute inhalation study, the LC₅₀ was measured at greater than >2000 mg/m³(2 mg/l) for both male and female rats.

4.2.1.3 Acute toxicity: dermal

A dermal LD₅₀ value of >2000 mg/kg bw was derived for both male and female rats.

4.2.1.4 Acute toxicity: other routes

No data available

4.2.2 Human information

No data available.

4.2.3 Summary and discussion of acute toxicity

Refer to section 4.2.1

4.2.4 Comparison with criteria

The oral LD₅₀ value of 300 – 2000 mg/kg bw for female rats is within the range $300 < LD_{50} \leq 2000$ for classification as Acute Tox 4; H302.

The inhalation LC₅₀ was $> 2000 \text{ mg/m}^3$ (2 mg/l) with an MMAD of 4.86 μm . Whilst a concentration of 5 mg/L (as included in the classification criteria) was not reached, this was the best atmosphere that could be achieved under controlled experimental conditions. Therefore no classification for acute inhalation toxicity is proposed.

The dermal LD₅₀ of $>2000 \text{ mg/kg bw}$ for rats is above the value for classification provided in the Regulations (i.e. 2000 mg/kg bw). No classification for acute dermal toxicity is proposed.

4.2.5 Conclusions on classification and labelling

Acute Tox 4; H302 Harmful if swallowed

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

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

Data from the acute oral, inhalation and neurotoxicity (oral) studies indicates that exposure to 1R-trans-Z-momfluorothrin results in neurotoxicity after a single exposure (refer to table 10).

4.3.2 Comparison with criteria

Classification as either STOT-SE1 or 2 is applicable to substances that have produced non-lethal toxicity in humans, or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant non-lethal toxicity in humans following a single exposure.

Classification as STOT-SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation.

Based on the clinical signs seen in the acute inhalation study (see table 11), STOT-SE2 should be considered given that a single exposure via the inhalation route induced signs indicative of acute neurotoxicity at doses of 0.5 mg/l and above, which in some cases persisted for up to 3 days post-exposure.

Table 11: Neurotoxic effects seen following exposure to S-1563 via the inhalation route

Dose mg/m ³ (mg/l)	Male						Female						
	500 (0.5)		1000 (1)		2000 (2)		500 (0.5)		1000 (1)		2000 (2)		
	No of animals	Time observed *	No of animals	Time observed *	No of animals	Time observed *	No of animals	Time observed *	No of animals	Time observed *	No of animals	Time observed *	
Neurotoxic signs observed during exposure													
Tremor of tail	-	-	-	-	-	-	-	-	-	-	-	2/5	2h
Tremor	-	-	-	-	-	-	-	-	-	-	-	1/5	3h
Death	-	-	-	-	-	-	-	-	-	-	-	1/5	4h
Neurotoxic signs observed post exposure													
Tremor	-	-	-	-	-	-	1/5	1h	-	-	-	-	-
Hypersensitivity	-	-	-	-	4/5	1-2h	-	-	-	-	1/4	1h	-
Ataxic gait	1/5	2 h	-	-	1/5	2h	-	-	1/5	2h	4/4	2h-d1	-
Tip toe gait	-	-	-	-	-	-	-	-	-	-	4/4	d2-d3	-
Muscular rigidity	-	-	-	-	1/5	1h	2/5	2h-1d	-	-	-	-	-
Urinary incontinence	-	-	-	-	-	-	1/5	2h	-	-	-	-	-

*Time of observation at which an effect was first and last observed

Animals when exposed to S-1563 via the oral route gave clear signs of neurotoxicity following a single exposure in both the acute oral toxicity study and the acute neurotoxicity study. In the acute oral toxicity study, tremor and urinary incontinence were seen at doses of 300 mg/kg bw. At the next dose level of 2000 mg/kg bw tremor, salivation, and clonic convulsion were seen in both sexes, together with tip toe gait in females. In the acute neurotoxicity study the highest dose tested was 200 mg/kg bw and at this dose, an increased incidence of tremors was seen in female rats (3/9) and increased salivation in males (3/10), together with Straub tail (1/10 males and 1/9) females). Whilst these effects fall within the guidance values for STOT-SE1 via the oral route, this classification is not considered appropriate given the proposed classification of for acute oral toxicity category 4 (section 4.2).

The guidance values for classification for STOT-SE for a dust aerosol are $C \leq 1$ mg/l/4h exposure for category 1 and $5.0 \geq C > 1.0$ mg/l/4h for category 2. Based on the neurotoxic effects seen at 2 mg/l (9/10 animals) in the acute inhalation study, classification for STOT-SE2 is proposed. Category 1 could be considered based on the muscular rigidity observed at 0.5 mg/l. However, effects seen at this dose level were only observed in a small number of animals (1 male and 2 females) and are inconsistent with the absence of effects at 1 mg/l.

While the data is not entirely consistent with a clear dose response relationship, 1R-trans-Z-momfluorothrin is a pyrethroid, a class of chemicals known to induce neurotoxic effects (Ray, 1991) so, on balance, classification for STOT-SE2 is proposed. No route of exposure is specified as the clinical findings reported in the acute oral study appear to indicate that inhalation is not the only route that leads to neurotoxicity, although it is noted that the substance is already classified for acute oral toxicity.

The criteria for classification as STOT-SE 3 are not met as the effects are not considered narcotic based on the mode of action of 1R-trans-Z-momfluorothrin which works by blocking sodium channels.

STOT-SE Category 2; H371 May cause damage to the organs (Central Nervous System)

4.4 Irritation

4.4.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
Rabbit, New Zealand White 3 males S-1563 Purity: 95.2% OECD 404 Study compliant with GLP	Average individual scores over 24, 48 and 72 hours were: Erythema: 0, 0, 0 Oedema: 0, 0, 0	No classification	Ota, M (2011a)

4.4.1.1 Non-human information

The skin irritation potential of 1R-trans-Z-momfluorothrin has been tested in a standard skin irritation study in three male New Zealand White rabbits. Neither erythema nor oedema was seen in any of the animals.

4.4.1.2 Human information

No data available

4.4.1.3 Summary and discussion of skin irritation

See section 4.4.1.1.

4.4.1.4 Comparison with criteria

1R-trans-Z-momfluorothrin did not cause erythema or oedema in any of the animals tested. Classification as a skin irritant is not required.

4.4.1.5 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification

4.4.2 Eye irritation

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Rabbit, New Zealand White 6 males (3 washed and 3 unwashed) S-1563 Purity: 95.2% OECD 405 Study compliant with GLP and OECD guidelines	Average individual scores over 24, 48 and 72 hours for the unwashed group were: Cornea: 0, 0, 0 Iris: 0, 0, 0 Conjunctiva redness: 0.3, 0.3, 0.3 Conjunctiva chemosis: 0.3, 0.3, 0.3	Not irritating	Ota (2011b)

4.4.2.1 Non-human information

The eye irritation potential of 1R-trans-Z-momfluorothrin has been tested in a standard eye irritation study in male New Zealand White rabbits. No corneal lesions were seen. Iridial congestion (grade 1) was seen in two animals at 1 hour post instillation but had resolved at 24 hours. Conjunctival redness (grade 1) and chemosis (grade 1) was seen in three rabbits at 24 hours, but all ocular reactions had resolved by 48 hours post-application.

4.4.2.2 Human information

No data available.

4.4.2.3 Summary and discussion of eye irritation

1R-trans-Z-momfluorothrin caused mild eye irritation with an average score of 0.3 from 24-72 hours for both conjunctival redness and chemosis. All reactions had resolved themselves by 72 hours post instillation. No classification required.

4.4.2.4 Comparison with criteria

1R-trans-Z-momfluorothrin caused mild, transient irritation of the eye in New Zealand White rabbits. Effects observed between 24 and 72 hours were conjunctival redness and swelling with an average score of 0.3. This does not meet the criteria for classification (average score for iritis ≥ 1 , and/or corneal opacity ≥ 1 , and/or conjunctival redness ≥ 2 , and/or conjunctival oedema ≥ 2 , in at least 2 of 3 tested animals).

4.4.2.5 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification
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4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

This endpoint was not investigated directly, however the respiratory effects observed during the acute and sub-acute inhalation studies gave no indication that 1R-trans-Z-momfluorothrin causes an irritant effect in the respiratory tract. As such, the available data do not indicate that classification is required for this end-point (see Sections 4.2 and 4.7.1.2).

4.4.3.2 Human information

No data available

4.4.3.3 Summary and discussion of respiratory tract irritation

See section 4.4.3.1.

4.4.3.4 Comparison with criteria

No signs of respiratory tract irritation (as set out in Annex 1: 3.8.2.2.1 of the Guidance on the Application of the CLP Criteria) were observed in the acute or sub-acute inhalation studies that are indicative of respiratory irritation.

4.4.3.5 Conclusions on classification and labelling

Not classified – data lacking

4.5 Corrosivity

4.5.1 Non-human information

1R-trans-Z-momfluorothrin did not lead to full thickness or irreversible skin damage in the skin irritation test nor were any corrosive effects seen in the eye irritation test (see Sections 4.4.1 and 4.4.2). Therefore 1R-trans-Z-momfluorothrin does not meet the criteria for classification as corrosive.

4.5.2 Human information

No data available

4.5.3 Summary and discussion of corrosivity

See section 4.5.1

4.5.4 Comparison with criteria

See section 4.5.1.

4.5.5 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 14: Summary table of relevant skin sensitisation studies

Species/Method	Doses	No. sensitised/total no.	Result	Reference
Guinea pig, Hartley (SPF) 20 test, 10 negative control, OECD 406, Magnusson and Kligman Maximisation test GLP	Induction: Intradermal: 5% (w/v) in corn oil. Topical: 50% in acetone Challenge: 50% in acetone Doses selected from a range finding study. Slight erythema was observed at an intradermal dose of 5%, no skin reactions were observed at a topical dose of 50%. S-1563 Purity: 95.2%	Test: 0/20 Negative Control (corn oil): 0/10 Positive control (HCA): 5/5 (100%) HCA control: 0/5.	Negative	Ota (2010)

4.6.1.1 Non-human information

In a guideline Magnusson and Kligman guinea pig maximisation test, 20 animals were treated with intradermal injections of S-1563 (0.1 ml) at 5% (w/v) in corn oil followed by topical induction with 0.4 ml of 50% S-1563 in acetone. No skin reactions were observed following challenge with 50% S-1563 in acetone. The concurrent positive control with HCA gave the expected results.

4.6.1.2 Human information

No data available.

4.6.1.3 Summary and discussion of skin sensitisation

None of the animals showed a sensitisation response in the guinea pig maximisation test.

4.6.1.4 Comparison with criteria

In a guideline Magnusson and Kligman guinea pig maximisation test, none of the animals tested showed a sensitisation response to 1R-trans-Z-momfluorothrin. A response in 30% of the animals in an adjuvant test is required for classification.

4.6.1.5 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

This potential of 1R-trans-Z-momfluorothrin to cause respiratory sensitisation was not investigated directly. However, given that 1R-trans-Z-momfluorothrin does not require classification for skin sensitisation and the sub-acute inhalation study gave no indication of respiratory sensitisation, 1R-trans-Z-momfluorothrin is considered unlikely to be a respiratory sensitiser (see sections 4.6.1 and 4.7.1.2). Therefore no classification is proposed.

4.6.2.2 Human information

No data are available.

4.6.2.3 Summary and discussion of respiratory sensitisation

See section 4.6.2.1.

4.6.2.4 Comparison with criteria

See section 4.6.2.1.

4.6.2.5 Conclusions on classification and labelling

Not classified – Data lacking

4.7 Repeated dose toxicity

Table 15: Summary table of relevant repeated dose toxicity studies

Method	Dose Levels	Observations and Remarks	Reference
Rat studies			
13 week (+ 6 week recovery) oral (dietary) Rat, Wistar 12/sex/group (main study) + 6/sex/group (recovery – control and high dose) OECD 408 Study compliant with GLP and OECD guidelines	0, 300, 1000, 3000, 6000 ppm (0, 23, 76, 223, 485 mg/kg bw/d – males 0, 25, 82, 236, 501 mg/kg bw/d – females) S-1563 Purity: 95.7% Guideline value for classification: ≥100 mg/kg bw/d	<p>300 ppm (23 mg/kg bw/d (males) and 25 mg/kg bw/d (females)) no test item-related effects were observed in either sex during the treatment and recovery periods.</p> <p>1000 ppm (76 and 82 mg/kg bw/d) ↓body weight gains in females (-13%), ↑ absolute and relative liver weights in males (11.2% and 12.1% respectively); brownish pigment in livers (both sexes). ↑ value of phospholipids and cholesterol (males and females), ↑protein content, ↑alpha2-globulin (males).</p> <p>Doses above the guideline value (>223 mg/kg bw/d) ↓body weights and ↓body weight gains, ↑absolute liver weight and both sexes. In clinical biochemistry, ↑phospholipids, triglycerides, cholesterol, gamma-glutamyl-transferase, and albumin (both sexes); ↑protein and alpha2-globulin (males) ↑alanine aminotransferase (females). Microscopic examination of livers showed a brownish pigment, hepatocellular hypertrophy (both sexes) and bile duct proliferation In the other organs, brownish pigment in kidneys in both sexes.</p> <p>Recovery groups All of the alterations recorded at 1000, 3000 and 6000 ppm, except for the brownish pigment in kidneys, had gradually recovered at the end of the recovery period.</p> <p>NOAEL: 23 mg/kg bw/d LOAEL: 76 mg/kg bw/d*</p>	Sommer (2010)
Neurotoxicity (90 day oral, dietary) Rat, Wistar Male and Female 12/sex/group OECD 424 Study compliant with GLP and OECD guidelines	0, 600, 2000, 6000 ppm (0, 37, 127, 402 mg/kg bw/d (males)) (0, 41, 135, 425 mg/kg bw/d (females)) S-1563 Purity: 95.7% Guideline value for classification: ≥100 mg/kg bw/d	<p>2000 (127/135 mg/kg bw/d) and 6000 ppm (402/425 mg/kg bw/d): ↓food consumption (attributed to palatability) in all groups of treated rats during the first week. ↓body weight and body weight gain in both sexes. The overall body weight changes at 2000 ppm and 6000 ppm in males and females were 14.1% and 18.2% or 11.9% and 21.4% of controls respectively.</p> <p>No effect was detected in the FOB</p> <p>Systemic NOAEL: 37 mg/kg bw/d LOAEL: 127 mg/kg bw/d *</p> <p>Neurotoxicity NOAEL: 402 mg/kg bw/d LOAEL: Not determined*</p>	Sommer (2011a)
52 week oral (dietary) Rat, Wistar	0, 200, 500, 1500, 3000 ppm	<p>200 ppm (11 mg/kg bw/d (males) and 12 mg/kg bw/d (females))</p> <p>No treatment-related symptoms or mortality, and no</p>	Sommer (2011b)

<p>21/sex/group OECD 452</p> <p>Study compliant with GLP and OECD guidelines</p>	<p>(0, 11, 27, 83, 169 mg/kg bw/day - males 0, 12, 34, 103, 199 mg/kg bw/day – females)</p> <p>S-1563 Purity: 95.7%</p> <p>Guideline value for classification is: 25 mg/kg bw/d</p>	<p>effects in the FOB, ophthalmoscopy and urinalysis.</p> <p>500 ppm (27 mg/kg bw/d (males) and 34 mg/kg bw/d (females))</p> <p>↓Body weight (-12.1%) and ↓body weight gain (-4.7%) in females. ↑Absolute (13.2% in males) and relative liver weights (17.9% females). Histologically, brown pigment deposition was seen in the liver with a dose-associated distribution. Slight ↑ in levels of phospholipids in females and mainly centrilobular hepatocellular hypertrophy in males and females were observed at minimal severities and incidences. ↑incidence of brown pigment deposition in the kidneys (females).</p> <p>Doses above the cut-off for classification</p> <p>A gradual worsening of treatment-related effects seen at 500 ppm was observed. Including ↓Body weight and ↓body weight gains, ↑increase total cholesterol, phospholipids, protein and albumin content, GGT and ↑total bilirubin values (both sexes); ↑ alpha1-globulin and alpha2-globulin, triglycerides (males); A/G ratio (females). ↑absolute and relative liver weights ↑brown pigment deposition in the liver. ↑incidence of mainly centrilobular hepatocellular hypertrophy (both sexes). ↑ incidence in bile duct proliferation (female) ↑incidence of brown pigment deposition in the kidney. Diffuse follicular cell hypertrophy in the thyroid of 1 female and 7 males. ↓food consumption was also observed in females of the highest dose group.</p> <p>In haematology alterations including shortening of PrT and PT); ↑increased incidence of diffuse acinar hypertrophy in the mandibular salivary gland (10 males, 16 females)</p> <p>NOAEL: 12 mg/kg bw/d LOAEL: 34 mg/kg bw/d*</p>	
<p>Dog studies</p>			
<p>14 day dietary study in Beagle dogs</p> <p>Non-guideline Male and female 1/sex/group</p> <p>Range finding study conducted in advance of the 13- and 52-week studies.</p> <p>Detail has been provided for completeness and only longer term studies have been used for classification purposes.</p>	<p>0, 50, 500, 1000 mg/kg bw/d</p> <p>Daily dose</p> <p>S-1563 Purity: 99.1%</p>	<p>50 mg/kg bw/d- vomiting and watery faeces on one single occasion.</p> <p>500 mg/kg bw/d- vomiting and watery faeces in both sexes, predominantly over the first 5 days</p> <p>1000 mg/kg bw/d- vomiting, tremors, salivation and watery faeces in both sexes, predominantly over the first 4 days. Male killed in extremis due to persistent signs and additional tachypnea.</p> <p>No treatment related changes in clinical chemistry, haematology, body weight, food consumption, organ weights or changes at necropsy at any dose level.</p> <p>NOAEL: 50 mg/kg bw/d LOAEL: 500 mg/kg bw/d*</p>	<p>Braun, L (2008)</p>

S-1563 Purity: 95.7%			
OECD 409 13 week dietary dog study (+ 6 week recovery) Male and female Main study- 4/sex/group Recovery group- 2/sex/group	0, 50, 200, 600 mg/kg bw/d Daily dose S-1563 Purity: 95.7% A guideline value of 100 mg/kg/d is considered for classification based on the value defined for the rat 90 day study.	50 mg/kg bw/d - no significant adverse effects. Doses above the cut-off for classification Vomiting, watery faeces and changes in biochemical parameters (e.g. increased cholesterol and triglycerides and decreased ALT and alpha-1-globulin) were reported at doses above the guideline value (200 and 600 mg/kg bw/d). In addition, absolute and relative liver weight increases and hepatocellular hypertrophy were recorded in both sexes at 600 mg/kg bw/d. These findings are consistent with those reported in the rat and of no concern for classification. NOAEL: 200 mg/kg bw/d LOAEL: 600 mg/kg bw/d*	Braun, L (2011)
OECD 452 52 week dietary dog study Male and female Main study- 4/sex/group	0, 25, 100, 400 mg/kg bw/d Daily dose S-1563 Purity: 95.7% A guideline value of 25 mg/kg/d is considered for classification based on the value defined for the rat (90 day study plus application of the Haber rule).	25 mg/kg bw/d: The only effect was decreased alpha-1-globulin at week 8 in females (0.7-fold) At doses above the guideline value for classification Liver hypertrophy was noted at 100 mg/kg bw/d (2/4 males and 1/4 females) and 400 mg/kg bw/d (4/4 males and females). Clinical signs included vomiting, watery faeces and salivation. The clinical biochemistry analysis showed a trend towards increased levels of triglycerides in both sexes with statistical significance generally observed at weeks 4, 8 and 13. Overall, there was no toxicity of concern at dose levels applicable to classification. NOAEL: 25 mg/kg bw/d LOAEL: 100 mg/kg bw/d*	Braun, L (2012)

*values cited in the CAR

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Rat

There are two studies investigating the repeat dose toxicity in the rat via the oral route; a 13 week (+ 6 week recovery) study and a 52 week study.

In a 13 week study to investigate the sub-chronic toxicity of 1R-trans-Z-momfluorothrin, rats were dosed at concentrations of 300, 1000, 3000 and 6000 ppm S-1563 in their diets for 13 weeks

(equivalent to 23, 76, 223, 485 mg/kg bw/d (males) and 25, 82, 236, 501 mg/kg bw/d (females)). This was followed by a 6-week recovery period for the control (0 ppm) and highest dose groups.

At doses below the guideline value of 100 mg/kg bw/d, the main effects were on body weight and the liver. Body weight was reduced in females by 12.1% while the absolute and relative liver weight increased in males by 11.2% and 12.1% respectively. Microscopic examination of livers, found a brownish pigment in the livers of males (4/12) and females (10/12). Changes in clinical biochemistry included increased levels of phospholipids and cholesterol in males and females, increases in protein and alpha2-globulin in males. These alterations in the clinical biochemistry are considered to be indicative of functional changes in the liver.

At doses above the guideline these effects gradually worsened with increasing dose. The liver was macroscopically enlarged in males. Hepatocellular hypertrophy and bile duct proliferation were recorded and ultrastructural changes showed a moderate amplification and enlargement of the smooth endoplasmic reticulum (SER), an augmentation of rough endoplasmic reticulum (RER), and an intracellular accumulation of solid dark bodies (lysosomes). Changes in clinical biochemistry included increased levels of phospholipids, triglycerides, cholesterol, gamma-glutamyl-transferase, and albumin in males and females, increases in protein and alpha2-globulin in males and in alanine aminotransferase in females. These alterations in the clinical biochemistry are considered to be indicative of functional changes in the liver. Brownish pigment in the kidneys was seen in both sexes together with a change in the urinalyses in females at the highest dose. A slight diffuse acinar hypertrophy in mandibular glands was also seen in both sexes and is considered treatment related. Minor changes to some haematology parameters were reported at the higher doses, including increased reticulocytes count and reduced mean corpuscular volume and mean corpuscular volume in both sexes and reduced haemoglobin and haematocrit in females.

Following the 6 week recovery period, all of the reported changes, except the brownish pigment in the kidneys, had reversed.

In the 52 week study in rats, groups of 21 male and 21 female rats received S-1563 in their diet at concentrations of 0, 200, 500, 1500, 3000 ppm (equivalent to 0, 11, 27, 83, 169 mg/kg bw/d (males) and 0, 12, 34, 103, 199 mg/kg bw/d (females)). At doses marginally higher than the guideline for classification (25 mg/kg bw/d) based on the 13 week study and the application of Haber's rule the main effects were on the liver and body weight. At doses 27 mg/kg bw/d mean absolute liver weights were increased in males at by 13.2% and in females the mean relative liver weight increased by 17.9%. These changes were accompanied by slight increases in phospholipid levels in females and mainly centrilobular hepatocellular hypertrophy at minimal severities and incidences in both sexes. In females a decrease in body weight of 15% as compared to the controls was recorded. At doses in excess of the cut-off (>82.6 mg/kg bw/d), an increased deposition of a brown pigment was reported in liver and kidney along with increased incidence of centrilobular hypertrophy. As with the 13 week study, the incidence of these effects increased at higher doses. At doses above the cut off, liver enlargement was found to be associated with hepatocyte hypertrophy, bile duct proliferation and lipofuscin pigment deposition. In addition diffuse follicular cell hypertrophy was seen in the thyroid and slight diffuse acinar hypertrophy of the mandibular gland was at the highest dose. Changes in clinical chemistry and haematology were observed at doses of 83 mg/kg bw/d and above. These findings are consistent with the results reported in the 13 week study in rats.

Dog

There are two dietary studies available for classification purposes: one 13 week study with a recovery period and a 52 week study.

Using the guideline value (100 mg/kg bw/d s-1563) as defined for the rat in a 13 week study, there were no treatment related findings at 50 mg/kg bw/d S-1563 in the dog. At doses greater than the cut-off value (200 and 600 mg/kg bw/d), there were reports of vomiting, watery faeces and changes in biochemical parameters e.g. increased cholesterol and triglycerides and decreased ALT and alpha-1-globulin. These findings suggested that the liver was a potential target organ and were consistent with the results in the rat.

A 52 week study in the Beagle dog was submitted in accordance with OECD guideline 452 and to GLP standards (Braun, 2012). Using the guideline value (25 mg/kg bw/d) as defined for the rat in a 52 week study, the only effect at 25 mg/kg bw/d in the dog was a decrease in alpha-1-globulin (0.7-fold). This effect was present at week 8 in females only. Due to the transient nature of the decrease in female dogs and the inconsistency across sexes, this finding is not a concern for classification purposes. At higher doses (100 and 400 mg/kg bw/d), there were reports of vomiting, watery faeces, salivation and changes in biochemical parameters e.g. increased cholesterol and triglycerides and decreased ALT and alpha-1-globulin. As these findings are consistent with those reported in the rat, they are not a concern for classification.

4.7.1.2 Repeated dose toxicity: inhalation

Table 16: Summary table of relevant repeated dose toxicity studies

Method	Dose Levels	Observations and Remarks	Reference
28 day inhalation (nose only) Rat (Sprague Dawley) 10/sex/group OECD412 Study compliant with GLP and OECD guidelines	Nominal concentration: 0, 50, 150, 300 mg/m ³ (Analytical concentration: 0, 62.2, 170, 320 mg/m ³) MMAD: 4.49, 5.00, 5.07µm respectively Purity: 95.7% Guidance value for classification ≤0.6 mg/l	All doses tested were below the cut-off value for classification. Following exposure, signs of transient effects on the CNS and an adaptive response in liver were seen. None of these effects (which are summarized below) were considered sufficient to justify classification. Clinical signs included transient tremor, ataxic gait, muscular rigidity and hypersensitivity after exposure in one male in the 300 mg/m ³ group and tip toe gait in 1 female each of the 150 and 300 mg/m ³ groups. Increased liver weight of >10% was observed in males of all test groups and females of the 150 and 300 mg/m ³ test groups only reaching statistical significance in females of the top dose group. Increases in relative liver weight were statistically significant in all dose groups in males and the top two dose groups in females. At the highest dose, males showed an increase in ASAT and changes in blood chemistry (increased total cholesterol and decreased blood glucose level). Slight increases in total cholesterol were found in males of the 150 mg/m ³ group. In females of the 150 and 300 mg/m ³ groups, increased liver weight was accompanied by an increase in total cholesterol and phospholipids. Changes in the brain weight of males and the adrenal weight of females in the 300 mg/m ³ group NOAEL: 50 mg/m ³ LOAEL: 150 mg/m ³ *	Deguchi, Y. (2011)

*values proposed in the CAR

Rat

Clinical signs observed were tremor, ataxic gait, muscular rigidity and hypersensitivity after exposure in 1 male in the 300 mg/m³ group and tip toe gait in 1 female each of the 150 and 300 mg/m³ groups. These disappeared after exposure on the same day or before exposure on the next day and, with the exception of hypersensitivity which was seen on Day28, were not observed after Day 3 of exposure. Wet fur was seen in all groups, however was seen to persist longer in the animals in the two highest dose groups suggesting general conditions were worsened by exposure to the test substance, with the result of extending the time to disappearance of wet fur. Thus, wet fur is possibly a secondary effect of the exposure to the test substance.

Increased liver weight was observed in both males and females of the 150 and 300 mg/m³ test groups. At the highest dose, males showed an increase in aspartate aminotransferase and changes in blood chemistry (increased total cholesterol and decreased blood glucose level). Only slight increases in total cholesterol were found in males of the 150 mg/m³ group; these were not statistically different from the controls and fell within the range of the historical data. No

underlying histopathological changes were observed in this group and so the observed change is considered to be of no toxicological significance. In females of both the 150 and 300 mg/m³ dose groups, increased liver weight was accompanied by an increase in total cholesterol and phospholipids. These results suggest a possible effect of 1R-trans-Z-momfluorothrin on lipid and glucose metabolism in the liver. Changes seen in the brain weight of males and the adrenal weight of females in the 300 mg/m³ group were considered to be of no toxicological significance because there was no underlying effect observed in related haematology, blood chemistry, or histopathological examination.

4.7.1.3 Repeated dose toxicity: dermal

Table 17: Summary table of relevant repeated dose toxicity studies

Method	Dose Levels	Observations and Remarks	Reference
28 day dermal Rat/ (SD) 10/sex/group OECD 410 Study compliant with GLP and OECD guidelines	0, 100, 300, 1000 mg/kg bw/d 6 hours/day	No treatment related effects at any dose	Ogata, H. (2012)

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

Carcinogenicity studies in rats and mice are presented in section 4.10. All the doses tested were above the 25 mg/kg bw/d and so according to the criteria effects observed at this level are not relevant for classification.

4.7.1.7 Summary and discussion of repeated dose toxicity

The short term repeat dose toxicity of 1R-trans-Z-momfluorothrin was investigated in rats and dogs. The long term repeat dose toxicity was addressed in the carcinogenicity studies with rats and mice (section 4.10) and has been reported as appropriate.

Body weight

At doses below the respective guideline values for classification, the effects of 1R-trans-Z-momfluorothrin are primarily on liver and body weight in rats. A decrease in body weight was reported in female rats at 13 weeks but this was not seen in males or in studies of longer duration. This effect worsened with increasing dose and was also reported in males at higher dose levels.

In dogs and mice, no effects were noted at doses below the guidance values for classification.

Liver

Effects on the liver were observed following treatment via both the oral and inhalation routes. Increased liver weight was reported in males and females at doses below or marginally above the guidance values for the 28 day inhalation and 13 and 52 week oral studies in rats. This was accompanied by changes in clinical biochemistry, hypertrophy and the deposition of a brown pigment in the liver.

In dogs and mice, no effects were noted at doses below the guidance values for classification.

Kidney

In the 52 week study, females dosed with 34mg/kg bw/d (above the guidance value) had deposition of brown pigment in the kidney. No further effects were seen in the kidney.

In dogs and mice, no effects were noted at doses below the guidance values for classification.

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

The repeated-dose toxicity of 1R-trans-Z-momfluorothrin has been investigated via the oral, dermal and inhalation routes in rats, mice and dogs. As discussed in Section 4.1.7, the consistent finding was an effect on the liver following dosing via the oral and inhalation exposure. The liver effects included increases in liver weight, liver hypertrophy and alterations in liver function as indicated by clinical biochemistry changes.

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

Classification as either STOT-RE1 or 2 is applicable to substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure.

Guidance values for classification for STOT-RE Category 2 are set at $<10 C \leq 100$ mg/kg bw/d based on a 90 day study or ≤ 300 mg/kg bw/d for a 28 day study in rats. In rats, hepatocyte hypertrophy and alterations in the liver function as shown by increased triglycerides, phospholipids and aspartate aminotransferase are consistently seen in the repeated-dose studies. However, while these changes occur at levels that would merit classification as STOT-RE they are considered to be adaptive and do not produce a significant adverse toxicological effect and so classification for STOT-RE is not justified.

In dogs and mice all treatment related responses were seen at levels above the guidance values for classification.

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

1R-trans-Z-momfluorothrin does not require classification for specific target organ toxicity following repeated dose.

Not classified – conclusive but not sufficient for classification

4.9 Germ cell mutagenicity (Mutagenicity)

Table 18: Summary table of relevant in vitro and in vivo mutagenicity studies

<i>In vitro data</i>				Reference
Method	Organism/strain	Concentrations tested	Result	
Bacterial reverse mutation test OECD 471 Study compliant with GLP and OECD guidelines	<i>S.typhimurium</i> TA1535, TA1537, TA98, TA100 and <i>E.coli</i> WP2uvrA	156 – 5000 µg/plate	Negative both in the presence and absence of S9.	Kitamoto, (2009a)
<i>In vitro</i> chromosome aberration assay in mammalian cells OECD 473 Study compliant with GLP and OECD guidelines	Chinese hamster lung cells (CHL/IU)	Experiment 1 6 hours treatment/18 hours recovery + and –S9 -S9- 39.1, 78.1, 156, 313, 625 and 1250 µg/mL +S9- 40.0, 60.0, 80.0, 100, 120, 140 and 160 µg/mL Experiment 2 24 treatment –S9; 6 hours treatment/18 hours recovery +S9 -S9- 4.88, 9.77, 19.5, 39.1, 78.1 and 156 µg/mL +S9- 40.0, 60.0, 80.0, 100, 120, 140 and 160 µg/mL	Experiment 1- there was no increase in the incidence of structurally or numerically aberrant cells in the absence of S9 but a marginal increase in the incidence of structurally aberrant cells was noted in the presence of S9 at 120 and 140µg/ml. Experiment 2- No increase in structural or numerical aberrations in the absence of S9 at any dose level. The marginal increase in structural aberrations was reproduced in the presence of S9 at 100, 120 and 140µg/ml. Cytotoxicity was seen both in the presence and absence of S9 mix (24 hours treatment). A dose-dependent growth inhibition was observed in the absence of S9 mix (6 hours treatment and 18 hours recovery), but there was no marked inhibition to growth rate of 50% or lower. This result is considered positive given the marginal increase in the incidence of structurally aberrant cells in the presence of S9.	Kitamoto (2009b)
<i>In vitro</i> gene mutation assay OECD 476 Study compliant with GLP and OECD guidelines	Chinese Hamster V79 cells	Experiment 1 -S9- 7.7, 15.3, 30.5, 61.0, 91.5 and 122.0 µg/mL +S9- 15.3, 30.5, 61.0, 76.8, 91.5, 106.8 and 122.0 µg/mL	In the absence of metabolic activation, no relevant and reproducible increase was observed in the mutation frequency. The induction factor exceeded the threshold of 3x the solvent control in experiment 1 at 15.3 µg/ml, but this was not repeated in the parallel culture. All values were within the historical control ranges. In the presence of metabolic activation, mutation frequencies were less than 3x the vehicle control for all treated groups. The	Wollny (2011)

		<p>Experiment 2 -S9- 7.7, 15.3, 30.5, 61.0, 91.5 and 122.0 µg/mL</p> <p>+S9-7.7, 15.3, 30.5, 61.0, 76.3 and 91.5 µg/mL</p>	<p>result is negative in both the presence and absence of S9 with no dose related increases in mutation frequency in any experiment. All mutation rates were within the relevant historical control ranges.</p>	
<i>In vivo data</i>				Reference
Method	Organism/strain	Concentrations tested and sampling times	Result	
<p>Mammalian erythrocyte micronucleus test OECD 474</p>	<p>Rat (SD) Male and female 5/sex/group</p>	<p>0, 150, 300, 600 mg/kg bw/d in males</p> <p>0, 50, 100, 200 mg/kg bw/d in females</p> <p>Once by oral gavage</p> <p>24 hours- all dose groups, vehicle and positive control.</p> <p>48 hours- vehicle and highest dose for each sex.</p> <p>In a pre-test toxicity study, one male rat died at 600 mg/kg and 4/5 females died at 400mg/kg. For these reasons, the lower doses for female were used in the main study.</p>	<p>Clinical observations- male rats had tremors at 4 hours post dose at 300 and 600 mg/kg bw/d and soft stool at all three doses of S-1563. Tremor was also noted in female rats at 4 hours post treatment with 200 mg/kg bw/d.</p> <p>24 h (all groups) - neither sex showed any significant change in the percentage of PCEs (range 45.4- 62.2% in males and females across control and treated).</p> <p>PCEs with micronuclei did not alter significantly or dose dependently compared to controls in either sex (range 0.08-0.20 % across females and males).</p> <p>48 h (high dose and controls only) – males showed no change in PCEs or PCEs with micronuclei.</p> <p>In contrast, the percentage of PCEs in females did decline at 200 mg/kg bw/d (40.0 versus 54.4% in controls). This demonstrated that the test substance reaches the target tissue i.e. the bone marrow. The decline in PCEs was not accompanied by any changes in micronuclei.</p> <p>Positive control (cyclophosphamide) decreased the number of PCEs and induced micronuclei which satisfied the laboratory’s criteria for validation.</p>	<p>Kitamoto (2010)</p>
<p>UDS assay OECD 486</p>	<p>Rat (SD) Male and female 3/sex/group</p>	<p>0, 100, 200 mg/kg bw/d in females</p> <p>0, 300, 600 mg/kg bw/d in males</p> <p>All dose levels were investigated at 2 and 16 hours post treatment.</p> <p>Once by oral gavage</p>	<p>2 and 16 hours- there were no significant differences in mean net nuclear grains or percentage of cells in repair at either exposure times or across sexes.</p> <p>Positive control at both time points showed enhanced net nuclear grains and cells in repair in both sexes of the rat. The results were in accordance with the laboratory’s criteria.</p>	<p>Tanaka (2010)</p>

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4.9.1 Non-human information

4.9.1.1 In vitro data

The bacterial reverse mutation assay and mammalian gene mutation assay with Chinese hamster V79 cells produced negative results in the presence and absence of S9. In contrast, a marginal positive result for structural aberrations was reported in the chromosome aberration assay in the presence of S9 at 100 µg/ml and above. This result indicates that 1R-trans-Z-momfluorothrin has genotoxic potential *in vitro*.

4.9.1.2 In vivo data

Two *in vivo* studies have been evaluated to determine the potential for 1R-trans-Z-momfluorothrin to induce cytogenetic damage and DNA repair in rats. No evidence of micronucleus formation was observed in either sex of the rat in the mammalian erythrocyte micronucleus test. To ensure this is a true negative result, it should be demonstrated that the test substance reaches the target tissue i.e. the bone marrow. The decline in PCEs in females at 48 hours supports this criterion and there is data from the toxicokinetic studies to suggest it is detected at low levels in the bone marrow following oral dosing (Mikata K, 2010).

In the UDS assay, there was also no evidence of enhanced DNA repair caused by 1R-trans-Z-momfluorothrin.

Overall, the results of these studies provide reassurance that 1R-trans-Z-momfluorothrin has no *in vivo* mutagenic potential on somatic cells.

No studies on germ cells have been submitted and this is justified based on the negative effects *in vitro* and *in vivo* with 1R-trans-Z-momfluorothrin.

4.9.2 Human information

No data available.

4.9.3 Other relevant information

None available.

4.9.4 Summary and discussion of mutagenicity

Mutagenicity of 1R-trans-Z-momfluorothrin has been investigated in 5 studies. Two *in vitro* studies were negative for mutagenicity (reverse mutation in bacteria and gene mutation in mammalian cells) but the chromosome aberration assay with metabolic activation did show a marginal increase in structurally aberrant chromosomes. *In vivo*, the assays showed that 1R-trans-Z-momfluorothrin did not induce micronuclei or DNA damage. Based on the weight of evidence approach, 1R-trans-Z-momfluorothrin is not mutagenic in the test systems used.

4.9.5 Comparison with criteria

Under CLP, substances can be classified as a Cat 1A, 1B or 2 germ cell mutagen. For Category 1 A and B, the substance should be known to induce heritable changes or regarded as if they induce heritable changes in germ cells of humans or produce positive results *in vivo* somatic cell tests in combination with evidence that the substance has the potential to cause mutations in germ cells. There are no human data or positive results *in vivo* to suggest that 1R-trans-Z-momfluorothrin causes heritable mutations and therefore is not a Cat 1A or Cat 1B mutagen.

To attain category 2 under CLP, the substance needs to show positive results in mammals and /or in some cases *in vitro* experiments. In the case of 1R-trans-Z-momfluorothrin, the combined findings from all 5 studies do not support classification for mutagenicity in Category 2. Overall, it is concluded that 1R-trans-Z-momfluorothrin should not be classified for mutagenicity.

4.9.6 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification
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4.10 Carcinogenicity

Table 19: Summary table of relevant carcinogenicity studies

Method	Dose levels	Observations and remarks (effects of major toxicological significance)	Reference
Oral- dietary intake Mouse, CD-1 Males and females 52/sex/group (main group) 12/sex/group (satellite group) OECD 451 Study compliant with GLP and OECD guidelines	0, 600, 2500, 5500 ppm for 52 weeks and 78 weeks (satellite and main groups respectively) Males - 0, 72, 308, 639mg/kg bw/d (main) 0, 74, 308, 672 mg/kg bw/d (satellite) Females - 0, 99, 427, 853 mg/kg bw/d (main) 0, 111, 433, 934 mg/kg bw/d (satellite) S-1563 Purity: 95.7%	There were no significant increases in mortality in any dose group. Nor were there any significant treatment related tumours in the mice in this study. All dose levels are above the guidance value for classification of non-neoplastic effects (Guidance value for classification of non-neoplastic effects: ≤25mg/kg bw/d). Treatment related effects include: Satellite groups: hepatocellular hypertrophy in females. Main groups: reduced body weight and body weight gain, decreased food consumption, increased liver weight accompanied by hypertrophy mainly centrilobular at minor severity, enhanced single cell necrosis in the liver and a hepatocellular brown pigment was recorded. NOAEL*: 600 ppm (72 mg/kg body weight/day in males and 99 mg/kg body weight/day in females).	Rached (2012a)
Oral- dietary intake Rat, Wistar (SPF) Males and females 51/sex/ group OECD 451	0, 200, 500, 1500, 3000 ppm for 104 weeks Males- 0, 9.5, 23, 73, 154 mg/kg bw/d Females- 0, 11.1, 28, 88, 182 mg/kg bw/d S-1563 Purity: 95.7%	<u>Males- Non-neoplastic findings</u> 3000 ppm- decreased mean body weight and body weight gain, increased relative liver weight (65.6%), liver cell hypertrophy, brown pigment, biliary cysts and cystic degeneration. Thyroid cell hypertrophy as a secondary effect to liver changes, brown pigment in the kidney and diffuse acinar hypertrophy in the mandibular glands were reported but not a concern. 1500 ppm- decreased body weight and body weight gain, biliary cystic degeneration, brown pigment of the liver and kidneys, hepatocyte hypertrophy and diffuse acinar hypertrophy in the mandibular glands. The latter is considered nonadverse as it did not increase in severity from sub chronic and chronic studies). 500 ppm- no adverse effects 200 ppm- no adverse changes <u>Males-neoplastic findings</u> Prior to scheduled necropsy, 3 decedents in the top dose group had liver tumours which were treatment related. 3000 ppm- liver nodules (13/51) and hepatic cysts (6/51) at necropsy. Increased incidence of eosinophilic cell foci (20/51), adenoma (8/51), carcinoma (9/51) and combined adenoma and carcinoma (17/51),	Rached (2012b)

		<p>Incidence of neoplasm with ascending dose</p> <p>Hepatocellular adenoma-2%, 0%, 4%, 8% and 16%</p> <p>Hepatocellular carcinoma- 0%, 0%, 0%, 8% and 18%</p> <p>There is a clear dose related trend and significance is attained at the top dose which is also above the historical control range provided.</p> <p><u>Females- Non-neoplastic findings</u></p> <p>3000 ppm- decrease in body weight and body weight gain and increased relative liver weight (46.1%), were significant. In addition, hepatic cell hypertrophy, brown pigment and biliary cysts were reported in the liver.</p> <p>Brown pigment recorded in the kidney and diffuse acinar hypertrophy in the mandibular glands were observed but all considered non adverse as they have not progressed in severity from the chronic studies.</p> <p>1500 ppm- decrease in body weight and body weight gain and increased salivary gland diffuse acinar hypertrophy (not adverse).</p> <p>500 ppm- decrease in body weight and body weight gain.</p> <p>200 ppm- no adverse changes.</p> <p><u>Female- neoplastic findings</u></p> <p>3000 ppm- hepatic cysts (13/51) at necropsy. Eosinophilic foci (9/51), adenoma (4/51), carcinoma (1/51) and combined adenoma and carcinoma (5/51).</p> <p>Incidence of neoplasm with ascending dose</p> <p>Hepatocellular adenoma- 0%, 0%, 2%, 2% and 8%</p> <p>Hepatocellular carcinoma- 0%, 0%, 0%, 0% and 2%</p> <p>Laboratory historical control data on lesions in Wistar rat recorded from 20, 104 week dietary studies conducted between 1981 and 2009</p> <table border="1" data-bbox="518 1377 1241 2027"> <thead> <tr> <th rowspan="2">Organ/ findings</th> <th colspan="3">Males</th> <th colspan="3">Females</th> </tr> <tr> <th>Mean (%)</th> <th>Min (%)</th> <th>Max (%)</th> <th>Mean (%)</th> <th>Min (%)</th> <th>Max (%)</th> </tr> </thead> <tbody> <tr> <td colspan="7">Liver</td> </tr> <tr> <td>Hepatocyte hypertrophy</td> <td>2.57</td> <td>0.00</td> <td>20.00</td> <td>2.93</td> <td>0.00</td> <td>27.00</td> </tr> <tr> <td>Biliary cysts</td> <td>1.22</td> <td>0.00</td> <td>8.00</td> <td>3.45</td> <td>0.00</td> <td>14.00</td> </tr> <tr> <td>Cystic degeneration</td> <td>1.03</td> <td>0.00</td> <td>10.13</td> <td>0.46</td> <td>0.00</td> <td>4.00</td> </tr> <tr> <td>Eosinophilic cell foci</td> <td>6.55</td> <td>0.00</td> <td>44.00</td> <td>7.42</td> <td>0.00</td> <td>56.00</td> </tr> <tr> <td>Hepatocellular adenoma</td> <td>2.37</td> <td>0.00</td> <td>8.00</td> <td>2.54</td> <td>0.00</td> <td>10.20</td> </tr> <tr> <td>Hepatocellular carcinoma</td> <td>0.26</td> <td>0.00</td> <td>2.80</td> <td>0.26</td> <td>0.00</td> <td>2.00</td> </tr> <tr> <td colspan="7">Thyroid glands</td> </tr> </tbody> </table>	Organ/ findings	Males			Females			Mean (%)	Min (%)	Max (%)	Mean (%)	Min (%)	Max (%)	Liver							Hepatocyte hypertrophy	2.57	0.00	20.00	2.93	0.00	27.00	Biliary cysts	1.22	0.00	8.00	3.45	0.00	14.00	Cystic degeneration	1.03	0.00	10.13	0.46	0.00	4.00	Eosinophilic cell foci	6.55	0.00	44.00	7.42	0.00	56.00	Hepatocellular adenoma	2.37	0.00	8.00	2.54	0.00	10.20	Hepatocellular carcinoma	0.26	0.00	2.80	0.26	0.00	2.00	Thyroid glands							
Organ/ findings	Males			Females																																																																				
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Thyroid glands																																																																								

		Follicular cell hypertrophy	5.60	0.00	36.00	3.57	0.00	24.74	
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* As cited in the CAR

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Two GLP compliant studies have been submitted and are in accordance with OECD test guideline 451.

Mouse

The dietary study in mice over 78 weeks did not produce a carcinogenic response. Liver abnormalities in both males and females at 2500 and 5500 ppm (308/427 (male/female) and 639/853 (male/female) mg/kg bw/d respectively), decreased body weight gain in males at 2500 and 5500 ppm and decreased food consumption at 5500 ppm are considered to be toxicologically significant.

Rat

In the rat study, mean body weight was significantly decreased in males treated with 1500 (11%) and 3000 ppm (21%) and female rats treated with 500 (5%), 1500 (13%) and 3000 ppm (19%). This was accompanied by a decrease in mean body weight gain in both sexes at these doses. The decreases in body weight and body weight gain are concluded to be treatment related. Mortality was monitored daily during the study and the rates of mortality were similar across controls and treated groups. Three males treated with 3000 ppm S-1563 that died prematurely did have liver tumours, however, that were interpreted to be treatment related. Other findings included increased relative liver weight in both sexes at 3000 ppm (65.6% in males and 46.1% in females), liver nodules in 13/51 male rats at 3000 ppm and hepatic cysts in both sexes at 3000 ppm (6/51 males and 13/51 females) at necropsy.

Non-neoplastic hepatic lesions included hypertrophy, brownish pigment and biliary cysts; these all occurred in both sexes at 3000 ppm and were statistically significant. The incidence of hypertrophy was 14/51 and 10/51 in males and females respectively, the brownish pigment was present in the liver of 36/51 males and 18/51 females whilst the incidence of biliary cysts was 8/51 and 17/51 for males and females respectively. Male rats were also reported to have a significant increase in cystic degeneration in the liver at 1500 (7/51) and 3000 ppm (7/51).

Hyperplastic and neoplastic findings were reported at the highest dose in the liver and included an increased incidence of eosinophilic cell foci (20/51), adenoma (8/51), carcinoma (9/51) and combined incidence of adenoma and carcinoma (17/51) in male rats and eosinophilic foci (9/51), adenoma (4/51), carcinoma (1/51) and combined incidence of adenoma and carcinoma (5/51) in females.

All the non-neo- and neoplastic liver effects reported in male and female rats were in excess of the mean value from historical control data but did not always exceed the maximum value quoted. In male rats, the incidences of adenoma, carcinoma, cystic degeneration, biliary cysts and hypertrophy, but not eosinophilic foci, were outside the ranges reported for historical controls. In female rats, only the incidence of biliary cysts was outside the historical range values stated.

Other effects that were recorded in the rat include diffuse follicular cell hypertrophy in the thyroid gland in males at 3000 ppm, brownish pigment in the kidney in both sexes at 3000 ppm, diffuse

acinar hypertrophy in the mandibular glands in both sexes at 1500 ppm and 3000 ppm. None of these findings are significant as they have not increased in severity from the chronic studies, are considered secondary to the liver effects or are not associated with other indicators of injury.

Overall, the incidence of adenoma/carcinoma in the rats is a concern but available evidence suggests that the tumour formation is not a result of genotoxic activity (see section 4.9). To address the potential non-genotoxic mechanism and its relevance to humans, a series of additional mode of action studies were undertaken (see section 4.10.3).

4.10.1.2 Carcinogenicity: inhalation

No information available.

4.10.1.3 Carcinogenicity: dermal

No information available.

4.10.2 Human information

No information available.

4.10.3 Other relevant information

The UK CA has had extensive discussions with the applicant regarding the mode of action for the liver tumours seen in rats treated with 1R-trans-Z-momfluorothrin. The applicant provided a document (See Annex 1) outlining their position and the mechanistic data available to justify the proposed mode of action: i.e. that the increased liver tumours seen in rats treated with 1R-trans-Z-momfluorothrin were linked specifically to a mechanism involving activation of the constitutive androstane receptor (CAR) that was not considered relevant to humans (see also the review by Elcombe *et al*, 2014). The mechanistic studies underpinning this position are summarised briefly below.

A number of *in vivo* and *in vitro* studies were submitted to address the mode of action responsible for the occurrence of liver tumours. These studies are not claiming GLP compliance but abided by GLP principles for these non-guideline tests.

In vitro studies with rat hepatocytes

Table 20: *In vitro studies with rat hepatocytes*

Test system	Conditions	Remarks	Result and conclusion	Reference
<p><i>Study to investigate gene expression specific to CAR activation</i></p> <p>Primary cultured hepatocytes sourced from 1 male Wistar rat and transfected with either:</p>	<p>Cultured hepatocytes transfected with siRNA (CAR) or siRNA (control) were exposed for days to:</p> <p>1R-trans-Z-momfluorothrin (S-</p>	<p>The RNA interference technique was employed to reduce CAR mRNA levels in rat hepatocytes and thus examine the importance of CAR in the CYP2B induction stimulated</p>	<p>In cells treated with CAR-siRNA, both exposure to 1R-trans-Z-momfluorothrin and phenobarbital reduced CAR mRNA levels, resulting in a significant reduction in the magnitude of induction of CYP2B1/2</p>	<p>Okuda, 2012a</p>

CLH REPORT FOR 1R-TRANS-Z-MOMFLUOROTHRIN

<p>1) siRNA for CAR (1 µg) + MA Tra-si reagent (1 µL) + serum/antibiotic free medium (200 µM)</p> <p>2) “negative” control siRNA (1 µg) + MA Tra-si reagent (1 µL) +serum/antibiotic free medium (200 µM)</p> <p>3) Untreated group – not exposed to transfection mixture</p> <p>Analysis and quantification of isolated mRNA (CAR, CYP 2B1/2 and GAPDH (used to normalize levels of CAR and CYP 2B1/2)) was conducted using quantitative real time PCR.</p>	<p>1563): 100 µM</p> <p>Phenobarbital: 50 µM (positive control)</p> <p>Untreated hepatocytes were not exposed to either 1R-trans-Z-momfluorothrin or phenobarbital.</p>	<p>by 1R-trans-Z-momfluorothrin and phenobarbital.</p>	<p>mRNA levels.</p> <p>1R-trans-Z-momfluorothrin, like phenobarbital, induced CYP2B1/2 mRNA in rat hepatocytes and this is mediated via activation of CAR (which is inhibited by treatment with siRNA).</p>	
<p><i>Study to investigate induction of mRNA coding for cytochrome P450</i></p> <p>Primary cultured hepatocytes sourced from male Wistar rats</p> <p>Analyses of isolated mRNA samples were made by quantitative real-time PCR (one sample per animal per treatment). Average taken across the results of all animals at each concentration.</p>	<p>Hepatocytes were exposed for 72 hours to either:</p> <p>1R-trans-Z-momfluorothrin (S-1563): 0, 1,5, 10, 50, 100, 500 and 1000 µM</p> <p>0 and 5-500 µM: 4 animals</p> <p>1 and 1000 µM: 3 animals</p> <p>Or</p> <p>Phenobarbital: 0, 500 or 1000 µM (5, 2 or 3 animals, respectively)</p>	<p>cDNA was prepared from total RNA by reverse transcription polymerase chain reaction (RT-PCR). Analysis and quantification of isolated mRNA (CYP2B1/2, CAR and GAPDH (used to normalize levels of CAR and CYP 2B1/2)) was conducted using quantitative real time PCR</p>	<p><i>1R-trans-Z-momfluorothrin</i>: 3-fold increase in CYP2B1/2 levels at 50 µM, moderate but insignificant changes at 100 and 500 µM compared with control</p> <p><i>Phenobarbital</i>: 45-fold increase in CYP2B1/2 levels compared with control</p> <p>1R-trans-Z-momfluorothrin induced CYP2B1/2 in cultured rat hepatocytes.</p>	<p>Okuda, 2013</p>
<p><i>Induction of replicative DNA synthesis in rat hepatocytes-</i></p> <p>Primary cultured hepatocytes sourced from male Wistar rats.</p>	<p>1R-trans-Z-momfluorothrin (S-1563): 0, 1, 5, 10, 50, 100, 500 and 1000 µM</p> <p>0-50 µM: 6 animals</p> <p>100-1000 µM: 3 animals</p>	<p><i>Cell proliferation (measured as replicative DNA synthesis)</i></p> <p>There was increased replicative DNA synthesis in cultures</p>	<p>Phenobarbital was used for comparison purposes as a CAR activator. HGF was used successfully to validate the experiment as human hepatocytes cells were responsive to</p>	<p>Okuda 2013</p>

<p>To measure DNA replication, 5-bromo-2'-deoxyuridine (BrdU) was added to the media of cells of all treatment groups during the last 24 hrs of the 48 hr treatment period. One sample per animal per treatment was reported and an average taken across the results of all animals at each concentration.</p>	<p>Phenobarbital: 0, 500 or 1000 μM (8, 4 or 4 animals respectively)</p> <p>HGF: 0, 10 and 100 ng/ml (4 animals at all doses)</p> <p>Cells were exposed for 48 hours before harvesting for analysis.</p>	<p>treated with 1R-trans-Z-momfluorothrin and phenobarbital.</p> <p>With HGF (Hepatocyte growth factor), there was a significant concentration dependent increase in replicative DNA synthesis (max 4-fold)</p>	<p>this mitogenic factor.</p> <p>No explanation was provided for the decrease in replicative DNA synthesis seen at the higher concentrations of 1R-trans-Z-momfluorothrin.</p>	
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In the first *in vitro* study, fresh hepatocytes were isolated from untreated male Wistar rats and incubated in serum-free conditions with CAR siRNA (CAR short interfering RNA 100 nM) for 4-hours (Okuda, 2012a). The medium was then changed to a standard hepatocyte serum-based medium supplemented with 1R-trans-Z-momfluorothrin or phenobarbital. Two controls were established, completely untreated hepatocytes and hepatocytes treated with the siRNA (negative control). After a further 2-day incubation period, total RNA was isolated, reverse transcribed to cDNA and assayed for CAR and CYP2B1/2 using real-time quantitative PCR (Polymerase Chain Reaction). The intended effect of the CAR siRNA is to block transcription of CAR mRNA and decrease the amount of functional CAR.

A statistically significant decrease in CAR mRNA (19% of negative controls) was observed in hepatocytes treated with CAR siRNA and Momfluorothrin at 100 μ M. When hepatocytes pre-treated with CAR siRNA were induced with 1R-trans-Z-momfluorothrin or phenobarbital, statistically significant decreases in CYP2B1/2 mRNA were observed (32% and 33% of negative control, with 1R-trans-Z-momfluorothrin and phenobarbital respectively). Overall, this study indicates that the CAR is involved in the induction of CYP2B1/2 mRNA.

In a second *in vitro* study, the effects of 1R-trans-Z-momfluorothrin and phenobarbital on CYP 2B1/2 mRNA expression and DNA replication, in rat hepatocytes were investigated (Okuda, 2013).

For CYP2B1/2 mRNA, primary cultures of rat hepatocytes were incubated for 48 hours with 1R-trans-Z-momfluorothrin or phenobarbital. At the end of this period, the cells were harvested for mRNA, which was then reverse transcribed and subject to real time quantitative PCR. To determine replicative DNA synthesis, the hepatocytes were incubated for 48-hours in 5% foetal bovine serum (FBS) medium containing 0.5 ng/ml epidermal growth factor (EGF) and either phenobarbital, 1R-trans-Z-momfluorothrin or hepatocyte growth factor (HGF) for 48 hours. BrdU was added 24 hours before assay termination and proliferation rate calculated compared to untreated controls.

Compared to controls, CYP2B1/2 mRNA was increased to a maximum of 3-fold in rat hepatocytes treated with 50 μ M and decreased at higher doses. Treatment with phenobarbital increased CYP2B1/2 mRNA levels to 45-fold of controls. Replicative DNA synthesis was statistically significantly increased in rat hepatocytes treated with 1R-trans-Z-momfluorothrin at concentrations of 5 and 10 μ M (1.6 and 1.8-fold) and in phenobarbital treated rat hepatocytes at 500 μ M and above (max 1.4-fold).

In vivo mechanistic studies in rats

Males

In the cancer study, dietary exposure of male rats with approx. 75 and 150 mg/kg/day 1R-trans-Z-momfluorothrin resulted in increased incidences of liver adenoma and carcinoma. The following data from short term studies provide a mechanistic basis for these findings.

Table 21: In vivo mechanistic studies in male rats

Method	1R-trans-Z-momfluorothrin (S-1563)	Endpoint	Reference
<p>Male rat, Wistar 10/group</p> <p>Oral, dietary</p> <p>CYP mRNA levels: Total RNA was extracted from a liver fraction and reverse transcribed to generate cDNA. Using primers specific to CYP2B1/2, the cDNA for the enzyme was quantified by real-time PCR.</p> <p>CYP activity: S9 fractions were harvested from the rats. CYP2B activity was measured as pentoxyresorufin O-depentyase (Deguchi <i>et al</i>, 2009).</p> <p>Hypertrophy: One section of the left lateral lobe and right medial lobe were fixed, stained and examined by light microscopy.</p> <p>Cell proliferation: Mini-pumps were inserted into the subcutaneous back region of the rats and BrdU released at a rate of 10µl/hour for 4 or 7 days preceding euthanasia</p>	<p>0- 3000ppm 0-137 mg/kg bw/d</p> <p>7 days</p>	<p>CYP2B activity: maximum fold change was 2.8 compared to controls</p> <p>Hypertrophy: 2/10 animals with hypertrophy at highest dose</p> <p>Cell proliferation: maximum fold change was 2.5 compared to controls</p>	Okuda, 2012b
	<p>0 and 3000 ppm 0 and 147 mg/kg bw/d</p> <p>7 days</p>	<p>CYP mRNA levels: maximum fold change was 17.8 compared to controls</p> <p>Hypertrophy: 3/10 animals with hypertrophy at highest dose</p> <p>Cell proliferation: maximum fold change was 1.4 compared to controls</p>	Okuda, 2012c
	<p>0- 6000 ppm 0- 258 mg/kg bw/d</p> <p>7 days</p>	<p>CYP2B activity: maximum fold change was 10.8 compared to controls</p> <p>Hypertrophy: 10/10 animals with hypertrophy at highest dose</p>	Okuda, 2012d
	<p>0 and 3000 ppm 0 and 175 mg/kg bw/d</p> <p>14 days</p>	<p>CYP mRNA levels: increased 16.4-fold compared to controls</p> <p>Hypertrophy: 4/10 animals with hypertrophy at highest dose but high incidence in control group (3/10).</p> <p>Cell proliferation: increased 1.8-fold compared to controls</p>	Okuda, 2012c
	<p>0, 3000 and 6000 ppm 0, 166 and 340 mg/kg bw/d</p> <p>14 days</p>	<p>Hypertrophy: 10/10 animals with hypertrophy at highest dose</p>	Okuda 2012d

Females

In the cancer study, dietary exposure of female rats with approx. 180 mg/kg/day S-1563 resulted in a small increased frequency in the incidence of hepatocellular adenoma. The following data from short term studies provide a mechanistic basis for this finding.

Table 22: In vivo mechanistic studies in female rats

Method	1R-trans-Z-momfluorothrin (S-1563)	Endpoint	Reference
Female rat, Wistar10/group Oral, dietary CYP activity: S9 fractions were harvested from the rats. CYP2B activity was measured as pentoxyresorufin O-depentylase (Deguchi <i>et al</i> , 2009). Hypertrophy: One section of the left lateral lobe and right medial lobe were fixed, stained and examined by light microscopy.	0- 3000ppm 0- 150.9 mg/kg bw/d 7 days	CYP2B activity: maximum fold change was 6.2 compared to controls Hypertrophy: 3/10 animals with hypertrophy at highest dose Cell proliferation: increased 2.8-fold compared to controls	Okuda, 2012e
Hypertrophy: One section of the left lateral lobe and right medial lobe were fixed, stained and examined by light microscopy. Cell proliferation: Mini-pumps were inserted into the subcutaneous back region of the rats and BrdU released at a rate of 10µl/hour for the 4 days preceding euthanasia	0 and 3000ppm 0- 163.8 mg/kg bw/d 14 days	CYP2B activity: an increase of 6.9-fold compared to controls Hypertrophy: 0/10 animals with hypertrophy at highest dose Cell proliferation: 1.7-fold increase compared to controls	Okuda, 2012e

In vivo effects- mouse

A range of comparable studies were reported in the mouse. They showed CYP 2B induction, increased hepatocellular hypertrophy and proliferation over 7 and 14 days at 5500 ppm S-1563 in the diet (equivalent to the highest dose in the carcinogenicity study) (Yamada, 2012a, b and c). There was also a slight increase in CYP4 induction, but electron microscopy did not show an accompanying increase in peroxisome proliferation. Although these results appear to indicate that 1R-trans-Z-momfluorothrin can produce CAR activation in the mouse, the exposure conditions employed in the mouse carcinogenicity study did not produce an increased frequency of liver tumours in this species. A full summary of these data are provided in Annexes IV and V of Annex I to the report.

In vitro studies with human hepatocytes

Cultures of human hepatocytes from up to a total of 10 donors were employed to investigate the relevance of the proposed mode of action to humans. These non-standard experiments indicated that human hepatocytes respond to 1R-trans-Z-momfluorothrin treatment with an increase in CAR activation but not increased cell proliferation. Similar findings were seen with phenobarbital. However, the hepatocytes did show a proliferative response to HGF, showing that they did have the potential to produce such a response.

These *in vitro* studies are of critical importance, as they provide the only direct evidence supporting the view that 1R-trans-Z-momfluorothrin does not present a hepatocarcinogenic hazard to humans.

Table 23: *In vitro* studies with human hepatocytes

Test system	Treatment conditions (no. of donors)	Results	Remarks	Reference
<p><i>Expression of CYP2B6 mRNA in human hepatocytes</i></p> <p>Primary cultures of human hepatocytes derived from 10 donors (5 males and 5 females).</p> <p>Human donors ranged from 10 months to 80 years old and were Caucasian (9/10) and Hispanic (1/10).</p> <p>Analyses of isolated mRNA samples were made by quantitative real-time PCR (one sample per donor per treatment). Average taken across the results of all donors at each concentration.</p>	<p>1R-trans-Z-momfluorothrin (as S-1563): 0 (5), 1 (3), 5 (5), 10 (4), 50 (5), 100 (5), 500 (5) and 1000 (1) μM</p> <p>Phenobarbital: 0 (7) and 1000 μM (7)</p> <p>Cells were exposed for 48 hours before harvesting for analysis.</p>	<p><i>CYP2B6 mRNA induction</i></p> <p>1R-trans-Z-momfluorothrin S-1563: significant increases were seen at 100 and 500 μM (1.7 and 1.8-fold, respectively) compared with control. Smaller increases were seen at 50 and 1000 μM.</p> <p>Phenobarbital: significant 4.8 fold increase in CYP 2B6 mRNA compared with control</p>	<p>The lowest number of donors were used at the extremes of low and high doses and do not detract from the outcome of the study.</p> <p>A trend towards increased CYP2B6 was observed from 0 to 500μM.</p> <p>The increases seen with 1R-trans-Z-momfluorothrin were of a comparable magnitude to those seen in studies with rat hepatocytes. However, the responses to phenobarbital were much greater in rat hepatocytes.</p>	Okuda, 2013
<p><i>Induction of replicative DNA synthesis</i></p> <p>Primary cultures of human hepatocytes derived from 10 donors (5 males and 5 females).</p> <p>Human donors ranged from 10 months to 80 years old and were Caucasian (9/10) or Hispanic (1/10).</p> <p>To measure DNA replication, 5-bromo-2'-deoxyuridine (BrdU) was added to the media of cells of all treatment groups during the last 24 hrs of the 48 hr treatment period. One sample per donor per treatment was reported and an average taken across the results of all donors at each concentration.</p>	<p>1R-trans-Z-momfluorothrin (as S-1563): 0 (8), 1 (8), 5 (8), 10 (8), 50 (8), 100 (5), 500 (5) and 1000 (5) μM</p> <p>Phenobarbital: 0 (10), 500 (8) and 1000 (6) μM</p> <p>HGF: 0 (10), 10 (5) and 100 (10) ng/ml</p> <p>Cells were exposed for 48 hours before harvesting for analysis.</p>	<p><i>Cell proliferation (measured as replicative DNA synthesis)</i></p> <p>There was no increased replicative DNA synthesis in cultures treated with 1R-trans-Z-momfluorothrin or phenobarbital. On the other hand, decreased replicative DNA synthesis was observed at 100-1000 μM 1R-trans-Z-momfluorothrin.</p> <p>With HGF, there was a significant concentration dependent increase in replicative DNA synthesis.</p>	<p>Phenobarbital was used for comparison purposes as a CAR activator. HGF was used successfully to validate the experiment as human hepatocytes cells were responsive to this mitogenic factor.</p> <p>No explanation was provided for the decrease in replicative DNA synthesis seen at the higher concentrations of 1R-trans-Z-momfluorothrin.</p>	Okuda, 2013

In an *in vitro* study, the effects of 1R-trans-Z-momfluorothrin and phenobarbital were investigated on CYP 2B6 mRNA expression and DNA replication in human hepatocytes (Okuda, 2013).

For CYP2B6 mRNA, cultures of human hepatocytes were incubated for 48 hours with S-1563 or phenobarbital. At the end of this period, the cells were harvested for mRNA, which was then reverse transcribed and subject to real time quantitative PCR. To determine replicative DNA synthesis, the hepatocytes were incubated for 48-hours in medium containing 0.5 ng/ml EGF and either phenobarbital, S-1563 or HGF for 48 hours. BrdU was added 24 hours before assay termination and proliferation rate calculated compared to untreated controls.

Compared to controls, CYP 2B6 mRNA was increased in a concentration dependent manner with significant increases at 100 and 500 μ M S-1563, 1.7 and 1.8-fold respectively. Treatment with phenobarbital increased CYP2B6 mRNA levels to 4.8-fold of controls. Replicative DNA synthesis was significantly increased in human hepatocytes by 1.6- and 3.7-fold when treated with HGF (10 and 100 ng/ml). In contrast, S-1563 and phenobarbital did not increase DNA synthesis compared to controls.

Consideration of other potential mechanisms

In determining a mode of action for a substance, other potential mechanisms should be discounted. Based on the results from the mutagenicity assays, 1R-trans-Z-momfluorothrin was not genotoxic and therefore a non-genotoxic mode of action is plausible. These include cytotoxicity, activation of CAR or PPAR α , porphyria and hormonal perturbation. Throughout the dossier, there has been no suggestion of hormonal perturbation, porphyria or increased iron deposition. Hepatocellular toxicity (e.g. fatty liver and necrosis) has not been reported in any of the short term or long term studies with 1R-trans-Z-momfluorothrin so cytotoxicity is not a contributing factor. Electron microscopy in rodents at 7, 14 and 90 days has shown that cellular ultrastructure changes are confined to augmentation of the smooth endoplasmic reticulum and not peroxisome proliferation as would occur for PPAR α stimulation.

To discount activation of other receptors, a study by Lake in 2009 (full study not available, see Annex) showed that only CYP2B1/2 was induced, consistent with CAR activation, but there was no induction of CYP1A2, 3A1, 3A2 or 4A1 which are more specific to the activation of other receptors: aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR) and PPAR α , respectively.

Taken together, these results suggest that 1R-trans-Z-momfluorothrin does not act via activation of PPAR α , AhR or PXR to provoke a hepatocarcinogenic response in rats, nor does it produce a consistent cytotoxic response, hormonal perturbations or porphyria that could also explain its carcinogenicity in this species. The most plausible explanation is that 1R-trans-Z-momfluorothrin acts in the rat by activation of CAR, which results in altered gene expression specific to CAR activation and subsequently increased cell proliferation and formation of altered hepatic foci.

Data gaps, uncertainties and inconsistencies

There is no experimental evidence available for several events that may be associated with the CAR-mediated mechanism of liver cancer induction in rats. No evidence has been seen of decreased apoptosis, inhibition of gap junction intercellular communication or altered epigenetic changes. However, as these are not regarded as key events, they are not critical data gaps.

It is unclear why no proliferative response to 1R-trans-Z-momfluorothrin was seen in cultured human hepatocytes. With no explanation, there remains a possibility that the findings *in vitro* might not be relevant *in vivo*. However, some degree of reassurance is provided by the observation that a

proliferative response was induced in human hepatocyte cultures by HGF. Thus, it was not that the cells were incapable of providing such a response *in vitro*.

The findings in mice are somewhat inconsistent. Although short term studies show a potential of 1R-trans-Z-momfluorothrin to activate CAR in this species, it did not induce a hepatocarcinogenic response. It is possible that the conditions employed in the mouse study were not optimised for a hepatocarcinogenic response and a different dosing schedule may have produced a positive result. However, any such finding would still have been considered of limited or no relevance to humans.

The applicant has proposed that the species difference is consistent with other pyrethroids, particularly a structural analogue, metofluthrin. Whilst the species differences have not been fully addressed, CAR activation remains a plausible mechanism based on all the available data in the rat.

Relevance to humans

As shown in table 24, there are only certain elements of the proposed mode of action for 1R-trans-Z-momfluorothrin-induced carcinogenicity in rats that are predicted to occur in humans.

Table 24: Relevance to humans

Key and associative events	Evidence in rats	Evidence in humans
Activation of CAR	Suggested through the <i>in vitro</i> study with RNAi for CAR and induction of CYP2B enzymes	Probable at high doses based on the induction of CYP2B <i>in vitro</i>
Altered gene expression	Only changes in CYP2B reported in this submission	None in this submission but does occur in other published studies
Induction of CYP2B as a marker for CAR activation	Experimental evidence <i>in vivo</i> and <i>in vitro</i> with cultured rat hepatocytes	Experimental evidence based on the induction of CYP2B <i>in vitro</i>
Hypertrophy	Experimental evidence <i>in vivo</i>	Possible based on published evidence in humans treated with anticonvulsant drugs
Increased hepatocellular proliferation	Experimental evidence <i>in vivo</i> and <i>in vitro</i> with cultured rat hepatocytes	Not predicted as not reported in cultured hepatocytes
Altered hepatic foci	Experimental evidence <i>in vivo</i>	Not predicted
Liver tumours	Yes	Not predicted
Inhibition of gap junctional intercellular communication	None in this submission	None in this submission
Altered DNA methylation/epigenetic changes	None in this submission	None in this submission
Decreased apoptosis	None in this submission	None in this submission

Overall, the differences between rat and human data with 1R-trans-Z-momfluorothrin were consistent with other compounds with a CAR mediated mode of action (see Elcombe *et al*, 2014 for a detailed review).

Statement of confidence

Taking all the available data into consideration, there is clear evidence to support CAR activation in male and female rats following 1R-trans-Z-momfluorothrin treatment and this being a plausible mode of action for the formation of hepatic tumours in this species. It has been demonstrated that 1R-trans-Z-momfluorothrin causes CYP2B induction, hepatocyte hypertrophy and cell replication *in vivo* and *in vitro* for rats by CAR activation. This is consistent with the potential to cause cell foci and tumours in long term studies. In contrast, available data suggest that 1R-trans-Z-momfluorothrin is capable of inducing CYP2B6 and hypertrophy but then does not increase cell replication in human hepatocytes, which is a prerequisite for tumour formation. Overall, the CAR mechanism in rats is of limited relevance to humans.

4.10.4 Summary and discussion of carcinogenicity

The carcinogenicity study in the mouse was negative for all tumour types but in the rat, particularly males, an increase in the incidence of adenoma and carcinoma of the liver was seen at the top dose of 1R-trans-Z-momfluorothrin (3000 ppm S-1563 in the diet; equivalent to approx. 150 mg/kg S-1563 in males and 180 mg/kg S-1563 in females). In males, there was also a slight increase in the frequency of liver adenoma and carcinoma at 1500 ppm (75 mg/kg).

The findings in an extensive set of short term assays have indicated that 1R-trans-Z-momfluorothrin is unlikely to have acted as a genotoxic carcinogen. In contrast, there are mechanistic data available that point towards a non-genotoxic mechanism of carcinogenesis, driven initially by activation of the nuclear constitutive androstane receptor (CAR) and later by a proliferative response in the liver.

Specifically, the postulated mode of action involves the following sequence of key events:

1. Nuclear membrane receptor activation (CAR)
2. Altered gene expression specific to CAR activation (e.g. CYP2B)
3. Liver hypertrophy
4. Cell proliferation (which can be studied *in vitro* and *in vivo*)
5. Clonal expansion to generate altered liver cell foci
6. Increased liver adenoma/carcinoma

With 1R-trans-Z-momfluorothrin, activation of CAR was shown *in vitro* by the increase in CYP2B transcription which was attenuated in the presence of CAR specific siRNA. Three short-term *in vivo* studies in the rat further demonstrated that 1R-trans-Z-momfluorothrin had a dose-dependent potential to increase hepatic CYP2B levels. Cultured rat hepatocytes also showed increased CYP2B mRNA levels in response to 1R-trans-Z-momfluorothrin.

Hepatocellular hypertrophy was observed throughout the liver lobule in the original carcinogenicity study and at a comparable dose level (3000 ppm) in the mode of action studies. In addition, examination by electron microscopy of liver sections from male and/or female rats given 3000 ppm S-1563 for 1 or 2 weeks and 6000 ppm S-1563 for 3 months in the repeat dose study (Sommer,

2011b) revealed increased smooth endoplasmic reticulum which is a characteristic of enzyme inducers.

Data from an *in vitro* study showed 1R-trans-Z-momfluorothrin can induce hepatocellular replication: DNA synthesis being increased in cultured rat hepatocytes at 5 -10 µM. A proliferative response was also seen in short-term *in vivo* studies.

The carcinogenicity study reported eosinophilic foci in the livers of rats at 3000 ppm 1R-trans-Z-momfluorothrin with an incidence of 20/51 in males and 9/51 in females. This can be considered indicative of preneoplastic lesions. Finally, the incidence of adenoma and/or carcinoma was enhanced in both sexes of the rat but more markedly in males (17/51 versus 5/51 in females).

Studies with human hepatocytes from a variety of male and female donors have shown that 1R-trans-Z-momfluorothrin can similarly induce activation of human hepatic CAR, but that DNA replication (leading to hepatocellular proliferation) does not then follow. The findings with 1R-trans-Z-momfluorothrin are therefore consistent with the conclusion expressed in the recent detailed review of Elcombe *et al* (2014) that this mode of action exemplified by phenobarbital is considered to be qualitatively not plausible for humans.

Taking into consideration all available evidence, it is concluded that although carcinogenic in the rat, 1R-trans-Z-momfluorothrin does not present a significant carcinogenic hazard to humans. The carcinogenicity in rats appears to proceed via CAR activation which is a mechanism with very limited or no relevance to humans.

4.10.5 Comparison with criteria

In accordance with the criteria under CLP, classification in category 1A for carcinogenicity is not justified as there is no evidence of 1R-trans-Z-momfluorothrin having caused cancer in humans. It is therefore necessary to decide whether 1R-trans-Z-momfluorothrin fulfils the criteria for category 1B, category 2 or does not require classification.

To attain category 1B there should be sufficient evidence for carcinogenicity in experimental animals. In the case of 1R-trans-Z-momfluorothrin, the animal data are only limited rather than sufficient due to tumour incidence being restricted to one species, in a single tissue, with no evidence of a genotoxic mode of action. A carcinogenic response was seen in rats, but not mice.

Ordinarily, this level of evidence in experimental animals would be sufficient for 1R-trans-Z-momfluorothrin to be classified in Category 2 for carcinogenicity, but taking into account the supporting *in vivo* and *in vitro* mechanistic studies, it can be argued that 1R-trans-Z-momfluorothrin causes tumours in rats by a mechanism that is not relevant to humans. In this instance, therefore, no classification for carcinogenicity seems most appropriate.

4.10.6 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

Table 25: Summary table of relevant reproductive toxicity studies - Fertility

Method	Dose levels	Observations and remarks (effects of major toxicological significance)	Reference
Oral (dietary) Rat Wistar 24/sex/group OECD 416 Study compliant with GLP	0, 200,500, 1500 ppm Estimated to be: <i>P animals:</i> pre-mating:0, 12.6, 32.1, 95.2 mg/ kg bw/d (males) 0, 14.7, 35.5, 106 mg/ kg bw/d (females) pre-mating to post pairing: 0, 11.6, 29.5, 87.6 mg/ kg bw/d (males) gestation period: 0, 13.1, 31.4, 97.8 mg/ kg bw/d (females) lactation period: 0, 28.0, 68.9, 209 mg/ kg bw/d (females) <i>F1 animals:</i> pre-mating period : 0, 14.1, 36.6, 113 mg/ kg bw/d (male) 0, 16.1, 41.3, 126 mg/ kg bw/d (female) pre-mating to post pairing: 0, 13.0, 33.6,	No test item related mortality or clinical signs observed during the study. No treatment related developmental malformations or abnormalities observed in any generation. At 200 ppm No test item-related effects were noted. At 500 ppm ↓Food consumption and relative food consumption in P generation females. ↓Body weight in the F1 generation males. ↑Absolute liver weights and the ratios of the liver weight to terminal body and brain weights in P generation males. ↑Relative food consumption in F1 generation females. ↓Absolute spleen weights and ratios of the spleen weight to terminal body and brain weights in F1 males and females and F2 females. ↓mean pup weights per dam of F1 and F2 offspring. At 1500 ppm ↓Food consumption and body weight in P and F1 generations. Relative food consumptions ↓ in P generation and ↑in F1 generation. ↑Absolute liver weights and the ratios of the liver weight to terminal body and brain weights in P and F1 generations; enlarged liver at necropsy in F1 generation. Sexual maturation was delayed in F1. ↓Body weight, absolute thymus weights, ratios of the thymus weight to brain weights, absolute spleen weights and the ratios of the spleen weight to terminal body (except F2 male pups) and brain weights of F1 and F2 pups. Histopathological lesions recorded in P and F1 generations in the liver (hepatocellular hypertrophy) correlating with increased liver weight.	Pal-Kutas (2012)

	104 mg/ kg bw/d (males) gestation: 0, 13.8, 35.4, 108 mg/ kg bw/d (females) lactation: 0, 28.9, 76.0, 247 mg/ kg bw/d (females)		
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4.11.1.1 Non-human information

The effects of 1R-trans-Z-momfluorothrin on fertility have been investigated in a multigeneration study in Wistar rats. No effects were seen on mating performance, number of pregnant animals, and number of implantations or post-implantation loss. An increase was seen in the time taken to reach preputial separation or vaginal opening which reached statistical significance in the highest dose group for both sexes. In both sexes the mean body weight at pubertal maturation was reduced. This effect is therefore considered to be secondary to general toxicity.

4.11.1.2 Human information

No data available

4.11.2 Developmental toxicity

Table 26: Summary table of relevant developmental toxicity studies - Development

Method	Dose levels	Observations and remarks (effects of major toxicological significance)	Reference																				
One generation developmental Oral (gavage) Rat, (SD) Female 22-24/group OECD 414 Study compliant with GLP and OECD guidelines	0, 10, 25, 75 mg/ kg bw/d in corn oil Gestation days 6-19 Purity 95.7%	<p>Maternal toxicity</p> <p>25 mg/kg bw/d Slight ↓food consumption sporadically throughout study.</p> <p>75 mg/kg bw/d Tremors in 6 animals at a frequency of 1-2 animals per day during late gestation. ↓body weight on day 20 of gestation. Slight ↓food consumption sporadically during study,</p> <p>Reproductive toxicity ↓number of corpora lutea, ↓number of implantations and ↓number of live foetuses.</p> <table border="1"> <thead> <tr> <th>Dose level, mg/kg bw/day</th> <th>0</th> <th>10</th> <th>25</th> <th>75</th> </tr> </thead> <tbody> <tr> <td>Mean gravid uterine weight (g)</td> <td>77.46</td> <td>77.25</td> <td>75.01</td> <td>71.32</td> </tr> <tr> <td>No. of corpora lutea/dam</td> <td>15.4</td> <td>15.1</td> <td>14.7</td> <td>14.2*</td> </tr> <tr> <td>No. of implantations/dam</td> <td>14.7</td> <td>14.3</td> <td>14.3</td> <td>13.7</td> </tr> </tbody> </table>	Dose level, mg/kg bw/day	0	10	25	75	Mean gravid uterine weight (g)	77.46	77.25	75.01	71.32	No. of corpora lutea/dam	15.4	15.1	14.7	14.2*	No. of implantations/dam	14.7	14.3	14.3	13.7	Izumi (2012)
Dose level, mg/kg bw/day	0	10	25	75																			
Mean gravid uterine weight (g)	77.46	77.25	75.01	71.32																			
No. of corpora lutea/dam	15.4	15.1	14.7	14.2*																			
No. of implantations/dam	14.7	14.3	14.3	13.7																			

		<table border="1"> <tr> <td>No of live foetuses/dam</td> <td>14.3</td> <td>13.6</td> <td>13.5</td> <td>13.0</td> </tr> </table> <p>Level of statistical significance: * 0.05 > p > 0.01 in comparison with control</p> <p>Foetal: No effects at the highest dose level tested.</p>	No of live foetuses/dam	14.3	13.6	13.5	13.0	
No of live foetuses/dam	14.3	13.6	13.5	13.0				
<p>One generation developmental</p> <p>Oral (gavage)</p> <p>Rabbit, New Zealand White (Kbl:NZW)</p> <p>Female</p> <p>24/group</p> <p>OECD 414</p> <p>Study compliant with GLP and OECD guidelines</p>	<p>0, 100, 300 1000 mg/kg bw/d in 0.5% aqueous methylcellulose</p> <p>Gestation days 6-27</p> <p>Purity 95.7%</p>	<p>Maternal toxicity</p> <p>300 and 1000 mg/kg bw/d slight ↓ in food consumption during the first 3 days of dosing.</p> <p>Foetal toxicity: No effects at the highest dose tested.</p>	Iwashita (2012)					

4.11.2.1 Non-human information

The potential for 1R-trans-Z-momfluorothrin to cause developmental toxicity has been investigated in rats and rabbits in two developmental toxicity studies and one multigeneration study in rats (see Section 4.11.1).

Rats

1R-trans-Z-momfluorothrin (as S-1563) was administered by gavage to groups of 22 to 24 female Crl:CD SD rats from days 6 to 19 of gestation to investigate the effects on dams and embryo-foetal development (Izumi, 2012). Animals were exposed to S-1563 at 10, 25 or 75 mg/kg bw/d. No deaths occurred in any of the groups. There was no effect on food consumption or necropsy findings. The changes in the number of corpora lutea, gravid uterine weight, number of implantations and live foetuses is considered non-treatment related as these parameter were established prior to the start of dosing. At the top dose level, tremor was observed in 6 animals at a frequency of 1-2 animals per day during late gestation. These are considered to be due to treatment with S-1563.

Caesarean section data showed no effect on embryo-foetal development. Similarly in the multigeneration study, no foetal malformations or abnormalities were reported up to the top dose.

Rabbits

1R-trans-Z-momfluorothrin as S-1563 was administered by gavage to groups of 24 female New Zealand White (Kbl:NZW) from days 6 to 27 post-insemination (Iwashita, 2011). Rabbits were dosed with test substance at 100, 300 or 1000 mg/kg bw/d. No maternal deaths occurred in any of the treatment groups and no treatment related clinical effects were seen in dams. Food consumption was significantly reduced in animals dosed at 300 and 1000 mg/kg bw/d during the first 3 days of

dosing. There was no other evidence of maternal toxicity. No evidence of an effect on embryo-foetal development was reported.

4.11.2.2 Human information

No data available.

4.11.3 Other relevant information

None available.

4.11.4 Summary and discussion of reproductive toxicity

The potential of 1R-trans-Z-momfluorothrin to cause reproductive toxicity has been investigated in two teratology studies in rats and rabbits and one multigeneration study in rats.

Fertility

No effects were seen on fertility.

Development

No effects were seen on developmental parameters (except the time taken to reach sexual maturity, which is considered secondary to general toxicity (the retarded growth of the pups)). No foetal malformations or abnormalities of concern were noted in any of the studies.

4.11.5 Comparison with criteria

Fertility

No effects were observed that provide evidence to suggest that 1R-trans-Z-momfluorothrin adversely affects sexual function or fertility in the absence of systemic toxicity.

Development

No effects were observed that provide evidence to suggest that 1R-trans-Z-momfluorothrin adversely affects development.

4.11.6 Conclusions on classification and labelling

No classification required

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

The neurotoxicity of 1R-trans-Z-momfluorothrin has been investigated in two guideline studies. In an acute neurotoxicity study, rats were dosed with 1R-trans-Z-momfluorothrin (as S-1563) in corn oil. Clinical signs of neurotoxicity included tremors (3/10F), increased levels of salivation (3/10M) and straub tail (1/10M and 1/10F). Refer to section 4.2 for full details. This finding is similar to

that observed in the acute oral toxicity test where clinical effects indicating a neurotoxic effect were observed at 300 mg/kg bw and above.

In a second neurotoxicity study animals dosed with up to 402/425 mg/kg/day (M/F) S-1563 (in the diet for 90 days showed no signs of neurotoxicity, although systemic toxicity (reduced body weight gain) was seen (refer to section 4.7).

4.12.1.2 Immunotoxicity

Table 27: Summary of immunotoxicity studies

Method	Dose Levels	Observations and Remarks	Reference
28 day study (oral, dietary) Rat, Wistar Crl: WI(HAN) Oral (dietary) 10 male/group Purity: 95.7% USEPA OPPTS870.7800 Study compliant with GLP and USEPA guidelines	0, 300, 1000, 3000 ppm (0, 26, 81, 241 mg/kg bw/d)	No effects observed on the functional humoral immune response. Reduced body weight (-7.3 %) and lower food consumption in high dose group. Negative control group received basal diet only. Positive control group was treated with 50 mg/kg bw/d of cyclophosphamide monohydrate (CPS) for four days.	Hosako (2011)

The only treatment-related effects seen in animals dosed with S-1563 were lower body weight and reduced food consumption in animals in the 3000 ppm test group. Treatment with S-1563 produced no statistically significant effects on spleen cell number, nor did it significantly suppress the humoral immune response when evaluated as either specific activity (AFC/10⁶ spleen cells) or as total activity (AFC/spleen) of splenic IgM AFC response to the T cell-dependent antigen sRBC. Animals treated with CPS showed the expected reduction in spleen cell numbers and total spleen activities of IgM antibody-forming cells.

4.12.1.3 Specific investigations: other studies

4.12.1.4 Human information

None available.

4.12.2 Summary and discussion

Neurotoxicity

A summary of the neurotoxic effects is provided in section 4.3.2.

Immunotoxicity

No treatment related effects on the functional humoral response were observed at systemically toxic doses.

4.12.3 Comparison with criteria

Neurotoxicity

Comparison with the criteria for classification on the basis of neurotoxic effects has been considered under section 4.3.2.

Immunotoxicity

No criteria are established under CLP for classification for immunotoxic effects. However as no functional humoral immune response was observed in tests and so 1R-trans-Z-momfluorothrin is considered not to be immunotoxic. No classification is proposed.

4.12.4 Conclusions on classification and labelling

Classification with Acute Tox 4; H302 Harmful if swallowed and STOT-SE 2; H371 May cause damage to organs (Central Nervous System) is proposed under sections 4.2 and 4.3
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5 ENVIRONMENTAL HAZARD ASSESSMENT

1R-trans-Z-momfluorothrin is an insecticide used as a spray or crack and crevice treatment (indoors and outdoors) to control flying insects (e.g. mosquitoes) and crawling insects (e.g. black ants, cockroaches and bed bugs). Available environmental fate and hazard studies have been reviewed under the Biocidal Products Regulation (BPR), (EU) 528/2012. The studies are summarised in the Competent Authority Report (CAR). The key information pertinent to determining a classification is presented below.

The technical material used for the generation of the majority of the environmental hazard data was referred to by the manufactures code 'S-1563' in the study reports. S-1563 is quoted as having a minimum purity of 95.2% (based on total momfluorothrin isomer content) in the study reports, but it is predominantly the RTZ isomer (>86% RTZ). Some of the fate data have been generated on the pure isomers (i.e. the RTZ or RTE isomers with a purity of >99%), where this is the case it is specified in the dossier.

The substance degrades to a number of degradants in the environment which are identified in Figure 1. Non GLP acute toxicity to algal, *Daphnia* and fish data (Miyamoto *et al*, 2013a, 2013b and 2013c) are available for the degradants MFOA-D, MFOA and *t*-COOH-CA indicating they are significantly less toxic than the parent. This report therefore focuses on the classification of 1R-trans-Z-momfluorothrin alone.

5.1 Degradation

A summary of available information on the fate of 1R-trans-Z-momfluorothrin is presented in Table 28 below.

Table 28: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Aquatic hydrolysis OECD Guideline 111, GLP	Stable at pH 4 DT ₅₀ at 40°C , pH 7: 56.3- 77.5 days DT ₅₀ at 25°C , pH 9: 6.5-7.2 days	Valid study	Ponte, 2011a
Aquatic photolysis OECD Guideline 316, GLP	DT ₅₀ 13.4 days equivalent to 25.9 OECD solar days DT ₅₀ (including photoisomerisation) 14.5 OECD solar days	Valid study	Ponte, 2012
Ready biodegradation OECD Guideline 301B, GLP	Not rapidly biodegradable -5.46 to 3.91% degradation	Valid study	Ilic, 2010
Water/sediment simulation OECD Guideline 308, GLP	DT ₅₀ 0.6 to 2.9 days based on parent dissipation whole system Mineralisation: 15% AR* day 100 to 43% AR day 105	Valid study	Ponte, 2011

*AR refers to Applied Radioactivity

5.1.1 Stability

Aqueous hydrolysis

An aqueous hydrolysis study (Ponte, 2011a) is available following GLP and OECD Guideline 111. The study used 3 radio labels (purity $\geq 99\%$):

- [alc-¹⁴C] 1R-trans-Z-momfluorothrin: [methoxymethylbenzyl- α -¹⁴C] 1R-trans-Z-momfluorothrin
- [acid-¹⁴C] 1R-trans-Z-momfluorothrin: [cyclopropyl-1-¹⁴C] 1R-trans-Z-momfluorothrin
- [acid-¹⁴C] 1R-trans-E-momfluorothrin: [cyclopropyl-1-¹⁴C] 1R-trans-E-momfluorothrin

A preliminary test was run at pH 4, 7 and 9 at $50 \pm 0.1^\circ\text{C}$ for up to 5 days with 2 isomers: [acid-¹⁴C] 1R-trans-Z-momfluorothrin and [acid-¹⁴C] 1R-trans-E-momfluorothrin. The momfluorothrin isomers were considered stable at pH 4 whilst significant hydrolysis was observed at pH 7 and 9. It was noted that hydrolysis of the 2 isomers was not significantly different.

Subsequently a definitive test was conducted at pH 7 (up to 33 days for 40, 50, and 60°C) and pH 9 (up to 21 days for 25, 40 and 50°C) using 2 isomers: [alc-¹⁴C] 1R-trans-Z-momfluorothrin and [acid-¹⁴C] 1R-trans-Z-momfluorothrin. Radiocarbon recovery was determined by Liquid Scintillation Counting (LSC). The degradation rates at pH 7 and 9 were calculated using pseudo-first order kinetics. Similarly, it was noted that hydrolysis of the 2 isomers was not significantly different.

The DT_{50} values were pH dependant and presented at follows:

- pH 7: 660 to 1394 days at 20°C
- pH 9: 11.7 to 12.2 days at 20°C

Parent and degradants were quantified by High Performance Liquid Chromatography (HPLC) and confirmed by Thin Layer Chromatography (TLC). The study concluded that 1R-trans-Z-momfluorothrin undergoes hydrolytic cleavage of the ester link to form carboxylic acid and alcohol, with degradants Z-CMCA and MFOA. Z-CMCA was the principal degradant of the acid label isomer and MFOA the principal degradant of the alcohol label isomer.

Aqueous Photolysis

An aqueous photolysis study (Ponte, 2012) is available following GLP and OECD Guideline 316.

The study used 3 radio labels (purity $\geq 99\%$):

- [alc-¹⁴C] 1R-trans-Z-momfluorothrin: [methoxymethylbenzyl- α -¹⁴C] 1R-trans-Z-momfluorothrin
- [acid-¹⁴C] 1R-trans-Z-momfluorothrin: [cyclopropyl-1-¹⁴C] 1R-trans-Z-momfluorothrin
- [acid-¹⁴C] 1R-trans-E-momfluorothrin: [cyclopropyl-1-¹⁴C] 1R-trans-E-momfluorothrin

The study was run at pH 4 with solutions exposed to continuous artificial light (Xenon arc lamp average light intensity of 443 W/m^2 for the 300-800nm range) considered equivalent to natural midsummer sunlight at 37.45°N latitude, for 13 days at $25^\circ\text{C} \pm 2^\circ\text{C}$. Under light conditions, extensive isomerisation was observed with no significant differences between the RTZ and RTE label. However, none of the other 7 isomers were $>4.7\%$ AR.

Radiocarbon recovery was determined by LSC. Parent and degradants were quantified by HPLC.

The Quantum Yield (calculated as the sum of 8 momfluorothrin isomers) was 0.0113 and including photoisomerisation 0.0205.

The mean DT₅₀ was 13.4 days under artificial light equating to 25.9 OECD solar days. Including photoisomerisation, the mean DT₅₀ was 7.5 days under artificial light equating to 14.5 OECD solar days.

The main degradants were identified as CMCA and MFOA via cleavage of the ester link. CMCA was the principal degradant of the acid label isomer and MFOA the principal degradant of the alcohol label isomer

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

None available.

5.1.2.2 Screening tests

A ready biodegradation study (Ilic, 2010) is available following OECD Guideline 301B (CO₂ Evolution) and GLP using S-1563 (purity 95.6%, total momfluorothrin isomer content). Test solutions were prepared with 100 mg test item in ~3 litres meaning the substance was tested above the water solubility of 0.6 to 1.4 mg/l. The study was run a pH 7.53 to 7.68 and between 21 and 24°C. Validation criteria for the Reference and Toxicity Controls were met. Ultimate biodegradation reached a maximum of 3.91 %. Overall, the substance is considered not readily biodegradable.

5.1.2.3 Simulation tests

A degradation in water-sediment system study (Ponte and Mannella, 2011) is available following OECD Guideline 308 and GLP. Two aerobic systems were used: Calwich, Derbyshire referred to as 'Abbey' and Chatsworth, Derbyshire referred to as 'Swiss'. The test conditions are included in table 29 below.

Table 29: Water-sediment system test conditions

Criteria	Abbey	Swiss
Sediment properties	33% sand; 56% silt; 11% clay Organic matter 8% pH in 1:1 sediment: water ratio: 7.6	95 % sand; 4% silt; 1% clay Organic matter 1.4% pH in 1:1 sediment: water ratio: 6.1
Water properties	pH: 8.1 Hardness: 233 mg equivalent CaCO ₃ /L Total dissolved solids: 304 ppm Total suspended solids: 16 ppm	pH: 7.1 Hardness: 22 mg equivalent CaCO ₃ /L Total dissolved solids: 72 ppm Total suspended solids: 14 ppm
Characteristics and maintenance of the test system during study	Oxidation reduction potential in water layer: 69 mV in sediment: -45 mV pH in water layer: 7.36 in sediment: 7.31 dissolved oxygen: 4.56 ppm	Oxidation reduction potential in water layer: 145 mV in sediment: 185 mV pH in water layer: 7.00 in sediment: 6.59 dissolved oxygen: 6.57 ppm

The study used 3 radio labels (>99% purity):

- [alc-¹⁴C] 1R-trans-Z-momfluorothrin: [Methoxymethylbenzyl- α -¹⁴C] 1R-trans-Z-momfluorothrin
- [acid-¹⁴C] 1R-trans-Z-momfluorothrin: [Cyclopropyl-1-¹⁴C] 1R-trans-Z-momfluorothrin
- [acid-¹⁴C] 1R-trans-E-momfluorothrin: [Cyclopropyl-1-¹⁴C] 1R-trans-E-momfluorothrin

Initial nominal dose rates were 7.7 to 8.4 μ g per sample with direct addition to the water phase. The study was run in the dark at $20 \pm 2^\circ\text{C}$ for between 100 and 146 days depending on the radio label. The water layers and sediment extracts were quantified by LSC. Following extraction, the residual radioactivity in sediment was determined by combustion and radioassay. 1R-trans-Z/E -momfluorothrin and degradants were quantified by HPLC. No significant further isomerisation was observed in any of the test systems.

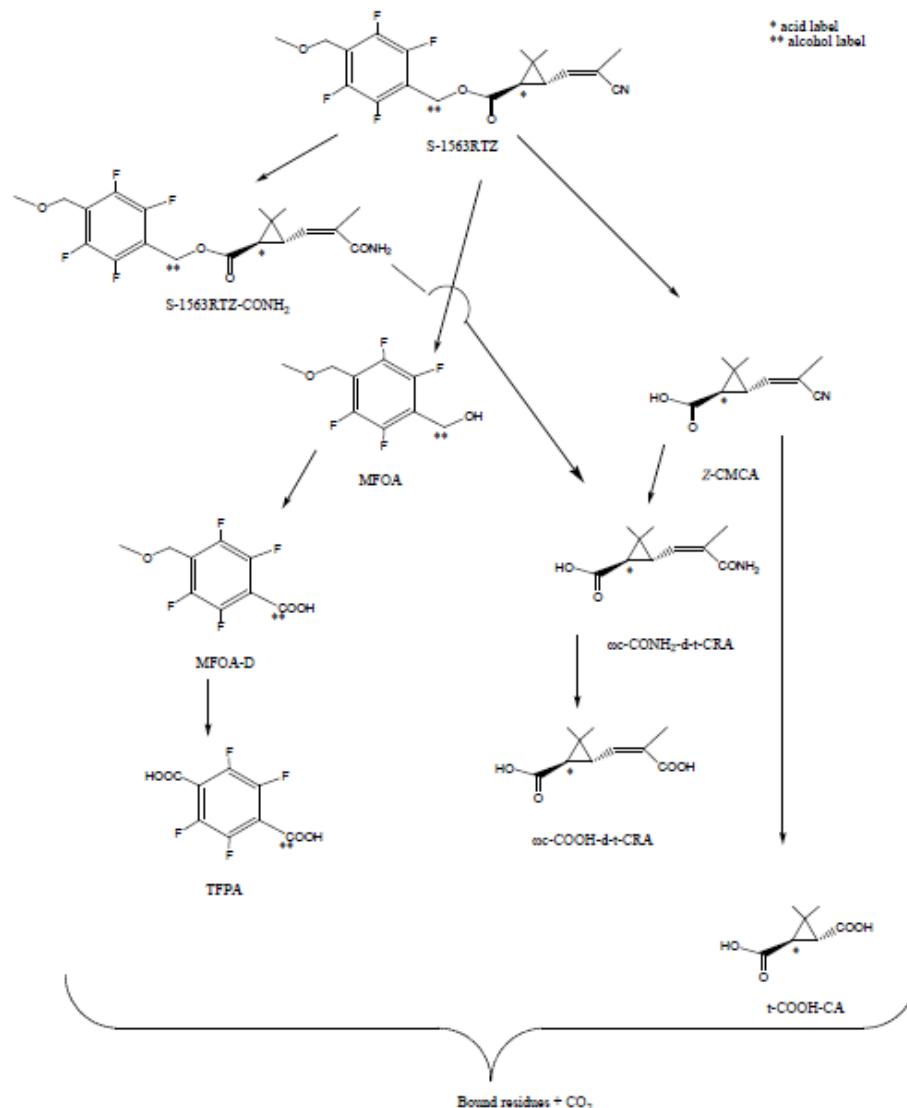
Overall, 1R-trans-Z -momfluorothrin and 1R-trans-E-momfluorothrin were observed to rapidly dissipate from the water column in both systems representing <4% Applied Radioactivity (AR) after 8 days. Identified degradants are presented in Table 30. Figure 1 shows the proposed degradation pathway. Table 31 presents the distribution of parent and degradants.

Table 30: Identified degradants in aerobic water-sediment system

Radiolabel and isomer	Degradants
[alc ¹⁴ C] 1R-trans-Z-momfluorothrin	Major degradants: MFOA (depending on test system), MFOA-D and TFPA
[acid ¹⁴ C] 1R-trans-Z-momfluorothrin	Major degradant: Z-CMCA Minor degradants: ωc-CONH ₂ -d-t-CRA and t-COOH-CA (depending on test system)
[acid ¹⁴ C]1R-trans-E-momfluorothrin	Major degradants: E-CMCA, ωt-CONH ₂ -d-t-CRA and t-COOH-CA (depending on test system)

Figure 1: Proposed degradation pathway of 1R-trans-Z-momfluorothrin (S-1563 RTZ) and 1R-trans-E-momfluorothrin (S-1563 RTE) in water-sediment systems under aerobic conditions

S-1563RTZ Pathway



S-1563RTE (acid only) Pathway

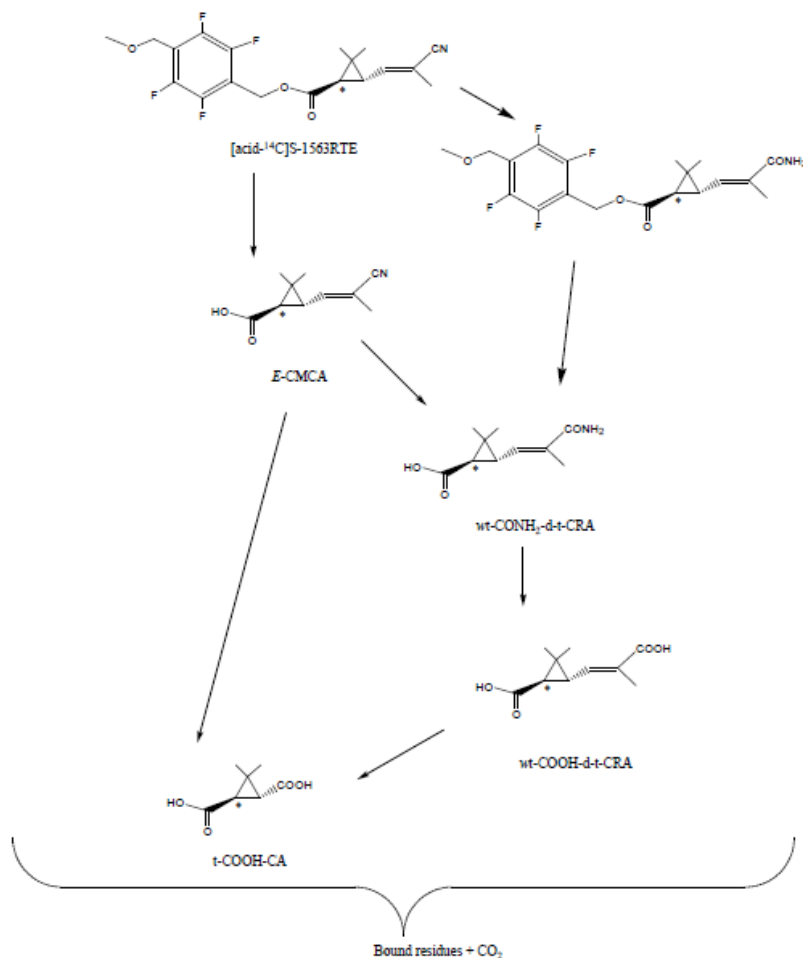


Table 31: Distribution of 1R-trans-Z-momfluorothrin (S1563 RTZ) and 1R-trans-E-momfluorothrin (S-1563 RTE) and degradants as % Applied Radioactivity in aerobic water-sediment systems

[alc- ¹⁴ C]S-1563RTZ									
Abbey Test System									
Time (days)	S-1563RTZ	S-1563RTE	S-1563RTZ-				Bound Residues	Organic Volatiles	(CO ₂)
			MFOA	CONH ₂	MFOA-D	TFPA			
0	88.6	3.0	0.7	0.0	1.1	0.0	1.9	NA	NA
1	30.4	0.0	19.3	3.7	39.4	1.2	5.0	0.0	0.6
3	14.6	0.0	23.1	2.5	47.5	1.0	0.7	0.1	0.0
8	2.9	0.7	35.0	0.0	49.3	0.2	1.1	0.0	0.2
15	1.5	0.5	24.9	0.4	61.7	0.5	1.6	0.0	0.1
31	0.3	0.5	23.0	0.0	59.7	4.6	2.6	0.0	0.6
63	0.7	0.0	7.0	0.0	68.1	6.0	3.1	0.1	2.6
100	0.5	0.0	0.3	0.0	72.9	10.5	3.0	0.1	6.6
146	0.0	0.0	0.8	0.2	64.1	5.3	4.8	0.3	18.7

Swiss Test System

CLH REPORT FOR 1R-TRANS-Z-MOMFLUOROTHRIN

Time (days)	S-1563RTZ-						Bound Residues	Organic Volatiles	(CO ₂)
	S-1563RTZ	S-1563RTE	MFOA	CONH ₂	MFOA-D	TFPA			
0	90.1	2.9	1.4	0.0	0.0	0.0	0.7	NA	NA
1	65.2	2.5	5.9	3.0	9.9	0.6	1.6	0.0	0.3
3	39.0	0.2	9.5	7.3	34.5	1.5	0.5	0.0	0.1
8	3.0	0.3	0.0	4.5	73.2	10.1	0.4	0.0	0.3
15	0.9	0.2	0.9	1.9	74.5	11.4	0.4	0.1	0.4
31	1.1	0.2	0.8	2.1	74.0	10.0	0.6	0.0	1.1
63	0.7	0.0	0.3	0.2	71.4	19.0	0.5	0.1	2.5
100	0.4	0.0	0.0	0.0	58.9	32.4	0.8	0.0	0.9
146	0.2	0.0	0.0	0.0	11.1	67.5	1.8	0.2	19.4

[acid-¹⁴C]S-1563RTZ

Abbey Test System

Time (days)	S-1563RTZ-			wc-CONH ₂ -		wc-COOH-		Bound Residues	Organic Volatiles	(CO ₂)
	S-1563RTZ	S-1563RTE	Z-CMCA	CONH ₂	d-t-CRA	t-COOH-CA	d-t-CRA			
0	85.9	4.2	1.4	0.0	0.0	0.0	0.0	1.3	NA	NA
1	46.0	2.1	39.6	2.3	1.1	0.0	0.0	3.8	0.0	0.1
3	14.9	1.4	69.6	3.0	2.4	0.0	0.0	2.2	0.1	0.9
8	1.4	0.7	83.7	0.0	3.6	0.0	0.0	1.9	0.1	1.0
13	0.9	0.5	78.1	0.0	5.5	1.1	1.3	3.0	0.0	2.7
30	0.6	0.0	71.6	0.0	7.4	3.1	1.0	5.0	0.0	3.3
58	0.5	0.0	37.0	0.0	6.0	10.3	0.0	16.5	0.5	15.4
105	0.0	0.0	4.1	0.0	2.3	4.2	0.0	27.2	0.3	43.0

Swiss Test System

Time (days)	S-1563RTZ-			wc-CONH ₂ -		wc-COOH-		Bound Residues	Organic Volatiles	(CO ₂)
	S-1563RTZ	S-1563RTE	Z-CMCA	CONH ₂	d-t-CRA	t-COOH-CA	d-t-CRA			
0	87.9	4.0	1.9	0.0	0.0	0.0	0.0	0.5	NA	NA
1	54.2	1.9	23.6	4.5	1.0	1.6	0.5	3.0	0.0	0.3
3	20.5	1.3	57.8	7.3	1.7	2.4	0.0	2.9	0.0	2.5
8	1.6	0.6	72.0	3.8	2.8	2.4	0.0	5.7	0.0	3.7
13	0.8	0.3	69.0	2.8	4.0	2.9	0.0	7.1	0.0	4.9
30	0.0	0.0	62.4	0.2	5.6	4.8	0.7	7.8	0.1	10.3
58	0.2	0.0	25.2	0.0	10.6	4.7	1.0	14.4	0.1	34.2
100	0.0	0.0	20.4	0.0	21.0	6.1	0.0	14.4	0.4	18.0

[acid-¹⁴C]S-1563RTE

Abbey Test System

Time (days)	S-1563RTE-			wt-CONH ₂ -		wt-COOH-		Bound Residues	Organic Volatiles	CO ₂
	S-1563RTE	S-1563RTZ	E-CMCA	CONH ₂	d-t-CRA	t-COOH-CA	d-t-CRA			
0	90.8	3.2	0.8	0.0	0.0	0.0	0.0	1.8	NA	2.1
1	53.5	2.3	29.0	4.3	1.7	1.8	0.0	4.7	0.5	0.3
3	15.8	0.7	62.1	4.2	4.2	4.1	0.1	1.9	0.1	0.6
7	1.3	1.5	64.3	2.6	8.0	8.5	1.2	4.0	0.0	1.6
14	1.4	0.0	58.8	0.8	11.5	9.2	0.6	4.8	0.0	3.1
30	0.8	0.3	53.2	0.1	12.1	11.7	0.7	7.3	2.1	5.0
59	0.5	0.0	22.9	0.1	20.1	21.5	0.6	14.3	0.4	14.2
100	0.5	0.0	2.6	0.0	9.4	6.9	0.3	28.5	0.9	38.2

Swiss Test System										
Time	S-1563RTE-			wt-CONH ₂ -		wt-COOH-		Bound	Organic	
(days)	S-1563RTRE	S-1563RTZ	E-CMCA	CONH ₂	d-t-CRA	t-COOH-CA	d-t-CRA	Residues	Volatiles	CO ₂
0	91.0	3.7	1.4	0.0	0.0	0.0	0.0	0.6	NA	3.3
1	54.8	2.8	22.2	7.3	5.8	1.5	0.6	2.6	0.0	1.0
3	22.7	0.9	43.5	7.2	11.4	4.2	2.7	1.4	0.0	1.5
7	2.4	1.6	54.8	4.0	16.7	6.3	4.1	1.9	0.0	0.4
14	1.0	0.0	51.4	3.1	13.8	13.7	1.8	4.9	0.1	4.5
30	0.7	0.3	59.8	0.8	9.9	10.8	2.4	3.5	0.0	5.7
59	1.0	0.1	9.9	1.4	12.9	23.3	0.8	12.2	0.1	27.4
100	0.2	0.0	7.4	0.7	31.7	26.1	3.8	7.9	0.0	15.0

In addition to the formation of degradants, mineralisation was observed and this is presented in Table 32.

Table 32: Mineralisation as % Applied Radioactivity in aerobic water-sediment systems

Radiolabel	Swiss	Abbey
[alc ¹⁴ C] 1R-trans-Z-momfluorothrin	19.4 % AR day 146	18.7 % AR day 146
[acid ¹⁴ C] 1R-trans-Z-momfluorothrin	34.2 % AR day 58	43 % AR day 105
[acid ¹⁴ C] 1R-trans-E-momfluorothrin	15 % AR day 100	38.2 % AR day 100

Degradation rates (DT₅₀ and DT₉₀) for 1R-trans-Z-momfluorothrin and 1R-trans-E-momfluorothrin and the degradants were calculated using Single First Order (SFO) model, Double First Order Parallel (DFOP) model and First Multi Component Order (FOMC) using KinGui version 1.1 software. The values are presented in Table 33.

Table 33: DT₅₀ half-lives and DT₉₀ values for 1R-trans-Z-momfluorothrin and 1R-trans-E-momfluorothrin and its degradants in aerobic water-sediment systems

[alc- ¹⁴ C] 1R-trans-Z-momfluorothrin							
Test System		Parent		MFOA		MFOA-D	
		Abbey	Swiss	Abbey	Swiss	Abbey	Swiss
Whole system	DT ₅₀	0.6	2.9	35.8	MFOA was not considered for calculation as it represented < 10% AR	>1000	103.2
	DT ₉₀	4.8	9.7	118.8		>1000	342.9
	Model	FOMC	SFO	SFO		SFO	SFO
Water layer	DT ₅₀	0.1	2.5	26.3	MFOA was not considered for calculation as it represented < 10% AR	>1000	107.9
	DT ₉₀	2.0	8.2	87.4		>1000	358.4
	Model	DFOP	SFO	SFO		SFO	

[acid- ¹⁴ C] 1R-trans-Z-momfluorothrin									
Test System		Parent		Z-CMCA					
		Abbey	Swiss	Abbey	Swiss				
Whole system	DT ₅₀	1.2	1.6	43.5	44.8				
	DT ₉₀	3.9	5.4	144.5	148.8				
	Model	SFO							
Water layer	DT ₅₀	1.0	1.4	30.4	41.7				
	DT ₉₀	3.3	4.7	101.1	138.6				
	Model	SFO							
[acid- ¹⁴ C] 1R-trans-E-momfluorothrin									
Test System		Parent		E-CMCA		ωt-CONH ₂ -d-t-CRA		t-COOH-CA	
		Abbey	Swiss	Abbey	Swiss	Abbey	Swiss	Abbey	Swiss
Whole system	DT ₅₀	1.3	1.6	33.6	36.5	>1000	*	>1000	*
	DT ₉₀	4.4	5.4	111.7	121.1	>1000		>1000	
	Model	SFO							
Water layer	DT ₅₀	1.0	1.4	25.4	36.1	>1000	*	>1000	*
	DT ₉₀	3.2	4.5	84.5	120.1	>1000		>1000	
	Model	SFO							

*Degradation rates were not determined for ω t-CONH₂-d-t-CRA and t-COOH-CA as concentrations increased until the end of the study.

5.1.3 Summary and discussion of degradation

1R-trans-Z-momfluorothrin and 1R-trans-E-momfluorothrin are considered to degrade similarly with no significant difference anticipated.

1R-trans-Z-momfluorothrin is considered stable under acidic conditions with limited hydrolysis at neutral pH. Under alkaline conditions, 1R-trans-Z-momfluorothrin undergoes hydrolysis with an experimental half-life of 6.5 to 7.2 days at 25°C. Converting this half-life to a more environmentally relevant temperature of 12°C results in values of 18.3 to 20.3 days (equation from the REACH *Guidance on information requirements and chemical safety assessment, Chapter R.7b*¹).

Overall, 1R-trans-Z-momfluorothrin is considered stable over the majority of the environmentally relevant pH range. At higher pH, abiotic degradation is significant although it is likely to reflect a DT₅₀ > 16 days.

Under experimental conditions 1R-trans-Z-momfluorothrin underwent photodegradation with a half-life of 13.4 to 14.5 OECD solar days. However, information on photodegradation is difficult to use for classification purposes given the actual degree of photodegradation in the aquatic

¹ Equation $DT_{50} \text{ at } x^{\circ}\text{C} = DT_{50} (t) \cdot e^{(0.08 \cdot (T-x))}$ where t is experimental half life at T temperature

environment depends on local conditions e.g. water depth, suspended solids, turbidity as well as seasonal influences.

In a ready biodegradation study minimal degradation (-5.46 to 3.91%) was observed.

In an aerobic water-sediment study 1R-trans-Z-momfluorothrin was removed rapidly with whole system DT_{50} values between 0.6 to 2.9 days. Various degradants were identified with longer DT_{50} values and mineralisation ranged from 15% AR at day 100 to 43% AR at day 105 in different systems. Data are not available on for the classification of such degradants.

Overall, the degradation information does not provide sufficient data to show 1R-trans-Z-momfluorothrin is ultimately degraded within 28 days (equivalent to a half-life < 16 days) or to non classifiable products. Consequently, 1R-trans-Z-momfluorothrin is considered not rapidly degradable for the purpose of classification and labelling.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Two GLP studies are available investigation the adsorption of 1R-trans-Z-momfluorothrin (purity >99%).

The first study (Ponte, 2011b) followed OECD Guideline 121 with K_{oc} values of 7079 and 7413 determined. This equates to $\log K_{oc}$ values of 3.85 and 3.87.

The second study (Ponte, 2012b) followed OECD Guideline 106 using four soils and one sediment. The test was conducted using 1R-trans-Z-momfluorothrin and no significant further isomerisation was observed. There was a high correlation between adsorption and the soil organic carbon content and cation exchange capacity (CEC) indicating increased adsorption with increased organic carbon or CEC. There was no evidence of pH dependency. K_{oc} values ranged from 1033 to 4344 with an average of 1748. This equates to $\log K_{oc}$ values between 3 and 3.6 with an average of 3.2. The K_{oc} values for desorption ranged from 1085 to 6219 with an average of 2484.

Overall the two studies indicate 1R-trans-Z-momfluorothrin will be relatively immobile in soil/sediment.

5.2.2 Volatilisation

Experimental data (Moseley, 2001d; Leslie, 2011 and Moseley, 2011e) indicate the vapour pressure is between 4.702×10^{-7} and 4.702×10^{-7} Pa at 20°C for the RTZ and RTE isomers. The Henry's Law Constants (Foster, 2012c; Foster 2012d; Foster, 2012e) between 2.792×10^{-4} and 2.985×10^{-4} Pa m³ mol⁻¹ at 20°C indicating 1R-trans-Z-momfluorothrin is unlikely to partition from the water phase to air.

5.2.3 Distribution modelling

Not relevant for classification and labelling.

5.3 Aquatic Bioaccumulation

A summary of available information on the bioaccumulation potential of 1R-trans-Z-momfluorothrin is presented in Table 34 below.

Table 34: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Partition coefficient <i>n</i> -octanol/water OECD Guideline 107, GLP	Log Pow: 2.99 at 25°C	Valid study RTZ isomer	Wright, 2011b
Partition coefficient <i>n</i> -octanol/water OECD Guideline 107, GLP	Log Pow: 2.88 at 25°C	Valid study RTE isomer	Wright, 2011c
Experimental aquatic BCF OECD Guideline 305, GLP	Steady state whole fish BCF: 600 to 612 l/kg Kinetic whole fish BCF: 753 to 784 l/kg (experimental 2.56% lipid). Lipid normalized to 5% kinetic whole fish BCF: 1471 to 1531 l/kg Depuration half-life DT ₅₀ whole fish: 9.76 to 11.7 days	Valid study Flow through, 35 days exposure, 28 days depuration Based on measured total radioactive [¹⁴ C] residues (TRR)	Kang, 2012

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

As experimental data are available, estimations are not included.

5.3.1.2 Measured bioaccumulation data

An experimental aquatic BCF s available following GLP and OECD Guideline 305 (Kang, 2012). The study used [methoxymethylbenzyl- α -¹⁴C] 1R-trans-E-momfluorothrin (purity >99%) and [methoxymethylbenzyl- α -¹⁴C] 1R-trans-Z-momfluorothrin (purity > 99%) in a combined ratio of 1:9.

A flow-through system was used with Bluegill Sunfish (*Lepomis macrochirus*) and two exposure concentrations; 0.1 and 0.3 µg/l. The exposure period ran for 35 days followed by a 28-day depuration period. Test conditions reflected the guideline with a water pH 7.1-8.4. Samples were analysed by LSC and HPLC with radiometric detection. Water concentrations were considered stable.

1R-trans-Z/E-momfluorothrin was only detected in fish tissue on day 1 of the exposure phase in edible, non-edible and whole body fish samples at both low and high concentrations. After this it was considered metabolised and only [¹⁴C] residues were observed. Major metabolites in fish were characterised as TFPA (detected from day 1 with maximum of 62 to 64.7% on day 3 in low and high doses) and MFOA-D (detected from day 14 with maximum of 2.6 to 4.7% on day 21 in low and high doses). Steady state and kinetic BCFs based on the parent 1R-trans-Z/E-momfluorothrin could not be calculated and BCFs were based on total radioactive residues (TRR).

Steady state (TRR) whole fish BCFs were 612 l/kg for the 0.1 µg/l nominal exposure concentration and 600 l/kg for the 0.3 µg/l nominal exposure concentration.

Kinetic whole fish BCFs were 753 l/kg for the 0.1 µg/l nominal exposure concentration and 784 l/kg for the 0.3 µg/l nominal exposure concentration. The higher concentration kinetic BCF was normalised to 5% lipid content wet weight considering an experimental lipid content of 2.56% giving BCFs of 1471 to 1531 l/kg at 5%.

At the end of the depuration period, TRR were less than 40%. Depuration half-lives (DT₅₀) for whole fish were calculated to be 9.76 to 11.7 days.

5.3.2 Summary and discussion of aquatic bioaccumulation

Experimental logK_{ow} values are 2.88 and 2.99 at 25°C for the RTE and RTZ isomers respectively. These values are below the CLP logK_{ow} trigger value of ≥ 4 intended to identify substances with a potential to bioaccumulate.

In an experimental BCF study, 1R-trans-Z-momfluorothrin was observed to be extensively metabolised resulting in a BCF less than 500. BCFs based on total radioactive residue were greater than 500 l/kg but less than 2000 l/kg reflecting metabolites. A clear depuration phase was observed.

5.4 Aquatic toxicity

A summary of available valid information on the aquatic toxicity of 1R-trans-Z-momfluorothrin is presented in Table 35 below. The studies used technical 'S-1563' with an overall purity of 95.4 to 95.8% (based on total momfluorothrin isomer content) and ≥ 86% 1R-trans-Z-momfluorothrin content.

No ecotoxicity data is available for degradants.

Table 35: Summary of relevant information on aquatic toxicity

Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg/l)	
Acute toxicity to fish OECD Guideline 203, GLP	Rainbow Trout (<i>Oncorhynchus mykiss</i>)	Mortality	Flow-through	96 hours	LC ₅₀	0.0012 (mm)	Fournier, 2011a
Acute toxicity to fish OECD Guideline 203, GLP	Fathead Minnow (<i>Pimephales promelas</i>)	Mortality	Flow-through	96 hours	LC ₅₀	0.0097 (mm)	Fournier, 2011b
Acute toxicity to fish OECD Guideline 203, GLP	Bluegill Sunfish (<i>Lepomis macrochirus</i>)	Mortality	Flow-through	96 hours	LC ₅₀	0.0029 (mm)	Fournier, 2011c
Fish Early Life-Stage (FELS) toxicity OECD Guideline 210, GLP	Fathead Minnow (<i>Pimephales promelas</i>)	Embryo hatching success; percentage embryos that produce live normal larvae at hatch; larval survival; and larval growth	Flow-through	28 days	NOEC	≥0.0031 (mm) Based on highest test concentration as no significant effects observed.	York, 2012
<i>Daphnia</i> sp Acute Immobilisation OECD Guideline, 202 GLP	<i>Daphnia magna</i>	Acute immobilisation	Flow-through	48 hours	EC ₅₀	0.0078 (mm)	Fournier, 2011d
<i>Daphnia magna</i> Reproduction OECD Guideline 211, GLP	<i>Daphnia magna</i>	Survival; reproduction; growth	Flow-through	21 days	NOEC	0.0005 (mm)	Fournier, 2012
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP	<i>Pseudo-kirchneriella subcapitata</i>	Cell multiplication inhibition	Static	72 hours	ErC ₅₀ NOErC	>4.8 (twa) 0.33 (twa)	Softcheck, 2011a
<i>Lemna</i> sp. Growth Inhibition Test OECD Guideline 221, GLP	<i>Lemna gibba</i>	Growth	Static	7 days	ErC ₅₀ NOErC	>2.5 (twa) ≥2.5 (twa) Based on highest test concentration as no significant effects observed.	Softcheck, 2011b

mm refers to mean measured

twa refers to time weighted average

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Three acute toxicity to fish studies using S-1563 are available following GLP and OECD Guideline 203.

Study 1 (Fournier, 2011b)

Using Rainbow Trout (*Oncorhynchus mykiss*), the nominal exposure range was 0.63, 1.3, 2.5, 5 and 10 µg/l. Exposure solutions were prepared with the aid of the solvent dimethylformamide (DMF) and a solvent control was included. Analytical measurement was determined using gas chromatography with electron capture detection (GC/ECD). Results were based on mean measured values: 0.64, 1.4, 2.2, 5 and 10 µg/l. Validity criteria were met and test is considered reliable. The 96 hour LC₅₀ was calculated to be 1.2 µg/l (equating to 0.0012 mg/l) with 95% confidence intervals of 0.64 to 2.2 µg/l.

Study 2 (Fournier, 2011b)

Using Fathead Minnow (*Pimephales promelas*), the nominal exposure range was 1.3, 2.5, 5, 10 and 20 µg/l. Exposure solutions were prepared with the aid of the solvent DMF and a solvent control was included. Analytical measurement was determined using GC/ECD. Losses were observed at lower concentrations and results were based on mean measured values: 0.94, 2.1, 4, 9.5 and 18 µg/l. Validity criteria were met and test is considered reliable. The 96-hour LC₅₀ was calculated to be 9.7 µg/l (equating to 0.0097 mg/l) with 95% confidence intervals of 7.7 to 13 µg/l.

Study 3 (Fournier, 2011c)

Using Bluegill Sunfish (*Lepomis macrochirus*), the nominal exposure range was 0.63, 1.3, 2.5, 5, and 10 µg/l. Exposure solutions were prepared with the aid of the solvent DMF and a solvent control was included. Analytical measurement was determined using GC/ECD. Results were based on mean measured values: 0.54, 1.0, 1.9, 4.1 and 8 µg/l. Validity criteria were met and test is considered reliable. The 96-hour LC₅₀ was calculated to be 2.9 µg/l (equating to 0.0029 mg/l) with 95% confidence intervals of 2.5 to 3.4 µg/l.

Overall, the three acute toxicity to fish studies, using three different species, show LC₅₀ values in the 0.001 to 0.01 mg/l range with the lowest 96-hour LC₅₀ of 0.0012 mg/l.

5.4.1.2 Long-term toxicity to fish

A 28-day chronic toxicity to fish study (York, 2012) using S-1563 following GLP and OECD Guideline 210 is available. This fish early life stage study used Fathead Minnow (*Pimephales promelas*) which was not the most acutely sensitive species. The following endpoints: mean embryo hatching success, live normal larvae at hatch, mean larval survival, mean larval length and mean larval dry weight. The nominal exposure range was 0.1, 0.23, 0.64, 1.6, and 4 µg/l. Exposure solutions were prepared with the aid of the solvent DMF and a solvent control was included. Analytical measurement was determined using GC/ECD. Results were based on mean measured values: 0.1, 0.2, 0.48, 1.3, and 3.1 µg/l. Validity criteria were met and test is considered reliable. Endpoint test data are presented in Table 36. Overall, no significant difference could be determined

for any endpoint at any exposure concentration and the 28-day NOEC reflects the highest test concentration at 3.1 µg/l (equating to 0.0031mg/l) based on mean measured concentrations.

Table 36: Percent hatching success and percent normal larvae at completion of hatch (test day 4) and survival, total length and dry weight of larvae at test termination of the early life-stage (28 days post-hatch)

S-1563 concentration		Mean embryo hatching success (%)	Live, normal larvae at hatch (%)	Mean larval survival (%)	Mean larval length (mm) (SD) ^a	Mean larval dry weight (mg) (SD) ^a
Nominal (µg/l)	Mean measured (µg/l)					
Control	Control	81	100	98	27.2 (0.60)	38.6 (2.8)
Solvent control	Solvent control	80	100	93	27.2 (0.83)	38.5 (4.3)
Pooled control	Pooled control	80	100	96	27.2 (0.67)	38.5 (3.4)
0.10	0.10	77	99	97	26.5 (0.46)	36.0 (1.9)
0.26	0.20	74	99	97	26.7 (0.46)	36.3 (1.8)
0.64	0.48	79	100	92	27.3 (0.78)	38.9 (4.3)
1.6	1.3	76	100	95	26.9 (0.38)	37.2 (1.4)
4.0	3.1	78	97 ^b	92	26.8 (0.46)	36.9 (0.7)

^a (SD) = Standard Deviation

^b Significantly reduced compared to pooled control, based on Wilcoxon's Test with Bonferroni's Adjustment. However, the 3% difference between the pooled control and the high exposure concentration falls within the normal variability for fathead minnows; therefore, the statistical difference between the pooled control and the high exposure concentration was determined to not be biologically relevant.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

An acute toxicity to *Daphnia magna* study (Fournier, 2011d) using S-1563 is available following GLP and OECD Guideline 202. Exposure solutions were prepared with the aid of the solvent DMF and a solvent control was included. The nominal exposure range was 4, 8, 16, 32, and 64 µg/l. Analytical measurement was determined using GC/ECD. Results were based on mean measured values: 3.6, 7.9, 17, 28 and 61µg/l. Validity criteria were met and test is considered reliable. The 48-hour EC₅₀ was calculated to be 7.8 µg/l (equating to 0.0078 mg/l) with 95% confidence intervals of 6.1 to 9.7 µg/l.

5.4.2.2 Long-term toxicity to aquatic invertebrates

A chronic toxicity to *Daphnia magna* study (Fournier, 2012) using S-1563 is available following GLP and OECD Guideline 211. Exposure solutions were prepared with the aid of the solvent DMF and a solvent control was included. The nominal exposure range was 0.082, 0.20, 0.51, 1.3, 3.2, and 8 µg/l. Analytical measurement was determined using GC/ECD. Results were based on mean measured values: 0.074, 0.21, 0.5, 1.3, 3.1 and 9.3 µg/l. Validity criteria were met and test is considered reliable. Endpoint test data is presented in Table 37 with endpoint NOEC values presented in Table 38.

Table 37: Survival, reproduction and growth data at day 21

S-1563 concentration		Mean cumulative percent survival of parents (%) (SD) ^a	Mean cumulative number of offspring per female (%) (SD) ^a	Mean total body length of parents (mm) (SD) ^a	Mean dry weight of parents (mg) (SD) ^a
Nominal (µg/l)	Measured (µg/l)				
Control	Control	85 (6)	106 (16)	4.14 (0.15)	0.71 (0.12)
Solvent control	Solvent control	95 (6)	156 (6)	4.55 (0.03)	0.96 (0.07)
Pooled control	Pooled control	90 (8)	n.a. ^b	n.a.	n.a.
0.082	0.074	95 (6)	182 (6)	4.64 (0.03)	1.04 (0.04)
0.20	0.21	90 (20)	155 (11)	4.46 (0.08)	0.84 (0.16)
0.51	0.50	100 (0)	141 (8)	4.44 ^{dc} (0.05)	0.86 (0.06)
1.3	1.3	90 (20)	127 ^{cc} (24)	4.20 ^{dc} (0.20)	0.63 ^c (0.17)
3.2	3.1	90 (0)	155 (11)	4.51 (0.14)	0.68 ^c (0.15)
8.0	9.3	73 ^f (42)	25 ^c (4)	3.48 ^d (0.29)	0.39 ^c (0.06)

^a (SD) = Standard Deviation

^b n.a. = not applicable. Treatment data were compared to the solvent control to determine effects for this endpoint

^c Significantly reduced compared to the solvent control, based on Dunnett's Multiple Comparison.

^d Significantly reduced compared to the solvent control, based on Steel's Many-One Rank Test. Due to the lack of statistical significance at treatment level (3.1 µg/l), the effects observed at the 0.50 and 1.3 µg/l treatment levels were determined to not be toxicant-related.

^e Due to the lack of statistical significance at treatment level (3.1 µg/l), the effect observed at the 1.3 µg/l treatment level was determined to not be toxicant-related.

^f Survival data did not meet the assumption fit a normal distribution normality, but did meet the assumption for homogeneity of variance. Therefore, survival data were evaluated using Wilcoxon's Test with Bonferroni's Adjustment (U.S. EPA, 2002), a non-parametric procedure, to establish treatment effects. This statistical analysis determined no significant difference in percent survival among daphnids exposed to any of the treatment levels tested compared to the pooled control data (i.e., 90%).

Table 38: NOEC data based on mean measured concentrations

Endpoint	NOEC (µg/l)
21-day survival	9.3
21-day reproduction	3.1
21-day total body length	3.1
21-day dry weight	0.50

The lowest study 21-day NOEC was 0.5 µg/l (equating to 0.0005 mg/l) based on total body dry weight. While statistical differences were observed between the 0.5 and 1.3 µg/l treatments and controls for parental body length, these were considered not due to the test substance due to a lack of clear dose-response. The UK CA notes that the resulting NOEC (0.21 µg/l), should such effects be taken into account, would be in the same 0.0001 to 0.001 mg/l range as the quoted study NOEC for the purpose of classification.

5.4.3 Algae and aquatic plants

Algae:

An algal growth inhibition study (Softcheck, 2011a) using S-1563 and *Pseudokirchneriella subcapitata* is available following GLP and OECD Guideline 201. Exposure solutions were prepared with the aid of the solvent DMF (dimethylformamide) and a solvent control was included.

The nominal exposure range was 0.19, 0.38, 0.75, 1.5, 3 and 6 mg/l. Analytical measurement was determined using GC/ECD. Results were based on time-weighted average measured values: 0.17, 0.33, 0.64, 1.3, 2.6 and 4.8 mg/l. Validity criteria were met and test is considered reliable.

At 72 hours 21% growth inhibition was observed at the highest exposure concentration meaning the E_rC_{50} was considered >4.8 mg/l. The 72-hour NOE_rC was determined to be 0.33 mg/l.

Aquatic plants:

A 7-day toxicity to *Lemna gibba* study (Softcheck, 2011b) using S-1563 is available following GLP and OECD Guideline 221. Exposure solutions were prepared with the aid of the solvent DMF and a solvent control was included. The nominal exposure range was 0.38, 0.75, 1.5, 3 and 6 mg/l. Analytical measurement was determined using GC/ECD. Results were based on time-weighted average measured values: 0.26, 0.53, 1, 1.9, and 2.5 mg/l. Validity criteria were met and test is considered reliable. The study endpoints were percentage reduction in frond density, dry weight biomass, growth rate based on frond density, yield and growth rate based on dry weight.

At 7 days, the percentage inhibition of growth rate based on frond density and dry weight was 4 and 5 % respectively at the highest exposure concentration of 2.5 mg/l. Therefore, the E_rC_{50} was considered >2.5 mg/l. As no significant reduction compared to controls was observed, the 7-day growth NOE_rC is considered to be ≥ 2.5 mg/l.

5.4.4 Other aquatic organisms (including sediment)

No aquatic exposure data available.

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

For the purpose of classification, 1R-trans-Z-momfluorothrin is considered not rapidly degradable.

1R-trans-Z-momfluorothrin has log Kow values below 4. In a fish bioaccumulation study 1R-trans-Z-momfluorothrin was extensively metabolised resulting in a BCF below 500.

Aquatic acute toxicity data are available for fish, invertebrates, algae and aquatic plants. Fish and invertebrates are the most sensitive trophic group with $L(E)C_{50}$ values in the range 0.001 to 0.01 mg/l. The lowest value is a 96-h LC_{50} of 0.0012 mg/l for fish. 1R-trans-Z-momfluorothrin should be classified as Aquatic Acute 1 with an M factor of 100.

Chronic toxicity data are available for fish, invertebrates, algae and aquatic plants. The lowest value is a 21-day NOEC for *Daphnia magna* of 0.0005 mg/l. Given this is the range 0.0001 to 0.001 mg/l, 1R-trans-Z-momfluorothrin should be classified as Aquatic Chronic 1 with an M factor of 100. The UK CA notes that while acute LC_{50} values are available for three fish species, the species used for the single chronic fish test did not reflect the most sensitive fish species resulting in a chronic NOEC greater than the LC_{50} values for two fish species. On this basis, it is appropriate to consider the surrogate approach for chronic toxicity to fish. This also results in a classification of Aquatic Chronic 1 with an M factor of 100. The UK CA notes that 1R-trans-Z-momfluorothrin is an insecticide and data are not available for this class of invertebrates. Therefore, it is possible that more stringent M factors may be applicable if such data were to be available in the future.

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

Aquatic Acute 1; H400: Very toxic to aquatic life

Acute M factor = 100

Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects

Chronic M factor = 100

6 OTHER INFORMATION

None.

7 REFERENCES

Physico-chemical properties

Author(s)	Year	Title.
Moseley, R. H.	2011a	S-1563PAI: Determination of melting/boiling point. Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, HG3 1PY, UK. Report No. 8243288 [Sumitomo Ref: RWP-0015] GLP Unpublished
Moseley, R. H.	2011b	S-1563RTZ: Determination of melting/boiling point. Covance Laboratories Ltd., Otley Road, Harrogate, North Yorkshire, HG3 1PY, UK. Report No. 8226992 [Sumitomo Ref: RWP-0017] GLP Unpublished
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8 ANNEXES

Annex I: An Evaluation of the Human Relevance of S-1563-induced Liver Tumours in Rats Based on Mode of Action