Committee for Risk Assessment

RAC

Annex 1

Background document

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

imiprothrin (ISO); reaction mass of: [2,4-dioxo-(2-propyn-1-yl)imidazolidin-3-yl]methyl(1R)-cis-chrysanthemate; [2,4-dioxo-(2-propyn-1-yl)imidazolidin-3-yl]methyl(1R)-trans-chrysanthemate

EC Number: 428-790-6
CAS Number: 72963-72-5

CLH-O-0000001412-86-197/F

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

Adopted

9 March 2018

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Imiprothrin

EC Number: **428-790-6**

CAS Number: **72963-72-5**

Index Number: **613-259-00-5**

Contact details for dossier submitter: **UK Competent Authority**

Chemicals Regulation Directorate

Health and Safety Executive

United Kingdom

Version number: **2** **Date:** **February 2016**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON IMIPROTHRIN (ISO); REACTION MASS OF: [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

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Part A.

Part B.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Imiprothrin***
EC number:	***428-790-6***
CAS number:	***72963-72-5***
Annex VI Index number:	***613-259-00-5***
Degree of purity:	***≥ 87%***
Impurities:	***There are a number of process impurities. These have been taken into account and are not considered to individually impact on the proposed classification. Refer to Part B – section 1.***

1.2 Harmonised classification and labelling proposal

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

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Acute Tox. 4*; H302: Harmful if swallowed Aquatic Acute 1; H400: Very toxic to aquatic life Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects
Current proposal for consideration by RAC	Acute Tox. 4; H302: Harmful if swallowed Acute Tox. 4; H332: Harmful if inhaled Repr. 2; H361d: Suspected of damaging the unborn child Aquatic Acute 1; H400: Very toxic to aquatic life Acute M-factor = 10

	Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects Chronic M-factor = 10
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 4; H302: Harmful if swallowed Acute Tox. 4; H332: Harmful if inhaled Repr. 2; H361d: Suspected of damaging the unborn child Aquatic Acute 1; H400: Very toxic to aquatic life Acute M-factor = 10 Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects Chronic M-factor = 10

1.3 Proposed harmonised classification and labelling

Table 3: Proposed classification

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON IMIPROTHRIN (ISO); REACTION MASS OF: [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

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 applicable	Not classified	Not considered in this proposal
2.2.	Flammable gases	-	Not applicable	Not classified	Not considered in this proposal
2.3.	Flammable aerosols	-	Not applicable	Not classified	Not considered in this proposal
2.4.	Oxidising gases	-	Not applicable	Not classified	Not considered in this proposal
2.5.	Gases under pressure	-	Not applicable	Not classified	Not considered in this proposal
2.6.	Flammable liquids	-	Not applicable	Not classified	Not considered in this proposal
2.7.	Flammable solids	-	Not applicable	Not classified	Not considered in this proposal
2.8.	Self-reactive substances and mixtures	-	Not applicable	Not classified	Not considered in this proposal
2.9.	Pyrophoric liquids	-	Not applicable	Not classified	Not considered in this proposal
2.10.	Pyrophoric solids	-	Not applicable	Not classified	Not considered in this proposal
2.11.	Self-heating substances and mixtures	-	Not applicable	Not classified	Not considered in this proposal
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	Not applicable	Not classified	Not considered in this proposal
2.13.	Oxidising liquids	-	Not applicable	Not classified	Not considered in this proposal
2.14.	Oxidising solids	-	Not applicable	Not classified	Not considered in this proposal
2.15.	Organic peroxides	-	Not applicable	Not classified	Not considered in this proposal
2.16.	Substance and mixtures corrosive to metals	-	Not applicable	Not classified	Not considered in this proposal
3.1.	Acute toxicity - oral	**Acute Tox. 4; H302: Harmful if swallowed**	Not applicable	Acute Tox. 4*; H302: Harmful if swallowed	-
	Acute toxicity - dermal	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

	Acute toxicity - inhalation	**Acute Tox. 4; H332: Harmful in inhaled**	Not applicable	Not classified	-
3.2.	Skin corrosion / irritation	-	Not applicable	Not classified	Not considered in this proposal
3.3.	Serious eye damage / eye irritation	-	Not applicable	Not classified	Not considered in this proposal
3.4.	Respiratory sensitisation	-	Not applicable	Not classified	Not considered in this proposal
3.4.	Skin sensitisation	-	Not applicable	Not classified	Not considered in this proposal
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	**Repr. 2; H361d: Suspected of damaging the unborn child**	Not applicable	Not classified	-
3.8.	Specific target organ toxicity –single exposure	Not classified	Not applicable	Not classified	Conclusive but not sufficient for classification
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 applicable	Not classified	Not considered in this proposal
4.1.	Hazardous to the aquatic environment	**Aquatic Acute 1; H400: Very toxic to aquatic life** **Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects**	**Acute M-factor = 10** **Chronic M-factor = 10**	Aquatic Acute 1; H400: Very toxic to aquatic life Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects	-
5.1.	Hazardous to the ozone layer	-	Not applicable	Not classified	Not considered in this proposal

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

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON IMIPROTHRIN (ISO); REACTION MASS OF: [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

Labelling:

Pictogram(s):	GHS07, GHS08, GHS09	
Signal word:	Warning	
Hazard statements:	H302+H332:	Harmful if swallowed or if inhaled
	H361d:	Suspected of damaging the unborn child
	H410:	Very toxic to aquatic life with long lasting effects
Precautionary statements:	Not included in Annex VI	

Proposed notes assigned to an entry: None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Imiprothrin is a biocidal active substance and has been reviewed under Regulation EU/528/2012 with the UK as the Rapporteur Member State (RMS). The substance was originally notified in the UK under Directive 67/548/EEC (DSD) (notification number 99-06-1196). As a result of this notification, the substance was considered for inclusion in Annex I to DSD with the classification and labelling agreed at the 16th Working Group of the Classification and Labelling of New Notified Substances (the classification for human health was agreed via written procedure in the 13th sending). The substance was included in the 30th ATP to DSD and added to Annex VI of CLP at the 1st ATP. This proposal seeks to amend the existing entry in Annex VI of CLP; to take account of data that do not appear to have been considered during the original discussions on classification and labelling, and to confirm the existing classification that was derived by translation from DSD.

2.2 Short summary of the scientific justification for the CLH proposal

Imiprothrin is a biocidal active substance used for controlling insects such as cockroaches and other crawling insects. Imiprothrin was found to be of low acute toxicity by the dermal route and therefore no classification is proposed for acute toxicity following this route of exposure. **Acute Tox. 4; H302 (Harmful if swallowed)** is proposed in this CLH report on the basis of an LD_{50} value of 550 mg/kg bw in female mice. Additionally, **Acute Tox. 4; H332 (Harmful if inhaled)** is proposed based on LC_{50} values of 1-8-2.2mg/L (males) and 1.4-1.8 mg/L (females).

Skin irritation, eye irritation, respiratory irritation, corrosivity, skin sensitisation and respiratory sensitisation were not considered in this proposal.

The liver, salivary gland and red blood cells were identified to be target organs in repeated dose studies. However, in the absence of confirmatory histopathological observations at doses lower than the guidance values, the effects are not considered to warrant classification. Clinical signs characteristic of neurotoxicity observed in the repeated dose inhalation study in rats are considered to be covered by the classification for acute inhalation toxicity.

Imiprothrin was not considered to be mutagenic. Low incidences of tumours observed in carcinogenicity studies in rats and mice were not considered to warrant classification. Therefore, no classification is proposed for these hazard classes.

In a two generation study in rats, there were no adverse effects on fertility parameters. The main effects observed in a developmental toxicity study in rats included increased incidences of lumbar rib, pre-sacral vertebrae, splitting of the vertebral body and increased numbers of thymic remnants in the neck. In a rabbit developmental study, fusion of the nasal bone, which is considered to be a malformation, was observed at the top dose. In addition, increased incidences of hypoplasia of the frontal bone and 27 pre-sacral vertebrae were observed. In both species, the effects occurred mainly at maternally toxic doses. However, there is a cause for concern for craniofacial development in rabbits and it cannot be unequivocally demonstrated that the developmental effects were secondary to maternal toxicity. Therefore, it is proposed that the criteria for classification as **Repro Tox. 2; H361d: Suspected of damaging the unborn child** are met.

The available degradation information does not provide sufficient data to show that imiprothrin is ultimately degraded within 28 days (equivalent to a half-life < 16 days) or transformed to non-classifiable degradants. Consequently, imiprothrin is considered non-rapidly degradable for the purpose of classification and labelling. The $\log K_{ow}$ is considered to be below the CLP $\log K_{ow}$ trigger value of ≥ 4 and the whole fish BCF for imiprothrin (or total radioactive residues (TRR)) is below the CLP trigger of ≥ 500 intended to identify substances with a potential to bioaccumulate.

Aquatic acute toxicity data on imiprothrin are available for fish, invertebrates and algae. Acute endpoints for fish and invertebrates lie in the range 0.01 to 0.1 mg/l. The lowest acute value is a 96-h LC_{50} of 0.038 mg/l for Rainbow trout. On this basis imiprothrin should be classified as **Aquatic Acute 1; H400 – Very toxic to aquatic life, with an acute M-factor of 10**.

Chronic toxicity data on imiprothrin for fish and invertebrates are not available. A chronic 72-h NOE_rC of 1.3 mg/l for algae would not result in an Aquatic Chronic classification. However, algae are not the most acutely sensitive trophic level. Adopting the surrogate approach using available acute fish and invertebrate data for a non-rapidly degradable substance would result in imiprothrin being classified as **Aquatic Chronic 1; H410 – Very toxic to aquatic life with long lasting effects, with a chronic M-factor of 10**.

2.3 Current harmonised classification and labelling

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

The current harmonised classification for imiprothrin in Annex VI to the CLP Regulation is:

Acute Tox. 4*, H302; Harmful if swallowed

Aquatic Acute 1, H400; Very toxic to aquatic life

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

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling

The information form the C&L Inventory at the time of submission is tabulated below:

Classification		**Labelling**	
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**
Acute Tox. 4	H302	H302	GHS07 GHS09 Wng
Aquatic Acute 1	H400		
Aquatic Chronic 1	H410	H410	

From 27 notifications.

RAC general comment
The Dossier Submitter (DS) proposed the classification of imiprothrin, a synthetic pyrethroid insecticide, for acute toxicity (oral, inhalation), reproductive toxicity (developmental toxicity) and hazard to the aquatic environment. Studies on acute toxicity (dermal), mutagenicity, carcinogenicity, reproductive toxicity (fertility) and STOT (single and repeated exposure) were also made available and assessed. However, the DS considered that the results for these latter hazard classes were conclusive, but not sufficient for classification.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Imiprothrin is a biocide active substance in the scope of the Biocidal Products Regulation (EU/528/2012). As imiprothrin already has an existing entry in Annex VI of CLP, this proposal is targeted to confirm the existing classification and to take account of additional information.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

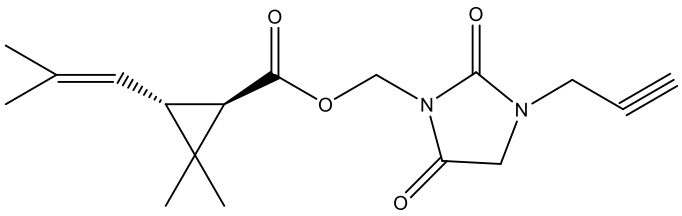
1.1 Name and other identifiers of the substance

Table 4: Substance identity

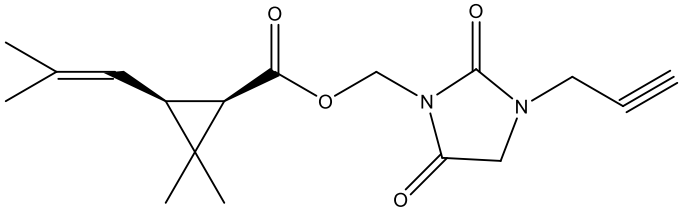
EC number:	428-790-6
EC name:	Reaction mass of: [2,4-dioxo-(2-propyn-1-yl)imidazolidin-3-yl]methyl(1R)-cis-chrysanthemate; [2,4-dioxo-(2-propyn-1-yl)imidazolidin-3-yl]methyl(1R)-trans-chrysanthemate* It is noted that the current name in the EC Inventory is [2,4-dioxo-(2-propyn-1-yl)imidazolidin-3-yl]methyl(1R)-trans-chrysanthemate
CAS number (EC inventory):	Not given
CAS number:	72963-72-5
CAS name:	Cyclopropanecarboxylicacid, 2,2-dimethyl-3-(2-methyl-1-propen-1-yl)-,[2,5-dioxo-3-(2-propyn-1-yl)-1-imidazolidinyl] methyl ester
IUPAC name:	Reaction mass of: 2,5-dioxo-3-prop-2-ynylimidazolidin-1-ylmethyl (1R)-cis-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; 2,5-dioxo-3-prop-2-ynylimidazolidin-1-ylmethyl (1R)-trans-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate (ca 20:80).[#]
CLP Annex VI Index number:	613-259-00-5
Molecular formula:	$C_{17}H_{22}N_2O_4$
Molecular weight range:	318.37

[#] Name in CAR

Structural formula:



Imiprothrin 1R-*trans* isomer



Imiprothrin 1R-cis *isomer*

1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Imiprothrin	≥ 87%		c.a. 80:20 Imiprothrin 1R-*trans* isomer *:* Imiprothrin 1R-*cis* isomer See IUCLID for full details

Current Annex VI entry:

Acute Tox. 4*; H302: Harmful if swallowed

Aquatic Acute 1; H400: Very toxic to aquatic life

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

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Confidential - Refer to IUCLID and confidential Annex I			

There are a number of 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 technical IUCLID dossier and the confidential Annex (Annex I) to this report.

Current Annex VI entry: One of the impurities is listed in Annex VI of CLP. However, taking account of the classification, the concentration at which this impurity is present and the available data on imiprothrin, this impurity is not considered to impact on the proposed classification for the active substance. Refer to Annex I (confidential) and the IUCLID for details on this impurity.

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
None				

Current Annex VI entry: N/A

1.2.1 Composition of test material

The material used in the studies is considered to be equivalent to that outlined above. However, it should be noted that the purity of the tested batches (as reported in the study summaries from the applicant), refers to the sum of all 4 possible isomers. In a number of cases the manufacturing use product (MUP) was tested and where this is the case it is indicated in the CLH report. The MUP contains 50% imiprothrin in isopropyl myristate.

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	Clear (amber) viscous liquid	Wojcieck BC (1993c) Doc IIIA A3.3.1	Purity 92.9%
Melting/freezing point	25ºC	Evans A J, Mullee D M. (2002) Doc IIIA A3.1.1	Method: 92/69/EEC, A1 (pour point) Purity 94%
Boiling point	Decomposes at 128 ºC at 746mmHg	Wojcieck BC (1993a) Doc IIIA A3.1.2	Method ASTM D 1120-89 The method involved boiling the test material in a round-bottom flask, with the boiling point compared to that of a standard material, toluene – considered a scientifically valid method.
Relative density	1.122	Wojcieck BC (1993b) Doc IIIA A3.1.3	Method: 92/69/EEC, A3 (Capillary pycnometry) Purity 92.9%
Vapour pressure	1.86 x 10^{-6} Pa at 25ºC 1.15 x 10^{-5} Pa at 35 ºC 9.64 x 10^{-5} Pa at 45 ºC	Lorence PJ (1996a) Doc IIIA A3.2	92/69EEC, A4 (Gas saturation method) Purity 92.9%
Surface tension	46.6 mN/m at 21 ºC	Betteley J.M.T. (1997) Doc IIIA A3.13	92/69/EEC, A5 OECD (harmonised ring method) Purity 91.6%
Water solubility	0.0935g/L at 25ºC and pH6.5	Lorence PJ (1994b) Doc IIIA A3.5	92/69/EEC, A6 (Shake flask method) Purity 92.9%
Partition coefficient n-octanol/water	2.9 at 25ºC and pH 6.2-6.6	Lorence PJ (1994d) Doc IIIA A3.9	92/69/EEC, A8 (Shake flask method) Purity 99.7% Since there are no ionisable moieties associated with S-41311, a change in pH will have no effect on the octanol:water coefficient.

Flash point	141ºC at 997 mbar	Betteley J.M.T. (1997) Doc IIIA A3.12/01	92/69/EEC, A9 Non-equilibrium method using closed cup as ASTM D93-80 Purity 91.6% A thermocouple was used in place of a thermometer. A blue halo was observed around the test flame at 121 ºC.
Explosive properties	Not explosive	Betteley J.M.T (1997) Doc IIIA A3.15	92/69/EEC, A14 Purity 91.6%
Self-ignition temperature	Auto-ignition temperature 359ºC	Betteley J.M.T. (1997) Doc IIIA A3.11	92/69/EEC, A15 ASTM-E659-78 Purity 91.6%
Oxidising properties	The substance has no functional groups which are capable of exhibiting oxidative capacity.	Wojcieck BC (1993e) Doc IIIA A3.16	-
Stability in organic solvents and identity of relevant degradation products	Stable over 1 year Mean % active ingredient in each of the 3 lots at: Zero time: 50.9, 50.8 and 50.3% 3 months: 50.3, 50.4 and 50.6% 6 months: 50.5, 50.5 and 50.5% 12 months: 50.7, 50.9 and 50.9%	Furuta R., Okada Y. (1995a) Doc IIIA A3.9	US EPA Guidelines, subdivision D, 63-17. Purity 50% MUP
Dissociation constant	No measurable dissociation constant could be obtained. Imiprothrin does not dissociate.	Furuta R (1995) Doc IIIA A3.6	OECD 112 (spectroscopic method) Purity 99.5%
Viscosity	**Dynamic viscosity** 59 centipose at 3 rpm, 60 centipose at 6 rpm, 60 centipose at 12 rpm **Temperature:** 25 ± 0.2ºC	Wojcieck BC (1993d) Doc IIIA A3.14	OECD 114 (Brookfield rotational viscometer) Purity 50% MUP

2 MANUFACTURE AND USES

2.1 Manufacture

Imiprothrin is produced outside of the EU for use as an insecticide.

2.2 Identified uses

Imiprothrin is an insecticide for use in pest control (product type 18 of the EU Biocidal Products Directive). Products containing imiprothrin are intended for use in insecticide formulations for controlling insects such as cockroaches and other crawling insects (e.g. bedbugs and cat fleas).

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Please refer to Table 8.

3.1 Physico-chemical Properties

3.1.1 Conclusions on classification and labelling

Physico-chemical properties are not considered further in this proposal.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

This information has been extracted from the draft Competent Authority Report (CAR) (2016) prepared by the UK under the Biocidal Product Regulation (EU/528/2012).

The toxicokinetics of imiprothrin has been investigated *in vivo* in rats by the oral route following single and multiple dosing of both the 1R-*trans* isomer and 1R-*cis* isomer. There was no great variation in the toxicokinetic profiles of the two isomers. No dermal penetration studies have been conducted with technical imiprothrin. However, the absorption of imiprothrin from a 1 % w/v formulation (in ethanol) has been investigated *in vitro* with human and pig skin.

Absorption

Imiprothrin is extensively absorbed following oral exposure and an absorption value of 100% was derived for this route. The only dermal absorption data available are for an ethanolic formulation containing 1% (w/v) imiprothrin for which a value of 5% is derived for human skin *in vitro*.

There are no data on absorption following inhalation exposure to imiprothrin. However, as the two isomers are almost completely absorbed from the gastrointestinal tract, it is predicted that imiprothrin will also be well absorbed from the respiratory tract. Therefore, a default value of 100% absorption following inhalation exposure has been proposed for use in the risk characterisation.

Distribution

The data suggest that imiprothrin is widely distributed and that no significant bioaccumulation (based on the speed of excretion) is expected to occur.

Following oral dosing of radiolabelled imiprothrin isomers, absorbed radioactivity is widely distributed to a range of organs and tissues including fat, kidney, skin, blood cells and lung, with the liver being the site of greatest localisation. Only minimal levels were found in the brain and reproductive organs (testis, ovary, and uterus). Less than 1% of administered radioactivity was found in tissues, 168 h after dosing in both studies. The level of tissue residues did not vary significantly following repeated administration for 14 days.

Metabolism

Following absorption, extensive metabolism occurs and imiprothrin and/or its metabolites will be widely distributed. No parent molecule of either isomer was found in the urine and only a minor amount of un-metabolised material remained in the faeces. The main metabolic pathways involve the hydrolysis of the ester linkage, dehydroxymethylation of the resultant alcohols, hydroxylation of the imidazolidine ring, oxidation and dealkylation of the 2-propynyl group. The major urinary metabolite was PGH-OH (5-hydroxy-2,4-dioxo-1- (2-propynyl)-imidazolidine) followed by hydantoin. It can be concluded that imiprothrin is extensively metabolized, probably initially by hepatic cytochrome P450-catalysed reactions. The data indicate that the *trans*-isomer is more readily metabolised than the *cis*-isomer.

There is no specific information to establish whether imiprothrin undergoes first pass metabolism. However, the speed of clearance, the high percentage of metabolites present in the urine, the

observation of neurotoxicity after intra-peritoneal injection in mice not seen following oral dosing in acute and repeat-dose studies, and the fact that toxicity following inhalation exposures occurs at lower dose levels than following oral exposures, suggests extensive first pass metabolism does occur.

Excretion

Elimination of radiolabel was rapid following oral administration, with 79 – 90% of either isomer, appearing in urine within 24 h. By seven days post-administration, 83 – 86% of the ^{14}C-*cis*-imiprothrin dose had been excreted in the urine, 14 – 16% in faeces and approximately 1 – 3% in expired air. In ^{14}C-*trans*-imiprothrin treated animals, the percentage of administered radiolabel eliminated into urine was slightly higher (89 – 92%; indicating that this isomer may be more readily metabolised), 8 – 9% was eliminated in faeces and less than 1 % was detected in expired air.

4.1.2 Human information

Dermal penetration of imiprothrin through human skin *in vitro* has been studied with a nominal 1 % w/v (10g imiprothrin/l) concentration in an ethanol formulation over a 24 h exposure period. Results demonstrate that skin penetration potential is minimal. Analysis of receptor fluid sampled at 6, 8 and 10 hours from start of exposure showed that 0.31%, 0.40% and 0.54% of the applied radiolabel had penetrated through the skin, respectively. Over the 24 h exposure period, 1.44% of the applied radiolabel was present in the receptor fluid and 1.41 % in the skin below the stratum corneum. Tape stripping of the skin at the end of exposure showed that 1.70% of the applied radiolabel was retained within the stratum corneum.

4.1.3 Summary and discussion on toxicokinetics

Imiprothrin is extensively absorbed following oral and inhalation exposure and absorption values of 100 % are derived for these routes. The only dermal absorption data available are for an ethanol formulation containing 1% (w/v) imiprothrin for which a value of 5% is derived for human skin *in vitro*. Following absorption, extensive metabolism occurs and imiprothrin and/or its metabolites will be widely distributed. The data indicate that first pass metabolism does occur. Elimination is rapid and occurs predominantly via the urine.

4.2 Acute toxicity

Table 9: Summary table of relevant acute toxicity studies

Acute Oral		
Method	**LD_{50}**	**Observations and remarks**
Rat, (SD) - 5/sex/grp M: 500, 1000, 1400, 2000, 2800, 4000 mg/kg F: 500, 700, 1000, 1400, 2000, 2800 mg/kg Gavage Imiprothrin; 95.3% Vehicle: Corn oil US-EPA 81-1, comparable to OECD 401 GLP CAR Doc IIIA A6.1.1/01 Sumitomo Chemical Co. Ltd (1992a)	Males LD_{50} : 1800 mg/kg Females LD_{50} : 900 mg/kg	Mortality observed (f: ≥700mg/kg, m: ≥ 1000mg/kg) - All deaths occurred within 24 hours post dose. Abnormal signs beginning 30-60 minutes post dose: • Tremor (females at ≥ 700mg/kg, males at ≥1400mg/kg) • Decrease in spontaneous activity, (females at ≥ 700mg/kg, males at ≥ 1000mg/kg) • Excretion of oily substance (males at ≥ 1000mg/kg) • Urinary incontinence, • Stained fur (males), • Ataxic gait (females at ≥ 1400mg/kg, males at 2000 and 4000mg/kg) • Irregular respiration, • Prone position (females at 1400mg/kg, males at 2000 and 4000mg/kg) • Lateral position (females at 1400 and 2000mg/kg, males at 4000mg/kg) Clinical signs in surviving animals disappeared within 3 days.
Mouse CD-1 - 5/sex/grp 300, 380, 480, 600, 760, 950 mg/kg for both sexes Gavage Imiprothrin; 95.3% Vehicle: Corn oil US-EPA 81-1, comparable to OECD 401 GLP CAR Doc IIIA A6.1.1/02 Sumitomo Chemical Co. Ltd (1992b)	Males LD_{50} : 724 mg/kg Females LD_{50}: 550 mg/kg	Mortality observed (f: ≥480mg/kg, m: ≥ 760mg/kg) - All deaths occurred within 24 hours post dose, and were reported to be preceded by tremors and clonic convulsions. Abnormal signs beginning 30 minutes post dose: • Decrease in spontaneous activity (at ≥ 380 mg/kg, both sexes) • Tremor (females at ≥ 380 mg/kg, males at ≥ 480 mg/kg) • Excretion of oily substance (males), • Clonic convulsion (females at ≥ 480 mg/kg, excluding the 600mg/kg dose group) Clinical signs in surviving animals disappeared within 4 hours.

Acute Inhalation		
Method	**LC_{50}**	**Observations and remarks**
Rat, (SD) - 5/sex/grp 418 or 1200 mg/m^3 (m+f) 4-hour, whole body exposure Imiprothrin; 92.9% Vehicle: Corn oil Aerosol particle size: < 10µm (MMAD mean: 0.74-0.85µm) US-EPA 81-3, comparable to OECD 403 GLP CAR Doc IIIA A6.1.3/01 Sumitomo Chemical Co. Ltd (1991)	LC_{50} > 1200 mg/m^3 (m+f) Equivalent to 1.2 mg/l	No deaths occurred in either exposure group. During the exposure period, the animals could not be observed in detail because of the high concentration of the mist. • Irregular respiration, • Dark red stain around the nose, • Wet fur, • Exaggerated startle response (at 1200mg/m^3) • Tip toe gait (at ≥ 418mg/m^3, both sexes) • Loss of abdominal and sub-mandibular hair in females. • Ataxic gait (females at ≥ 418mg/m^3, males at 1200mg/m^3) Only the hair loss was present at study termination.
Acute Dermal		
Method	**LD_{50}**	**Observations and remarks**
Rat, (SD) - 5/sex/grp 2000 mg/kg Imiprothrin; 95.3% Vehicle: Corn oil Area covered - 30cm^2 Semi-occlusive, 24h US-EPA 81-2, comparable to OECD 402 GLP CAR Doc IIIA A6.1.2/01 Sumitomo Chemical Co. Ltd (1992e)	LD_{50} > 2000 mg/kg (m+f)	No deaths No clinical signs of toxicity

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Two guideline acute oral toxicity studies are available; 1 in rats and 1 in mice. Deaths were observed in both studies. All deaths occurred within 24 hours post dose.

In the first study, Sprague-Dawley rats (5/sex/group) were exposed to imiprothrin in corn oil by gavage. At a dose of 500mg/kg, no abnormal signs were observed. Deaths in females were reported at ≥700mg/kg. In males, death was reported at ≥1000mg/kg. Observations of abnormal clinical signs included tremor, a decrease in spontaneous activity, excretion of an oily substance, urinary incontinence, stained fur, ataxic gait, prone position, lateral position and irregular respiration.

The animals that died during the observation period showed retention of an oily substance in the stomach and autolysis of the intestine. In surviving animals, no treatment-related gross pathological changes were observed.

The LD_{50} value was 1800mg/kg in males and 900 mg/kg in females.

In the mouse study, CD-1mice (5/sex/group) were exposed to imiprothrin in corn oil by gavage. No abnormal signs were observed at 300mg/kg. Deaths were reported at ≥480mg/kg in females and at ≥760mg/kg in males. All deaths were reported to be preceded by tremors and clonic convulsions. Abnormal clinical signs observed in this study included a decrease in spontaneous activity, tremor, excretion of an oily substance and clonic convulsion. In surviving animals, these clinical signs disappeared within 4 hours. There were no significant treatment-related macroscopic findings at necropsy.

The animals that died during the observation period showed retention of an oily substance in the stomach and autolysis of the intestine.

The LD_{50} value was 725mg/kg in males and 550mg/kg in females.

4.2.1.2 Acute toxicity: inhalation

One guideline acute inhalation toxicity study in rats is available.

Sprague-Dawley rats (5/sex/group) were exposed (whole body) to aerosolised imiprothrin at a concentration of 418mg/m^3 or 1200mg/m^3 (equivalent to 0.418mg/L and 1.2mg/L respectively) for four hours. The mass median aerodynamic diameter (MMAD) was 0.74-0.85 µm.

No deaths were recorded in this study. Although the animals could not be observed in detail during the exposure period due to the high concentration of the mist, some abnormal signs were observed and reported. At both 418mg/m^3 and 1200mg/m^3, the rats has a dark red stain around the nose, wet fur, and their respiration was irregular. These signs disappeared after between 1 and 8 days post dose.

At 1200mg/m^3, the animals exhibited an exaggerated startle response, tip toe gait and loss of abdominal and sub-mandibular hair in females. Of these, only the hair loss was present at study termination.

There were no significant macroscopic or microscopic findings noted at necropsy.

The LC_{50} was established as being >1.2mg/L for both males and females.

4.2.1.3 Acute toxicity: dermal

One guideline acute dermal toxicity study in rats is available.

Sprague-Dawley rats (5/sex/group) were exposed to a single application of imiprothrin in corn oil at 2000 mg/kg. The area of exposure was covered with a semi-occlusive dressing for 24 hours and the animals were subsequently observed for 14 days.

No deaths or clinical signs of toxicity were reported. The LD_{50} was > 2000 mg/kg bw for both sexes.

4.2.1.4 Acute toxicity: other information

Four further acute toxicity studies are available. In these studies, the test material was the Manufacturing Use Product (MUP); a 50:50 w/w mixture of imiprothrin and isopropyl myristate.

Table 10: Summary of relevant acute toxicity studies with the MUP

Acute Oral		
Method	**LD_{50}**	**Observations and remarks**
Rat, (SD) - 5/sex/grp M: 1000, 2000, 3200, 4000, 5000 mg/kg F: 1000, 2000, 2600, 3200, 4000 mg/kg Gavage S-41311 MUP (50:50 w/w mixture of imiprothrin and isopropyl myristate) Purity – Not stated US-EPA 81-1, comparable to OECD 401 GLP CAR Doc IIIA A6.1.1/03 Sumitomo Chemical Co. Ltd (1992c)	Males LD_{50}: 4500 mg/kg (equivalent to **2250 mg/kg** imiprothrin) Females LD_{50}: 2400 mg/kg (equivalent to **1200 mg/kg** imiprothrin)	Mortality observed - All deaths occurred within 24 hours post dose. Abnormal signs beginning 30-60 minutes post dose: • Decreased spontaneous activity (at ≥2000mg/kg, both sexes, excluding females at 3200mg/kg) • Tremor (at ≥2000mg/kg, both sexes, excluding the 4000mg/kg dose group) • Prone position (females at ≥2000mg/kg, excluding the 2600mg/kg dose group, males at ≥ 4000mg/kg) • Ataxic gait (females at 2000 and 3200mg/kg, males at 2000, 3200, 4000 and 5000mg/kg) • Irregular respiration (females), • Blotted fur, • Urinary incontinence • Lateral position (females at ≥3200mg/kg), • Clonic convulsion (females at 4000mg/kg, males at 5000mg/kg) The duration of clinical signs in surviving animals administered 3200 mg/kg was not stated. At all other doses, clinical signs in surviving animals disappeared within 3 days.
Mouse CD-1 - 5/sex/grp 500, 680, 910, 1230, 1660, 2240 mg/kg for both sexes Gavage S-41311 MUP (50:50 w/w mixture of imiprothrin and isopropyl myristate) Vehicle: Corn oil Purity - Not stated US-EPA 81-1, comparable to OECD 401 GLP CAR Doc IIIA A6.1.1/04	Males LD_{50} : 1350 mg/kg (equivalent to **675 mg/kg** imiprothrin) Females LD_{50}: 1300 mg/kg (equivalent to **650 mg/kg** imiprothrin)	Mortality observed - All deaths occurred within 24 hours post dose. Abnormal signs beginning 30 minutes post dose: • Decreased spontaneous activity (at ≥ 680mg/kg, both sexes, excluding females at 2240mg/kg) • Tremor (females at ≥ 680mg/kg, males at ≥ 910mg/kg) • Prone position (males at 910mg/kg) • Clonic convulsions (males at ≥ 910mg/kg, females at ≥ 1230 mg/kg) • Irregular respiration, • Excretion of oily substance (males), • Ataxic gait (males at ≥ 1660 mg/kg, females at 1660mg/kg)

Sumitomo Chemical Co. Ltd (1992d)		Clinical signs in surviving animals disappeared within 1 day.
Acute Inhalation		
Method	**LC_{50}**	**Observations and remarks**
Rat, (SD) - 5/sex/grp 2810, 3620, 4430 mg/m^3 (m+f) 4-hour, whole body exposure S-41311 MUP (50:50 w/w mixture of imiprothrin and isopropyl myristate) Purity - Not stated Aerosol particle size: < 10µm (MMAD: 3.19 - 3.75 µm) US-EPA 81-3, comparable to OECD 403 GLP CAR Doc IIIA A6.1.3/02 Sumitomo Chemical Co. Ltd (1993)	Males LC_{50} : 3620- 4430 mg/m^3 equivalent to 3.6-4.4 mg/l Equivalent to **1.8-2.2mg/L** imiprothrin Females LC_{50} : 2810 - 3620 mg/m^3 equivalent to 2.8-3.6 mg/l Equivalent to **1.4-1.8 mg/L** imiprothrin	Mortality observed. Time range of death was 4 hours – 1 day. Abnormal clinical signs: • Muscular fibrillation (males at 2810 mg/m^3, females at 2810 and 3620mg/m^3) • Irregular respiration (observed after termination of exposure to doses ≥ 2810 mg/m^3) • Lacrimation, • Nasal discharge, • Red substance attaching around the snout (males), • Salivation, • Urinary incontinence, • Ataxic gait (observed after termination of exposure to 2810 and 3620 mg/m^3) • Tip toe gait (observed after termination of exposure to 2810 and 3620 mg/m^3) • Ocular discharge, • Wet fur, • Decrease in spontaneous activity (observed after termination of exposure to 2810 mg/m^3) • Tremor (some females at 3620 mg/m^3) • Hypersensitivity (males after termination of exposure to 3620mg/m^3), Clinical signs in surviving animals had disappeared by Day 7. During the exposure period at **4430 mg/m^3**, precise clinical observations could not be made due to the dense aerosol mist generated. The one animal (male) surviving after exposure exhibited: • Muscular fibrillation, • Ataxic gait, • Bradypnea, • Wet fur, • Closed eyelids, • Salivation, • Urinary incontinence. This animal was found dead on day 1.

Acute Dermal		
Method	**LD_{50}**	**Observations and remarks**
Rat,(SD) - 5/sex 2000 mg/kg S-41311 MUP (50:50 w/w mixture of imiprothrin and isopropyl myristate) Area covered – 50cm^2 Semi-occlusive, 24h Purity – Not stated US-EPA 81-2, comparable to OECD 402 GLP CAR Doc IIIA A6.1.2/02 Sumitomo Chemical Co. Ltd (1992f)	LD_{50} > 2000 mg/kg (m+f) Equivalent to >1000mg/kg imiprothrin	No deaths No clinical signs of toxicity No treatment-related gross pathological changes

The observations and LD_{50} values from the oral and dermal acute toxicity studies using MUP are consistent with those that used imiprothrin as the test substance.

Inhalation

In the inhalation study, Sprague Dawley rats (5/sex/group) were exposed (whole body) to aerosolised S-41311 (MUP) undiluted test substance at a concentration of 2810 mg/m^3, 3620 mg/m^3 or 4430 mg/m^3 (equivalent to 2.81mg/L, 3.62mg/L and 4.43mg/L respectively) for four hours.

Deaths were reported in both males and females at doses ≥ 2810 mg/m^3. At 4430 mg/m^3, all animals died, but it was not possible to make precise clinical observations during the exposure period due to the dense aerosol mist generated. At lower doses, the following abnormal signs were noted: muscular fibrillation, irregular respiration, lacrimation, nasal discharge, a red substance around the snout, salivation, urinary incontinence, ataxic gait, tip top gait, wet fur, ocular discharge, tremor and hypersensitivity in males.

There were no significant treatment-related findings at necropsy.

The LC_{50} was established as being 3.6-4.4mg/L for males and 2.8–3.6mg/L for females, equivalent to 1.8-2.2mg/L and 1.4 -1.8mg/L imiprothrin for males and females, respectively.

4.2.2 Human information

There are no human data available.

4.2.3 Summary and discussion of acute toxicity

Acute toxicity studies via the dermal, oral and inhalation routes of exposure were conducted in rats and mice using imiprothrin and the MUP (Manufacturing Use Product).The MUP is a mixture (50% imiprothrin, 50% isopropyl myristate), rather than the neat substance. However, there is no indication that the results from the studies using the mixture gave an inaccurate reflection of the toxicity of imiprothrin. The LD_{50} values obtained in the oral and dermal acute toxicity studies with the MUP are consistent with the respective studies using imiprothrin. In the inhalation studies, the obtained LC_{50} values were >1.2mg/L with imiprothrin and 1.8-2.2mg/L (males) & 1.4-1.8mg/L (females) with MUP. As the study with MUP used higher concentrations of the test substance, it expands upon the available information from the imiprothrin acute inhalation study rather than contradicts it. The LC_{50} value of isopropyl myristate is very high (>33-41mg/L), indicating low acute toxicity. This value suggests that isopropyl myristate is highly unlikely to have contributed to the toxicity observed in the acute toxicity studies. As the toxicity seems to be driven by imiprothrin itself, it appears reasonable to consider the results of the studies using MUP as being relevant for classification.
Imiprothrin was found to be of low toxicity by the oral, inhalation and dermal routes following a single exposure in rats and mice, with LD_{50} = 550 – 2250mg/kg for the oral route, LC_{50} = 1200-4430 mg/m^3 for the inhalation route and LD_{50} > 1000mg/kg for the dermal route. Clinical signs in the oral and inhalation studies included ataxic gait, tremor, decreases in spontaneous activity urinary incontinence, and clonic convulsions. These are discussed further in section 4.3 (STOT SE).

4.2.4 Comparison with criteria

Via the oral route, the LD_{50} values ranged from 550-2250 mg/kg in rats and mice, with female mice being the most sensitive. A substance fulfils the criteria for classification in category 4 (oral) if $300 < LD_{50} \leq 2000$ mg/kg. Therefore, imiprothrin warrants a classification in category 4 via the oral route. Based on the lowest LD50 value obtained from the acute oral toxicity studies, an Acute Toxicity Estimate (ATE) value of 550 mg/kg is proposed.
Via the inhalation route, the LC_{50} of imiprothrin (neat) was found to be >1.2 mg/l in male and female rats. In rats exposed to the MUP LC_{50} values of 1-8-2.2 and 1.4-1.8 mg/L were noted in males and females, respectively. Whilst it is acknowledged that the data is derived from a mixture, the toxicity is considered to have been a result of imiprothrin itself rather than isopropyl myristate. These data are therefore considered to be acceptable for the purpose of classification. When $1.0 < LC_{50} \leq 5.0$ mg/L (dusts and mists), the substance meets the criteria for classification in Acute Tox. Cateogry 4 and therefore, imiprothrin should be classified for acute toxicity (inhalation) in category 4. On this basis, an Acute Toxicity Estimate (ATE) value of 1.4mg/L for the inhalation route (dusts and mists) is proposed.
The dermal LD_{50} value was found to be >2000mg/kg in a study in rats with neat imiprothrin and was > 1000 mg/kg with the MUP. A substance fulfils the criteria for classification in Category 4 when $1000 < LD_{50} \leq 2000$ mg/kg. Therefore, imiprothrin does not fulfil the criteria and should not be classified as being acutely toxic by the dermal route.

4.2.5 Conclusions on classification and labelling

Acute Tox 4; H302 + H332 - Harmful if swallowed or if inhaled

ATE oral = 550 mg/kg

ATE inhalation = 1.4 mg/L

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute toxicity studies via the dermal, oral and inhalation routes of exposure were conducted in rats and mice using imiprothrin and the MUP (Manufacturing Use Product).The MUP is a mixture (50% imiprothrin, 50% isopropyl myristate). The DS considered that the studies using the MUP could also be used to support the classification proposal given the low acute toxicity of isopropyl myristate. Similar LD_{50} values were obtained in the oral and dermal acute toxicity studies with the MUP and the pure substance imiprothrin.

In addition to the acute toxicity studies an acute neurotoxicity study with imiprothrin in rats was also available.

Acute oral toxicity

Acute Oral Studies with Imiprothrin

Rat study (Study SGT-20-0026, 1992)

In a GLP OECD TG 401 comparable study, SD rats (5/sex/group) were treated by gavage with imiprothrin in corn oil at dose levels of 500, 1000, 1400, 2000, 2800 or 4000 mg/kg bw (males) and 500, 700, 1000, 1400, 2000 or 2800 mg/kg bw (females). At a dose of 500 mg/kg bw, no abnormal signs were observed. Deaths in females were reported at ≥700 mg/kg bw. In males, death was reported at ≥1000 mg/kg bw. Observations of abnormal clinical signs included tremor, a decrease in spontaneous activity, excretion of an oily substance, urinary incontinence, stained fur, ataxic gait, prone position, lateral position and irregular respiration. The animals that died during the observation period showed retention of an oily substance in the stomach and autolysis of the intestine. In surviving animals, no treatment-related gross pathological changes were observed. The LD_{50} value was 1800 mg/kg bw in males and 900 mg/kg bw in females.

Mouse study (Study SGT-20-0028, 1992)

In a GLP OECD TG 401 comparable study, CD-1 mice (5/sex/group) were treated by gavage with imiprothrin in corn oil at dose levels of 300, 380, 480, 600, 760 or 950 mg/kg bw (both sexes). Clinical signs began 30 minutes after dosing and included decrease in spontaneous activity (at ≥380 mg/kg bw, males/females); tremors (females at ≥380 mg/kg bw, males at ≥480 mg/kg bw); excretion of oily substance (males); clonic convulsion (females at ≥480 mg/kg bw, excluding the 600 mg/kg bw dose group). All signs in surviving animals disappeared within 4 hours. Deaths were reported at ≥480 mg/kg bw in females and at ≥760 mg/kg bw in males. All deaths were reported to be preceded by tremors and clonic convulsions. The animals that died during the observation period showed retention of an oily substance in the stomach and autolysis of the intestine. The LD_{50} value was 724 mg/kg bw in males and 550 mg/kg bw in females.

Acute Oral Studies with MUP

Rat study (Study SGT-20-0030, 1992)

In a GLP OECD TG 401 comparable study, SD rats (5/sex/group) were treated by gavage with MUP at dose levels of 1000, 2000, 3200, 4000 or 5000 mg/kg bw (males) and 1000, 2000, 2600, 3200 or 4000 mg/kg bw (females). In the cases where mortality was observed it occurred 24 h post dosing. With all other doses except 3200 mg/kg bw the clinical signs in surviving animal disappeared within 3 days. Irregular respiration (females), blotted fur and urinary incontinence were observed. At doses ≥2000 mg/kg bw there was decrease in spontaneous activity, tremor, prone position (females). Ataxic gait was observed in females at 2000 and 3200 mg/kg bw, and in males at 2000, 3200, 4000 and 5000 mg/kg bw. When dosing at 4000 mg/kg bw (females) and 5000 mg/kg bw (males), clonic convulsion was observed. The LD_{50} value for MUP was 4500 mg/kg bw in males and 2400 mg/kg bw in females, equivalent to 2250 and 1200 mg/kg bw of imiprothrin, respectively.

Mouse study (Study SGT-20-0032, 1992)

In a GLP OECD TG 401 comparable study, CD-1 mice (5/sex/group) were treated by gavage with MUP at dose levels of 500, 680, 910, 1230, 1660 or 2240 mg/kg bw (both sexes). Clinical signs began 30 minutes after dosing and included decrease in spontaneous activity (at ≥680 mg/kg bw, males/females); tremors (females at ≥680 mg/kg bw, males at ≥910 mg/kg bw); prone position (males at 910 mg/kg bw); clonic convulsion (males at ≥910 mg/kg bw; females at ≥1230 mg/kg bw); irregular respiration; excretion of oily substance (males); ataxic gait (males at ≥1660 mg/kg bw, females at 1660 mg/kg bw). All signs in surviving animals disappeared within 1 day. The LD_{50} value for MUP was 1350 mg/kg bw in males and 1300 mg/kg bw in females, equivalent to 675 and 650 mg/kg bw of imiprothrin, respectively.

Acute Neurotoxicity Study with Imiprothrin

In a GLP compliant US-EPA 81-8 acute neurotoxicity study (Study SGT-51-0073, 1995), SD rats (4/sex/dose, replicated over 3 days) were treated by oral gavage with imiprothrin in corn oil at doses of 0, 200, 600 or 1000 mg/kg bw (males) and 0, 100, 300 or 1000 mg/kg bw (females). A few females in all treated group displayed flicking of the forelimbs. No structural changes to nervous system tissues were detected (neuropathology was conducted for the control and high dose animals). At 300 mg/kg bw (females only) fur staining along the ventral thoracic, abdominal and urogenital regions was observed. Tremors were noted in one female. At 600 mg/kg bw (males only) it was reported slight ataxic gait in one male. At 1000 mg/kg bw two females were reported dead. There was increase in tremors, wet muzzle and overall gait incapacity (females). Decrease in motor activity, arousal, body tone and extensor thrust (females) was reported. Slight tremors were noted in one male and slight ataxic gait was exhibited by one male. The LD_{50} was >1000 mg/kg bw for both sexes.

Conclusion

Taking all oral studies together, the DS concluded that imiprothrin should be classified as Acute Tox. 4; H302 (Harmful if swallowed) with an ATE value of 550 mg/kg on the basis of the lowest obtained LD_{50} value of 550 mg/kg bw in female mice.

Acute dermal toxicity

Acute Dermal Study with Imiprothrin

In a GLP OECD TG 402 comparable study (Study SGT-20-0027, 1992), SD rats (5/sex) were exposed to a single application of imiprothrin in corn oil at 2000 mg/kg bw. The area of exposure was covered with a semi-occlusive dressing for 24 hours and the animals were subsequently observed for 14 days. No deaths or clinical signs of toxicity were reported. The LD_{50} was >2000 mg/kg bw for both sexes.

Acute Dermal Study with MUP

In a GLP OECD TG 402 comparable study (Study SGT-20-0031, 1992), SD rats (5/sex) were exposed to a single application of MUP at 2000 mg/kg bw. The area of exposure was covered with a semi-occlusive dressing for 24 hours and the animals were subsequently observed for 14 days. No deaths or clinical signs of toxicity were reported. The LD_{50} was >2000 mg/kg bw for both sexes (equivalent to >1000 mg/kg bw imiprothrin).

Conclusion

The DS concluded that imiprothrin does not fulfil the criteria and should therefore not be classified for acute toxicity following the dermal route of exposure.

Acute inhalation toxicity

Acute Inhalation Study with Imiprothrin

In a GLP OECD TG 403 comparable study (Study SGT-10-0003, 1991), SD rats (5/sex/group) were exposed (whole body) to aerosolised imiprothrin in corn oil at a concentration of 418 or 1200 mg/m^3 (equivalent to 0.418 and 1.2 mg/L, respectively) for four hours. The mass median aerodynamic diameter (MMAD) was 0.74-0.85 µm. No animals died during the study. No detailed observation of the animals was possible during the extent of the test due to the density of the mist caused by the aerosol. Nevertheless, signs of irregular respiration, dark red staining around the nose and wet fur were noted. These signs disappeared between 1 and 8 days post dose. At 1200 mg/m^3, the animals exhibited an exaggerated startle response, tip toe gait and loss of abdominal and sub-mandibular hair in females. At study termination the only reported clinical observation was the hair loss. No significant macroscopic or microscopic findings were noted at necropsy. The LC_{50} was established as being >1.2 mg/L for both males and females.

Acute Inhalation Study with MUP

In a GLP OECD TG 403 comparable study (Study SGT-30-0064, 1993), SD rats (5/sex/group) were exposed (whole body) to aerosolised MUP undiluted at a concentration of 2810, 3620 or 4430 mg/m^3 (equivalent to 2.81, 3.62 and 4.43 mg/L) for four hours. The MMAD was 3.19-3.75 µm. Deaths were reported in both males and females at doses ≥2.81 mg/L. At 4.43 mg/L, all animals died, but it was not possible to make precise clinical observations during the exposure period due to the dense aerosol mist generated. At lower doses, the following abnormal signs were noted: muscular fibrillation, irregular respiration, lacrimation, nasal discharge, a red substance around the snout, salivation, urinary incontinence, ataxic gait, tip toe gait, wet fur, ocular discharge, tremor and hypersensitivity in males. There were no significant treatment-related findings at necropsy. The LC_{50} was

established as being 3.6-4.4 mg/L for males and 2.8-3.6 mg/L for females, equivalent to 1.8-2.2 and 1.4-1.8 mg/L imiprothrin for males and females, respectively.

Conclusion

Given that the study with MUP used higher concentrations of imiprothrin, and that the toxicity in that study seems to be driven by imiprothrin rather than isopropyl myristate (which is reported to have a very high LC_{50} of >33-41 mg/L), the DS concluded that the MUP LC_{50} values place imiprothrin in Category 4 (Acute Tox. 4; H332; LC_{50} values between 1 and 5 mg/L). On this basis, an Acute Toxicity Estimate (ATE) value of 1.4mg/L for the inhalation route (dusts and mists) was proposed.

Comments received during public consultation

One MSCA asked for clarification on the number of deaths in the oral mouse study with imiprothrin at the dose level of 760 mg/kg bw. This was clarified by the DS (3/5). Another MSCA expressed support for the proposed classification for acute oral and inhalation toxicity, but found the presentation of the inhalation data confusing.

Assessment and comparison with the classification criteria

As described above, eight guideline studies investigating the effects of a single dose of imiprothrin via oral, dermal and inhalation routes are available (four studies with imiprothrin as test substance, four studies with the MUP containing 50% imiprothrin and 50% isopropyl myristate). In addition there is a guideline acute oral neurotoxicity test available with imiprothrin in rats. RAC agrees with the DS that also the studies using the MUP are relevant for classification, given the low acute toxicity of isopropyl myristate, oral and dermal LD_{50} values in the range of those found for neat imiprothrin, and the higher imiprothrin concentration tested for inhalation. In the table below the LD_{50}/LC_{50} values as observed in the nine available studies are presented and compared with the classification criteria. From this, it follows that imiprothrin fulfils the criteria for classification in category 4 for the oral and inhalation route, but not for the dermal route.

Table: Overview of LD_{50}/LC_{50} values (expressed as imiprothrin dose in mg/kg bw (oral/dermal) or in mg/L (inhalation)) in acute toxicity studies with imiprothrin (neat and in MUP)

	Acute oral		**Acute dermal**		**Acute inhalation**	
	Study with imiprothrin	Study with MUP	Study with imiprothrin	Study with MUP	Study with imiprothrin	Study with MUP
Rat **male** **female**	 1800 900	 2250 1200	 >2000 >2000	 >1000 >1000	 >1.2 >1.2	 1.8-2.2 1.4-1.8
Rat (neurotox) **male/female**	 >1000					
Mouse **male** **female**	 724 550	 675 650				
Criteria Category 4	300-2000		1000-2000		1-5 (dusts and mists; 4h)	
	Fulfilled		Not fulfilled		Fulfilled	

Overall, RAC agrees with the proposal of the DS and considers that imiprothrin should be classified as **Acute Tox. 4; H302** and **Acute Tox 4; H332**, with **ATE values** respectively of **550 mg/kg bw (oral)** and **1.4 mg/L (inhalation)**.

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

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

Table 11: Summary of relevant neurotoxicity studies

Neurotoxicity Studies		
Method	**Dose Levels**	**Observations and remarks**
Acute neurotoxicity study Rat, (SD) - 12/sex/group Oral (gavage) Single dose Purity – 92.1% US-EPA 81-8 GLP CAR Doc IIIA A6.9/01 Bio-Research Laboratories Ltd (1995a)	M: 0, 200, 600 or 1000 mg/kg F: 0, 100, 300 or 1000 mg/kg LD_{50} > 1000mg/kg bw/d	Few females in all treated group displayed flicking of the forelimbs **200mg/kg (males only)** 1 death due to gavage error. **300mg/kg (females only)** fur staining along the ventral thoracic, abdominal and urogenital regions tremors (one female) **600mg/kg (males only)** Slight ataxic gait (1 male) **1000mg/kg** 2 deaths (females) ↑ tremors, wet muzzle, overall gait incapacity (females) ↓ motor activity, arousal, body tone and extensor thrust (females) Tremor (1 male) Slight ataxic gait (1 male)

Eight guideline studies investigating the effects of a single dose of imiprothrin via oral, dermal or inhalation routes are available (4 with imiprothrin as the test substance and 4 with MUP – refer to section 4.2 for information) in addition to an acute neurotoxicity study. There were no signs of clinical toxicity in acute dermal studies.

Whilst some of the clinical signs occurred at high doses and could be related to the lethal effects, a number of observations indicative of neurotoxicity were observed in oral studies at doses below the LD_{50} value. In the imiprothrin study in rats, tremor and a decrease in spontaneous activity were observed. In the MUP study in rats, tremor, a decrease in spontaneous activity and ataxic gait were observed in both sexes at doses below the LD_{50} value. Prone position was also noted in females. In the imiprothrin study in mice, the neurotoxic effects occurring at relevant doses were tremor, a decrease in spontaneous activity and clonic convulsion. A decrease in spontaneous activity, tremor,

prone position and clonic convulsions were observed in the MUP study in mice. Clinical signs in surviving animals disappeared shortly after the cessation of the exposure period.

In a four hour whole-body exposure inhalation study in rats, the animals showed an exaggerated startle response at 1.2mg/L. At 0.418 and 1.2mg/L, tip toe gait was observed in both sexes. Ataxic gait was observed in both sexes. At 2.8mg/L in the acute inhalation study with MUP in rats, there was evidence of muscular fibrillation at 1.4mg/L. After termination of exposure to 1.4mg/L, ataxic gait, a decrease in spontaneous activity and tip toe gait were observed. Hypersensitivity was observed in males after termination of exposure to 1.8mg/L.

In the acute neurotoxicity study, imiprothrin was administered by gavage to Sprague Dawley rats (4/sex/dose, replicated over 3 days) at 0, 200, 600 or 1000mg/kg in males and 0, 100, 300 or 1000mg/kg in females.

In females administered 300mg/kg imiprothrin, fur staining along the ventral thoracic, abdominal and urogenital regions was observed and tremors were seen for one female.

At 600 mg/kg, one male showed slight ataxic gait.

There were two female deaths after dosing, on the day of treatment, in the 1000mg/kg group. There was one male death in the 200mg/kg group due to a dosing error.

At 1000mg/kg, slight tremors were noted in one male and slight ataxic gait was exhibited by one male. Females in the 1000 mg/kg group showed several statistically significant effects on Day 0: severe tremors in the head, body and/or limbs after dosing, wet muzzle, overall gait incapacity, decreases in locomotor activity, arousal, extensor thrust and body tone, delays for the positional passivity test and altered olfactory response and visual placing test response. In addition, a few females in this group showed no/reduced response for toe/tail pinch testing, corneal/pinna reflexes and an increase for the auricular startle test. Grip strengths were also slightly reduced for this group.

Motor activity levels were not affected by treatment in males. Females in the 1000 mg/kg group showed a markedly lower group average on Day 0 when compared with controls.

No structural changes to nervous system tissues were detected.

4.3.2 Comparison with criteria

Specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture. According to Table 3.8.1 in Annex I of Regulation (EC) No. 1272/2008, STOT SE 1 is reserved for, "*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 single exposure*."

Category 2 is reserved for, "*substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure*."

Category 3 of STOT SE only includes narcotic effects and respiratory tract irritation. Section 3.8.2.2.2 of Annex I of the CLP Regulation states that, *"narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure."*

Signs of possible neurotoxicity were observed in acute toxicity and acute neurotoxicity studies below the LD_{50} values and in the range for classification with STOT RE 2 (Oral: $300 < C \leq 2000$mg/kg bw; Inhalation: $1.0 < C \leq 5.0$mg/L/4h). Guidance values do not apply for STOT SE 3. However, the overall profile is not typical of narcosis.

Imiprothrin is a synthetic pyrethroid insecticide. Pyrethroid insecticides act on the sodium channel in the nerve membranes of the invertebrate nervous system and are termed sodium channel modulators. They cause pronounced repetitive activity and a prolongation of the transient increase in sodium permeability of the nerve membranes. This results in continual nerve impulse transmission leading to tremors and death.

The observed adverse effects are considered to be most likely related to the neurotoxic mode of action, outlined above, that underpins the biocidal activity of imiprothrin.

As the effects in the acute neurotoxicity study occurred at the top dose, at which 2 females died, and given the mortalities in the acute oral and inhalation studies, it is proposed to classify for acute toxicity, as outlined in section 4.2 of this report, instead.

Therefore no classification for single target organ toxicity is proposed.

4.3.3 Conclusions on classification and labelling

No classification, conclusive but not sufficient for classification

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

Summary of the Dossier Submitter's proposal

There are eight acute toxicity studies and one acute oral neurotoxicity study available investigating the effects of a single dose of imiprothrin. The results of these studies have been described in detail in the section on 'Acute toxicity' above. As to clinical signs of toxicity, these were observed following oral and inhalation exposure, but not following dermal administration. The clinical signs observed in the oral and inhalation studies included ataxic gait, tremor, decreases in spontaneous activity, urinary incontinence and clonic convulsions. These effects are most likely related to the neurotoxic mode of action of imiprothrin, a synthetic pyrethroid insecticide that acts on the sodium channel in the nerve membranes of the invertebrate nervous system. Sodium channel modulators cause pronounced repetitive activity and a prolongation of the transient increase in sodium permeability of the nerve membranes, resulting in continual nerve impulse transmission leading to tremors and death. In the acute oral and inhalation toxicity studies, some neurotoxic effects occurred at high doses that were also lethal, but some effects were also

observed at doses below the LD_{50}/LC_{50} values and in the range of classification with STOT SE 2 (oral: between 300 and 2000 mg/kg bw; inhalation: between 1 and 5 mg/L/4h). Given however the mortalities in these studies, and the fact that the neurotoxic effects in the acute oral neurotoxicity study were limited to the high dose of 1000 mg/kg bw at which two animals died, the DS proposed to classify for acute toxicity rather than for STOT SE 2.

Comments received during public consultation

One MSCA commented that an additional classification in STOT SE 1 should be considered in view of clinical signs of (acute) neurotoxicity following inhalation at clearly sublethal doses and below the guidance value of 1 mg/L/4h in a 28-day study in rats. The DS in response indicated that the findings in the 28-day study do not describe clearly whether the effects were observed after a single exposure. Considering all of the data, and the nature of the general acute hazard, the DS felt that the proposed classification for acute toxicity was already adequate.

Assessment and comparison with the classification criteria

Following single administration, clinical signs indicative of neurotoxicity were observed for the oral and inhalation route, but not for the dermal route.

In the acute oral toxicity studies with imiprothrin and MUP in rats and mice, clinical signs indicative of neurotoxicity appeared 30-60 minutes post dosing. In surviving animals these signs disappeared within 3 days (rats) or 1 day (mice). Whereas the more serious effects (like e.g. clonic convulsions) were mostly observed at the higher, lethal doses, some effects were also seen at doses not resulting in mortality.

In the imiprothrin study in rats, neurotoxic effects only occurred at doses that also caused mortality. The same was true for female rats in the MUP study, but in male rats tremor, a decrease in spontaneous activity and ataxic gait were observed at non-lethal doses corresponding to 1000 and 1600 mg imiprothrin/kg bw. Irregular respiration was additionally noted in males at 1600 mg/kg bw.

In the imiprothrin study in mice, tremor and a decrease in spontaneous activity were seen at non-lethal doses of 380 (no mortality in males and females) and 480 mg/kg bw (no mortality in males). A decrease in spontaneous activity and tremor were also observed at non-lethal doses corresponding to 340 (no mortality in males and females) and 460 (no mortality in males) mg imiprothrin/kg bw in the MUP study in mice. Males at the latter dose additionally showed prone position, clonic convulsion and irregular respiration.

In the acute oral neurotoxicity study in rats at imiprothrin doses of 0, 200, 600 or 1000 mg/kg bw for males and 0, 100, 300 or 1000 mg/kg bw for females, no histopathological lesions in nervous system tissues were found. Treatment-related mortalities only occurred at 1000 mg/kg bw (2/12 females, dying on the day of treatment). At 300 mg/kg bw, one or two females showed ungroomed fur and fur staining, and one female had tremor. At 600 mg/kg bw, one male showed slight ataxic gait. At 1000 mg/kg bw, there was one male with slight ataxic gait and slight tremors. Females at 1000 mg/kg bw showed several effects, including severe tremors in the head, body and/or limbs after dosing, wet muzzle, overall gait incapacity, decreases in locomotor activity, arousal, extensor thrust and body

tone, delays for the positional passivity test and altered olfactory response and visual placing test response. In addition, a few females in this group showed no/reduced response for toe/tail pinch testing, corneal/pinna reflexes and an increase for the auricular startle test. Grip strengths were also slightly reduced for this group, and motor activity levels were markedly reduced.

In the acute inhalation toxicity studies with imiprothrin and MUP in rats, clinical signs indicative of neurotoxicity appeared from 30-60 minutes post dosing. They disappeared within a couple of hours to 7 days at the latest.

In the acute toxicity study with imiprothrin, male and female rats showed irregular respiration, tip toe gait and ataxic gait at 0.418 and 1.2 mg/L and an exaggerated startle response at 1.2 mg/L, but no mortality. In the acute study with MUP in rats, signs of neurotoxicity were observed at all tested concentrations (corresponding to 1.4-2.2 mg imiprothrin/L) and included muscular fibrillation, ataxic and tip toe gait, decrease in spontaneous activity in both sexes and irregular respiration and hypersensitivity in males. Death was however also seen at these concentrations.

Clinical signs of toxicity characteristic of neurotoxicity have also been observed at the highest tested concentration of 186 mg/m^3 (0.186 mg/L) in a 28-day inhalation study in rats, in the absence of mortalities. These signs included decreased spontaneous activity (in 1 to 9 males and females), tip toe gait (in 1 to 6 animals), and jumping, hypersensitivity and tremor (in 1 female). Irregular respiration (in 1 to 10 animals), nasal discharge (in 1 to 4 animals), salivation (in 1 to 3 animals) and urinary incontinence (in 1 to 3 animals) were also seen. RAC notes that the degree of severity and the exact onset of these signs is not reported (although they are likely to be acute in nature, as supported by the absence of histopathological or functional long term findings investigated through detailed examination and FOB in a 90-day oral neurotoxicity study in rats).

Conclusion

Neurotoxicity was consistently observed across all acute oral and inhalation studies, at both lethal and non-lethal doses. Whereas RAC notes that for lethality the substance is already proposed to be classified, the fact that effects are also seen at non-lethal doses makes it necessary to consider if additional classification for STOT SE is warranted. As the overall profile of toxic signs is not typical of narcosis, classification with STOT SE 3 is not appropriate. This leaves STOT SE 1 or 2. The lowest non-lethal doses at which the neurotoxic effects are observed fall within the guidance values for STOT SE 2 ($300 < C \leq 2000$ mg/kg bw) for the oral route and for STOT SE 1 (≤ 1 mg/L) for the inhalation route. RAC notes though, that details on the severity and incidence of each finding in the acute toxicity studies is missing, that most findings were transient in nature, and that their relevance to fulfil the severity criteria for STOT SE 1/2 is not totally clear. It is further noted that the sublethal dose levels with neurotoxic findings were mostly within a factor 2 lower than the lethal dose levels, with the exception of two rat studies with imiprothrin (the acute inhalation study and the acute oral neurotoxicity study in males) where no lethality was seen. Nevertheless, given the consistent picture, and further supported by the fact that imiprothrin belongs to the group of pyrethroids, which is known to induce neurotoxic effects, RAC considers it important for classification to note the neurotoxic properties of imiprothrin in this case.

RAC therefore concluded that **classification as STOT SE 2; H371 for its effects on the nervous system by the oral and inhalation route is warranted**.

4.4 Irritation

4.4.1 Skin irritation

Not addressed in this assessment.

4.4.2 Eye irritation

Not addressed in this assessment.

4.4.3 Respiratory tract irritation

Not addressed in this assessment.

4.5 Corrosivity

Not addressed in this assessment.

4.6 Sensitisation

4.6.1 Skin sensitisation

Not addressed in this assessment.

4.6.2 Respiratory sensitisation

Not addressed in this assessment.

4.7 Repeated dose toxicity

Table 12: Summary table of relevant repeated dose toxicity studies

Method	Dose Levels	Observations and Remarks	Reference
Oral			
90 day oral (diet) study Rat, (SD) 12/sex/grp Imiprothrin; 92.9% US-EPA 82-1, similar to OECD 408 GLP CAR Doc IIIA A6.4.1/01	0, 100, 3000, 6000, 10000 ppm equivalent to m: 0, 5.9, 179, 350, 611 mg/kg/d f: 0, 7, 197, 399, 657 mg/kg/d Guidance value for classification ≤ 100 mg/ kg bw/day (90 day rat study)	No mortality observed. In this 90 day oral study in the rat, the low dose of 100ppm (m: 5.9mg/kg/d; f: 7mg/kg/d) was below the guidance value for classification. No treatment-related adverse effects were noted at this dose. Effects seen at higher doses are as follows: **3000 ppm: (m: 179mg/kg/d; f: 197mg/kg/d)** *Observations* ↓ food consumption *Organ weights* ↑ liver: 12%, males (relative) *Haematology* ↑ reticulocyte numbers: 22%, females *Clinical Chemistry* ↑ cholesterol: 24%, males ↓ triglyceride: 34%, males *Histopathology* Salivary gland: ↑ incidence of swelling of acinar cells in submandibular gland (5/12, minimal, males) **6000 ppm: (m: 350mg/kg/d; f: 399mg/kg/d)** *Observations* ↓ bw: 11%, females;14%, males *Organ weights* ↓ adrenal: 11%, females;12%, males (absolute) ↑ liver: 18-26 % (relative) ↑ spleen: 24%, females (relative) *Haematology* ↑ reticulocyte numbers: 14%, males;40%, females ↑ platelet count: 11%, males ↑ leucocyte count: 28%, males ↑ lymphocytes: 29%, males *Clinical Chemistry* ↑ cholesterol: 43%, males ↑ phospholipid: 32%, males ↓ triglyceride: 25%, males	Sumitomo Chemical Co. Ltd (1992)

		Histopathology Liver: ↑ incidence of hepatocellular hypertrophy (2/12, minimal, males) Spleen: haemosiderin pigment deposit (4/12 males, minimal; 5/12 females, minimal - slight), extramedullary haematopoiesis (EMH) (5/12 males, minimal; 3/12 females, minimal) Salivary gland: swelling of acinar cells in submandibular gland (7/12 males, minimal; 6/12 females, minimal-slight), oedema in submandibular gland (4/12 males, minimal; 4/12 females, minimal) **10000 ppm: (m: 611mg/kg/d; f: 657mg/kg/d)** *Observations* ↓ body weights: 11-16% *Organ weights* ↑ liver: 14%, females;18%, males (absolute); 3141% (relative) ↑ spleen: 18%, females (absolute); 20-35% (relative) ↓ pituitary: 14%, males (absolute) ↓ adrenals: 13%, males; 14%, females (absolute) ↑ heart: 14%, males (relative) ↑ brain: 15%, males (relative) ↑ testes: 28% (relative) *Haematology* ↓ Hb conc.: 9%, males;12%, females ↓ Hct: 9%, males;14%, females ↓ erythrocyte count: 8%, males;13%, females ↑ reticulocyte numbers: 66%, males;109%, females ↑ platelet counts: 15-16% *Histopathology* Liver: ↑ incidence of hepatocellular hypertrophy (9/12, minimal, males; 7/12, minimal , females), eosinophilic hepatocytes (8/12, minimal, males; 5/12, minimal , females) Spleen: haemosiderin pigment deposit (9/12 males, minimal-slight; 10/12 females, minimal-slight), EMH (11/12 males, minimal-slight; 8/12 females, minimal-slight) Salivary gland: swelling of acinar cells in submandibular gland (11/12 males, minimal-slight; 8/12 females, minimal-slight), oedema in submandibular gland (6/12 males, minimal; 4/12 females, minimal) *NOAEL*: m: 5.9 mg/kg and f: 7 mg/kg*	

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON IMIPROTHRIN (ISO); REACTION MASS OF: [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

2 year oral (diet) combined chronic toxicity/carc-inogenicity study Rat (SD)/ 64/sex/grp 14 male and 14 female sacrificed after 52 weeks Imiprothrin; 92.9% OECD guideline 453 GLP CAR Doc IIIA A6.5/01	0, 50, 250, 2500, 5000 ppm equivalent to m: 0, 2, 9, 90 or 180 mg/kg/d f: 0, 2, 11, 109, 219 mg/kg/d Guidance values for classification ≤ 12.5 mg/ kg bw/day (based on a 90 day rat study)	No treatment-related mortality observed. In this 2 year oral study in the rat, the two lower doses were below the guidance value for classification. No treatment-related adverse effects were noted at ≤ 12.5mg/ kg bw/d in this study. The most significant effects seen at higher doses are as follows: **2500 ppm: (m: 90mg/kg/d; f: 109mg/kg/d)** *Histopathology* ↑ incidence of acinar cell hypertrophy of the sub-mandibular gland (12/58 vs 0/57 in control) **5000 ppm: (m: 180mg/kg/d; f: 219mg/kg/d)** *Organ weights* ↑ heart: 15%, males (relative) ↑ prostate: 60%, males (relative) ↑ brain: 22%, males (relative) ↑ thyroid: 50%, males (relative) ↑ salivary gland, both sexes (relative) *Haematology* ↓ Hct value, males ↓ MCV, males ↑ MCHC, females *Clinical Chemistry* ↑ AST, ALT and gamma-GTP activity *Histopathology* ↑ incidence of acinar cell hypertrophy of the salivary sub-mandibular gland (23/58 vs 0/57 in control) ↑ incidence of pitted foci of the liver (19/31 vs 8/30 in control) *NOAEL*: m- 9 mg /kg/d; f- 11 mg/kg/d*	Sumitomo Chemical Co. Ltd (1995)

90 day oral (diet) study Mouse/ CD-1/ 12/sex/grp Imiprothrin; 92.9% US EPA 82-1 similar to OECD 408 GLP CAR Doc IIIA A6.4.1/02	0, 1000, 3000, 5000, 7000 ppm equivalent to: m: 0, 130, 371, 643, 883 mg/kg/d f: 0, 150, 435, 803, 1239 mg/kg/d Guidance value for classification ≤ 100 mg/ kg bw/day (90 day rat study)	No mortality observed. In this 90 day oral study in the mouse, all of the doses were above the guidance value for classification. The most significant effects observed in the study are as follows: **<u>1000 ppm: (m: 130mg/kg/d; f: 150mg/kg/d)</u>** <u>*Organ weights*</u> ↑ liver: 11%, female; 13%, male (relative) **<u>3000 ppm: (m: 371mg/kg/d; f: 435mg/kg/d)</u>** <u>*Organ weights*</u> ↑ liver: 18%, females;24%, males (absolute); 21%, females; 22%, males (relative) <u>*Haematology*</u> ↓ Hb conc: 5% ↓ Hct value 6%, males;7%, females **<u>5000 ppm: (m: 643mg/kg/d; f: 803mg/kg/d)</u>** <u>*Observations*</u> ↓ bw gain: 19%, males <u>*Organ weights*</u> ↑ liver: 27%, females; 34%, males (relative) ↓ ovary: 17% (absolute) <u>*Haematology*</u> ↓ RBC count: 5%, females;7%, males ↓ Hb conc.: 6%; females;7%, males ↓ Hct value: 8% females;9%, males ↑ reticulocyte count: 18%, males **<u>7000 ppm: (m: 883mg/kg/d; f: 1239mg/kg/d)</u>** <u>*Observations*</u> ↓ bw gain: 16%, males;28%, females <u>*Organ weights*</u> ↑ liver: 20%, females;33%, males (absolute); 31%, females; 39%, males (relative) ↑ spleen: 33% males (absolute) ↓ ovary: 26 % (absolute) <u>*Haematology*</u> ↓ RBC count: 8%, females;9%, males ↓ Hb conc.: 9%, females;10%, males ↓ Hct value: 10%, females;11%, males ↑ reticulocyte count: 17%, females;28%, males ↑ leucocyte count: 44%, males	Sumitomo Chemical Co. Ltd (1992)

		Histopathology Liver: ↑ incidence of hepatocellular hypertrophy (4/12, males) Spleen: ↑ incidence of EMH (6/12 males, slight; 6/12 females, slight). *NOAEL*: m: 130 mg/kg/d and f: 150 mg/kg/d*	

18 month oral (diet) carcinogenicity study Mouse/ CD-1/ 66/sex/grp Imiprothrin; 92.9% US EPA 40 CFR, Section 158.340, Guideline 83-2 GLP CAR Doc IIIA A6.5/02	0, 100, 3500, 7000 ppm equivalent to: m- 0, 10, 354, 702 mg/kg/d f- 0, 12, 409, 814 mg/kg/d Guidance values for classification ≤ 16.4 mg/ kg bw/day (based on a 90 day rat study)	In this 18 month oral study in mice, the low dose of 100ppm (m: 10mg/kg/d; f: 12mg/kg/d) was below the guidance value for classification. **<u>100 ppm: (m: 10mg/kg/d; f: 12mg/kg/d)</u>** <u>*Organ weights*</u> ↑ absolute liver weight: 14%, males Effects at higher doses included the following: **<u>3500 ppm: (m: 354mg/kg/d; f: 409mg/kg/d)</u>** <u>*Observations*</u> ↑ mortality rate: 27.5% vs 13.7% in controls ↑ hair loss, females: 8/37 vs 2/44 in controls ↓ bw gain ↓ food consumption <u>*Organ weights*</u> (18 months): ↑ liver: 18%, males (absolute); ↑ 33%, females (relative) ↓ spleen: 50% (absolute) <u>*Histopathology*</u> ↑ incidence of black livers: 14/31 vs 1/66 in controls hepatocellular hypertrophy, and with clear cell change or altered hepatic foci. **<u>7000 ppm: (m: 702mg/kg/d; f: 814mg/kg/d)</u>** <u>*Observations*</u> ↑ mortality rate: 45.1% vs 13.7% in controls ↑ hair loss, females: 13/28 vs 2/44 in controls ↓ bw gain ↓ food consumption <u>*Organ weights*</u> At 78 weeks: ↑ liver weight: 45%, males (absolute); ↑ 56%, males and 41%, females (relative) ↑ kidney: 15 %, females (relative) ↓ kidney: 15% (absolute, females) ↓ spleen: 65% (absolute) <u>*Haematology*</u> ↓ RBC Hb conc. and Hct value: 9–10% ↑ WBC counts <u>*Histopathology*</u> ↑ incidence of black livers (21/27 vs 1/66 in control) hepatocellular hypertrophy, and with clear cell change or altered hepatic foci; ↑ incidence of hair follicle atrophy (14/28 vs 7/44 in control).	Sumitomo Chemical Co. Ltd (1994)

		NOAEL: m:10 mg/kg/d; f: 12 mg/kg/d*	
90 day oral (daily gelatine capsule) study Dog/ Beagle/ 4/sex/grp and additional 2m + 2f included in control & high dose groups Imiprothrin; 92.9% US EPA 82-1, similar to OECD 409 GLP CAR Doc IIIA A6.4.1/03	0, 10, 100, 1000 mg/kg/d Guidance values for classification ≤ 100 mg/ kg bw/day (90 day rat study)	In this 90 day oral study in dogs, the low and mid doses of 10 mg/kg/d and 100mg/kg/d were at or below the guidance value for classification. No mortality observed. **<u>100 mg/kg/d:</u>** <u>*Observations*</u> Increased salivation ↑ incidence of loose & watery faeces <u>*Organ weights*</u> ↑ salivary sub- mandibular gland weight: 15%, females;28%, males (relative) ↑ liver: 11%, females;14%, males (relative) Effects at higher doses included the following: **<u>1000 mg/kg/d:</u>** <u>*Observations*</u> Increased salivation, incidence of emesis, loose & watery faeces <u>*Organ weights*</u> ↑ salivary sub- mandibular gland: 22%, females;24%, males (absolute); 34%, males;36%, females (relative) ↑ liver:14%, females;27%, males (absolute); 32%, females;40%, males (relative) <u>*Haematology*</u> ↓ RBC count: 13% ↑ platelets count: 37%, males;65%, females <u>*Clinical Chemistry*</u> ↑ total cholesterol: 45%, week 4, males ↑ ALP (88 & 77% at weeks 8 & 12 respectively, males) ↓ AST (17 & 21% at weeks 4 & 12 respectively, males) ↑ LDH (110 & 140% at weeks 8 & 12 respectively, females) <u>*Histopathology*</u> ↑ incidence of liver enlargement (5/8) ↑ incidence proliferation of serous gland of the sub-mandibular salivary gland (7/8). The abnormal findings at 1000mg/kg bw/d were absent in recovery animals. *NOAEL*: 10 mg/kg/d*	Sumitomo Chemical Co. Ltd (1992)

1 year oral (daily gelatine capsule) study Dog/Beagles/ 4/sex/grp Imiprothrin; 92.9% OECD guideline 452 GLP CAR Doc IIIA A6.5/03	0, 5, 50, 500 mg/kg/d Guidance values for classification ≤ 24.7 mg/ kg bw/day (based on a 90 day rat study)	In this 1 year oral study in dogs, the low dose was below the guidance value for classification. No treatment-related adverse effects were noted at ≤ 24.7mg/kg bw/d in this study. The most significant effects seen at higher doses are as follows: No treatment-related mortality observed. **<u>50 mg/kg/d</u>** *<u>Observations</u>* Increased salivation, incidence of liquid faeces and vomiting *<u>Organ weights</u>* ↓ uterus: 43% (absolute) *<u>Clinical Chemistry</u>* ↓ AST activity: 24%, females *<u>Histopathology</u>* dark liver in one female **<u>500 mg/kg/d</u>** *<u>Observations</u>* Increased salivation Increased incidence of liquid faeces and vomiting ↓ bw gain: 24% males; 62% females ↓ food consumption *<u>Organ weights</u>* ↑ liver: 25%, males (relative) ↑ prostate: 41%, males (relative) ↑ salivary gland: 26%, females (relative) ↓ uterus: 78% (absolute) ↓ testes: 18% (absolute) *<u>Haematology</u>* ↓ Hb level: males - weeks 13 and 26: 16 and 17% respectively; females - weeks 13 and 39: 12 and 15%, respectively ↓ RBC count: males - weeks 13–52: 10-18%; females - weeks 13 and 39: 15-16% ↓ PCV: males - weeks 13 and 52:17 and 12%, respectively; females - weeks 13 and 39: 14 and 12%, respectively *<u>Clinical Chemistry</u>* ↑ ALT - males: 152-272% (weeks 13–52); females: 82-122% (weeks 26–52) ↓ AST: 22-28% (weeks 13-39), females ↑ phospholipid: 14-32%, (weeks 13, 39 and 52), males ↑ triglycerides (week 26 only): 71%, males; 32%, females ↑ cholesterol (week 52);34%, males *<u>Histopathology</u>* ↑ incidence of black liver in all treated animals Treatment-related macroscopic and histopathology findings seen in the liver at ≥ 50 mg/kg/d, with severity increasing with dose	Huntingdon Research Centre Ltd (1994)

		NOAEL: 5 mg/kg/d*	
Inhalation			
28-day inhalation study (males: 28 days, females: 29 days) Rats, (SD) / 10/sex/group Whole body exposure 4h daily Imiprothrin; 92.9% Aerosol/ MMAD: 0.80-0.86µm US EPA 82-4 GLP CAR Doc IIIA A6.3.3	0 (vehicle and air controls), 2.4, 22, 186 mg/m^3 Guidance values for classification (dusts and mists) Cat. 1 ≤ 0.06mg/L/6h/d Cat. 2 0.06 < C ≤ 0.6mg/L/6h/d	All doses were below the guidance value for classification. The most significant effects observed in the study are as follows: No mortality observed. **<u>186 mg/m^3 (0.186mg/L)</u>** <u>*Observations*</u> ↓ body weight (bw) : 7%, females;14%, males ↓ bw gain: 20%, females; 27%, males Clinical signs of toxicity characteristic of neurotoxicity including decreased spontaneous activity (1 to 9 males and females), tiptoe gait (1 to 6 males and females), hypersensitivity (1 female) and tremor (1 female) <u>*Organ weights*</u> ↑salivary gland: 52%, females;58%, males (relative) ↓ thymus: 17%, males;23%, females (absolute) ↑ liver: 11%, males;21%; females (relative) ↑ kidneys: 11% males;16% females (relative) ↑ brain: 9% females;13%, males (relative) ↑ ovaries: 11% (relative) ↑ testes: 19% (relative) ↑ thyroid: 31%, males (relative) ↑ adrenals: 19%, females (relative) <u>*Haematology*</u> ↑ reticulocyte count: 27%, males;87%, females ↓ prolongation of activated partial thromboplastin in females: 43% <u>*Clinical Chemistry*</u> ↑ total cholesterol: 20%, females;22%, males ↓ triglyceride: 56%, males *NOAEC: 22 mg/m^3** Sumitomo Chemical Co. Ltd. (1992)

Dermal			
21-day dermal study Rat,(SD)/5/sex/grp Imiprothrin; 92.9% (vehicle: corn oil) Semi-occlusive 6 h daily exposure US EPA 82-2 GLP CAR Doc IIIA A6.3.2	100, 300, 1000 mg/kg/d Guidance values for classification Cat. 1 ≤ 60mg/kg/d Cat. 2 60 < C ≤ 600mg/kg/d	In this 21 day dermal rat study, the low and mid doses were below the guidance value for classification. No treatment-related adverse effects were noted at ≤ 600/kg bw/d in this study. The most significant effects seen at the top dose are as follows: No mortality observed. No treatment related clinical observations. **1000 mg/kg/d:** ↑ salivary gland weight**:** 15% ↑ incidence of acanthosis (8/10 animals, slight) ↑ hyperkeratosis (3/10 animals, slight) in the skin *NOAEL $_{syst}$: 300 mg/kg/d (m+f)** *NOAEL $_{local}$: 300 mg/kg/d**	Corning Hazleton Incorporated (1995)

*As reported in the Competent Authority Report

- EMH – extramedullary haematopoiesis; Hb – haemoglobin; Hct – haematocrit; RBC – red blood cell; WBC – white blood cell; PCV – packed cell volume; MCV – mean cell volume

4.7.1 Non-human information

None.

4.7.1.1 Repeated dose toxicity: oral

Six guideline oral toxicity studies carried out to GLP standards are available: 2 in rats, 2 in mice and 2 in dogs.

Studies in rats

90 day oral toxicity study in rats

In the first study, Sprague-Dawley rats (12/sex/group) received imiprothrin (purity 93%) in their diet at 0, 100, 3000, 6000 or 10000ppm (equivalent to 0, 5.9, 179, 350, 611 mg/kg/d (males) and 0, 7, 197, 399, 657 mg/kg/d (females)) daily for 90 days. The 100ppm dose (m: 5.9mg/kg/d; f: 7mg/kg/d) was below the guidance value for classification (cat 1: ≤ 10mg/kg/d; cat 2: ≤ 100mg/kg/d).

There were no deaths and no clinical signs of toxicity noted up to the highest dose tested. Decreases in bodyweight parameters associated with lowered food consumption were observed at doses ≥ 6000 ppm. The clinical signs observed during the study included, loss of hair, scabs, ocular discharge and lacrimation (no dose dependency).

Red blood cell count (RBC), haemoglobin concentration (Hb) and haematocrit (Hct) were statistically significantly reduced (compared to controls) in a dose-related manner in both sexes. Hb and Hct levels were reduced in males at ≥179mg/kg bw/d (Hb: 5, 7 & 9% and Hct: 6, 7 & 9% at 179, 350 & 611mg/kg bw/d, respectively) and females at ≥ 399mg/kg bw/d (Hb: 5 & 12% and Hct: 6 & 14% at 399 & 657 mg/kg bw/d, respectively). RBC levels were only statistically significantly lowered at the top dose by 8 and 13% in male and females, respectively. Statistically significant increases in reticulocyte numbers were also seen in females at ≥ 197mg/kg bw/d (22, 40 & 109% at 197, 399 & 657mg/kg bw/d, respectively) and in top dose males (66%).

Secondary changes in both sexes at ≥ 6000ppm (m: 350mg/kg bw/d; f: 399mg/kg bw/d) included regenerative responses in the spleen (extramedullary haematopoiesis), indicating that the haematological effects will be reversible following cessation of exposure, and haemosiderin deposits in the spleen and liver. These alterations are consistent with regenerative haemolytic anaemia.

Absolute liver weight was statistically significantly increased (compared to controls) at the top dose in both sexes (males 18%; females 14%) whereas absolute spleen weight was statistically significantly increased (compared to controls) in top dose females only (18%). Gross necropsy revealed enlarged liver in 2/12 males of the top dose group and enlarged spleen in 1/12 animals of each sex in the top dose group. Blackish spleen was observed in 8/12 males and 12/12 females of the top dose group and 2/12 females of the 399mg/kg bw/d group.

Histopathological examination revealed hepatocyte hypertrophy (grade: minimal) in 9/12 males and 7/12 females of the top dose group and in 2/12 males of the 350mg/kg bw/d group. In the salivary gland, swelling of the acinar cells of the sub-mandibular gland (grade: minimal – slight) was noted in both males (5/12, 7/12 & 11/12 at 179, 350, 611mg/kg bw/d, respectively) and females (1/12, 6/12 & 8/12 at 197, 399 and 657mg/kg bw/d, respectively); oedema in the submandibular gland (grade: minimal) was noted in both males (4/12 & 6/12 at 350 & 611mg/kg bw/d, respectively) and females (4/12 & 4/12 at 399 & 657mg/kg bw/d, respectively).

There was a dose-dependent increase in total cholesterol in males at ≥ 179mg/kg bw/d (24, 43 & 69% at 179, 350 & 611mg/kg bw/d, respectively) and in females at 657mg/kg bw/d (20%). An increase in phospholipids was reported in males at the top 2 dose levels (32 and 54% at 350 & 611mg/kg bw/d,

respectively); while a non-dose-related decrease in triglycerides was noted in males (34, 25 & 25% at 179, 350 & 611mg/kg bw/d, respectively). Decreases in liver enzyme activity (AST and APT) were observed in males from 179mg/kg bw/d and in females from 197mg/kg bw/d.

2 year oral toxicity study in rats

In a guideline carcinogenicity study, Sprague-Dawley rats (50/sex/dose for 2 years plus satellite groups of 14/sex/dose to be sacrificed after 52 weeks) were exposed to imiprothrin (purity 93%) at 0, 50, 250, 2500 or 5000ppm (equivalent to 0, 2, 9, 90 or 180 mg/kg/d in males and 0, 2, 11, 109 or 219 mg/kg/d in females) in their diet for 104 weeks. The doses below the guidance value for classification were 50ppm (m & f: 2 mg/kg bw/d) and 250ppm (m: 9 mg/kg bw/d; f: 11mg/kg bw/d) (Guidance value: ≤ 12.5 mg/ kg bw/day (based on a 90 day rat study)).

A minor deviation has been noted in this study. The OECD 453 guideline requires 20 animals in the high dose satellite group for evaluation of pathology, whereas only 14 animals were used. However, 14 animals/sex were also included in the study for the other dose levels and pathology conducted on these for the major organs (lung, liver, kidney and thyroid) and any grossly abnormal tissues. As the liver and submandibular salivary gland were noted as the target organs at both 52 and 104 weeks, the slight deviation in animal numbers can be considered not to have affected the overall conclusions of the study.

No treatment-related effect on mortality and no clinical signs of toxicity were observed up to the highest dose tested. No biologically significant changes in bodyweight were reported.

Minor changes in haematological parameters (increase in MCHC and platelet count, decrease in MCV and extension of prothrombin time/activated partial thromboplastin time) were observed at the 26- and/or 52-week sampling period only. These findings were observed at and above 2500 ppm, but did not occur in a dose-dependent manner and apart from a decrease in MCV, were not reproduced at the end of the study. The study author commented that although S-41311 caused haemolytic anaemia and, as a consequence, haemosiderosis of the spleen during the early phase of the treatment, the anaemia didn’t progress for the duration of treatment but rather it improved, and haemosiderosis of the spleen returned to physiological level.

At 104 weeks, a significant increase in relative weight of the heart (15%), prostate (60%), brain (22%) and thyroid (50%) was reported in males only at the top dose.

Histopathological examination at the end of the study revealed an increase in pitted foci of the liver in males (19/31 vs 8/30 in control) and in females (13/29 vs 7/28 in control) of the top dose group. There was an increased incidence of acinar cell hypertrophy of the sub-mandibular gland in both sexes in the top two dose groups group (104 wks: 0/57, 12/58 and 23/58 in control, 2500 and 5000 ppm groups, respectively). There were no abnormal histopathological findings in the liver; however, increases in transferase enzyme activities (i.e. AST and ALT; 137 and 176%, respectively) were noted at the end of the study in top dose males.

Studies in mice

90 day oral toxicity study in mice

CD-1 mice (12/sex/group) were exposed to imiprothrin (purity 93%) in their diet at 0, 1000, 3000, 5000 or 7000ppm (equivalent to 0, 130, 371, 643, 883 mg/kg/d in males and 0, 150, 435, 803, 1239 mg/kg/d in females) daily for 90 days. All of the doses were above the guidance value for classification (cat 1: ≤ 10mg/kg/d; cat 2: ≤ 100mg/kg/d (based on a 90-day rat study)).

No mortality was observed and there were no clinical signs of toxicity up to the highest dose tested (883 mg/kg/d and 1239 mg/kg/d in males and females, respectively). This is in contrast to the LD_{50} (i.e. 724 and 550 mg/kg/d in males and females, respectively) observed in the acute toxicity study. The lack of mortality in this study may be related to the method of administration of imiprothrin (dietary versus gavage dosing).

Decreased bodyweight gain was observed in males (19% and 16% at 643 & 883 mg/kg bw/d, respectively) and in high dose females (28%).

Significant increases in absolute liver weight were observed in all treated males (14%, 24%, 27% and 33% increase at 130, 371, 643 and 883 mg/kg bw/d, respectively) and in females (18%, 19% and 20% at 435, 803 & 1239 mg/kg bw/d, respectively). Increase in relative liver weight was also observed in all treated males (13, 22, 34 and 39% at 130, 371, 643 and 883 mg/kg bw/d, respectively) and females (11, 21, 27 and 31% at 150, 435, 803 and 1239 mg/kg/d, respectively). These observations were not supported by histopathological findings with slight hepatocyte hypertrophy noted only in top dose males (4/12). Generally, minimal increase in liver weight not associated with histopathological changes is regarded as a physiological response to increased metabolic demand. However, there is no information on liver enzyme induction by imiprothrin. Nevertheless, given that the liver weight increase at is the low dose was marginal, it is not considered as biologically adverse. Absolute spleen weight was increased by 33% in high dose males; while reduction in ovary weight was reported at the top two doses (17% and 26% decreases at 803 and 1239mg/kg bw/d, respectively).

Minor changes in haematological parameters were observed including statistically significant reductions in RBC counts seen in both sexes. In males, decreases of 7% and 9% were seen at 643 and 883mg/kg bw/d, respectively; while decreases of 5% occurred in females at 435mg/kg bw/d, rising to 8% at the highest dose. Hb and Hct levels were statistically significant and dose-dependently decreased, compared to control values at 371 mg/kg bw/d and above in males (Hb: 5, 7 & 10% and Hct: 6, 9 & 11% at 371, 643 & 883 mg/kg/d, respectively) and females (Hb: 5, 6 & 9% and Hct: 7, 8 & 10% at 435, 803, 1239 mg/kg/d, respectively. Statistically significant increases in reticulocyte count (18% and 28% at 643 and 883 mg/kg/d, respectively) and leucocyte levels (44% at 883mg/kg bw/d) were noted in males only.

Secondary to the haemolytic effects was an increased incidence of extramedullary haemopoeisis (slight in severity) in both sexes at the top dose (6/12 males and 6/12 females). The increase in extramedullary haematopoietic activity together with increased numbers of reticulocyte indicates a compensatory increase in RBC production.

18 month oral toxicity study in mice

CD-1mice (51/sex/dose for 78 weeks plus satellite groups of 15/sex/dose to be sacrificed after 52 weeks) were exposed to imiprothrin (purity 93%) in their diet daily at 0, 100, 3500 or 7000ppm (equivalent to 0, 10, 354 or 702 mg/kg/d in males and 0, 12, 409 or 814 mg/kg/d in females) for 18

months. No urinalysis or clinical chemistry parameters were assessed in the study. The 100ppm dose (m: 10mg/kg/d; f: 12mg/kg/d) was below the guidance value for classification (cat 1: ≤ 2.4mg/kg/d; cat 2 ≤ 24.7mg/kg/d (based on a 90 day rat study)).

A treatment-related increase in mortality was seen in females in the mid and high dose groups (14/51 and 23/51 at 409 and 814 mg/kg bw/d, respectively, compared to 7/51 in controls).

Decreases in body weight gain were observed at the mid and high doses in both males (22 and 43% at 354 and 702mg/kg bw/d, respectively) and females (23% and 54% at 409 and 814mg/kg bw/d, respectively) associated with a significant reduction in food consumption at the top dose. Loss of hair and defects of the whiskers were seen in males at the top dose and in females in the mid and high dose groups which corresponded with histopathological evidence of increased atrophy of hair follicles in females (7/44, 11/37 and 14/28 at 0, 409 and 814mg/kg bw/d, respectively).

At the top dose, a statistically significant decrease in circulating red cell mass (RBC, Hb and Hct) was seen following treatment for 52 weeks in males; however, the difference (9 - 10%) was not statistically significant at 78 weeks. This effect was accompanied by increases in the reticulocyte count. These data are consistent with regenerative anaemia, although this was not supported by histopathological data.

In the top dose group, there were significant increases in monocyte, basophil and lymphocyte counts at 78 weeks.

The toxicological significance of the dose dependent decrease in spleen weight observed in male mice at 78 weeks is unclear in the absence of associated histopathology.

At 78 weeks, a significant increase in absolute liver weight was reported in males (18 and 45% at 354 and 702mg/kg bw/d, respectively); increased relative liver weight was reported in females (33 and 41% at 409 and 814mg/kg bw/d, respectively), while in males an increase of 56% was reported at the top dose. The increase in absolute liver weight in males at 78 weeks was dose-dependent. In the absence of any pathology, the increase at the lowest dose is not considered biologically significant. Gross necropsy revealed an increased incidence of black livers at 78 weeks (males: 14/31 and 21/27 animals at 354 and 702mg/kg bw/d, females: 3/37 and 18/28 animals, at 409 and 814mg/kg bw/d, respectively).

Histopathological examination revealed hepatocyte hypertrophy at the mid and high doses in both sexes with clear cell foci in males at ≥ 354mg/kg bw/d and an increase in foci of cellular alterations in females at the top dose.

Studies in dogs

90 day oral toxicity study in dogs

Beagle dogs (4/sex/group plus an additional 2 males and 2 females included in control and high dose groups) were exposed to imiprothrin (purity 93%) in a gelatine capsule daily for 90 days at dose levels of 0, 10, 100 and 1000 mg/kg/d. The doses below the guidance value for classification were 10 and 100 mg/kg/d (cat 1: ≤10mg/kg/d; cat 2: ≤100mg/kg/d (based on a 90 day rat study).

Transient salivation and increased incidence of loose and watery faeces were observed at doses ≥100 mg/kg/d. Incidence of emesis was slightly higher in treated animals at the top dose in weeks 1 and 2 and decreased spontaneous activity was found in two males during this period. No mortality was observed and there were no significant effects on body weight parameters.

Three males and 2 females in the top dose group had an enlarged liver; 2 females had white spots and/or white areas in the liver. A non-statistically significant increase (compared to controls) in absolute liver weight (27% and 14% in males and females, respectively) was seen at the top dose and there was a dose dependent increase in relative liver weight in males (-2, 14 and 40% at 10, 100 and 1000 mg/kg/d, respectively) and females (-2, 11 and 32% at 10, 100 and 1000 mg/kg/d, respectively) reaching statistical significance at the top two doses in males and top dose in females.

A statistically significant increase in alkaline phosphatase (ALP) activity was seen in males at the top dose (88 and 77% at weeks 8 and 12, respectively); in contrast, levels of aspartate aminotransferase (AST) were statistically significantly lower (by 17 and 21% at weeks 4 and 12, respectively) at this dose compared to controls. Total serum cholesterol was increased in all treated males, but this only reached statistical significance when measured after 4 weeks (45% increase); a non-statistically significant increase was also reported in top dose females on week 4 of administration (18%). Bromosulphophthalein (BSP) retention did not vary significantly in treated animals as compared to controls. However, the retention rate was dose-dependently higher in the treated dogs compared to control values and the difference was statistically significant at the top dose (65% in treated males compared to 43% in the control and 67% in treated females vs. 47% in controls) indicating that BSP retention was more prolonged in these groups. This result suggests an alteration in hepatic blood flow or reduction in bile flow following exposure to imiprothrin. A slight increase in smooth endoplasmic reticulum (SER) in hepatocytes was also noted in one male and two females at the top dose.

An increase in absolute weight of the sub-mandibular salivary gland was observed at the mid dose in males (23%) and at the top dose in both sexes (24% and 22% in males and females, respectively); but these were not statistically significant. However, the increase in the corresponding relative weight was dose-dependent and statistically significant, compared to controls, in males (0%, 28% and 34% at 10, 100 and 1000 mg/kg/d, respectively). In the female, a statistically significant difference was observed at the high dose only (15 and 36% at 100 and 1000 mg/kg/d, respectively). These findings were associated with proliferation of the serous gland of the sub-mandibular salivary gland (0, 0, 1/8 and 7/8 in controls, 10, 100 and 1000 mg/kg/d, respectively).

Haematological changes characterised by reduction in RBC count (13%), Hb concentration (11%) and Hct value (10%) were observed at the high-dose in both male and female, although the difference relative to control was not statistically significant.

None of the reported results seen after 90 days was evident in recovery animals six weeks post-exposure which indicates that the liver, salivary gland and haematological effects are reversible.

1 year oral toxicity study in dogs

Imiprothrin (purity 93%) was administered to beagle dogs (4/sex/group) as a gelatine capsule at 0, 5, 50 or 500 mg/kg/d daily for 1 year. The 5mg/kg/d dose was below the guidance value for classification (cat 1: ≤ 1.2 mg/kg/d; cat 2: 12.3 mg/kg/d (based on a 90 day rat study)).

No deaths were reported in this study, but clinical signs of toxicity including salivation, liquid faeces and emesis were evident from 50 mg/kg/d.

A treatment-related reduction in body weight gains (24% and 62% for males and females, respectively) was observed at the top dose.

In top dose males, absolute and relative liver weights were statistically significantly increased (24 and 25%, respectively). At the top dose, a reduction in the absolute weights of the testes (18%),

prostate (42%), and an increase in relative salivary gland weight (26%) in females were observed. The absolute uterus weight in females was significantly decreased at ≥50 mg/kg/d (by 43% and 78% at 50 and 500 mg/kg/d, respectively).

An increased incidence of dark liver was observed in all animals at the top dose and in one mid-dose female. Histopathological examination of the liver revealed changes to the centrilobular section at the mid and high doses, with incidence and severity increasing with dose. These changes were characterised as centrilobular/portal fibrous tissue and fibrous bridging (7/8 and 8/8 animals at 50 and 500 mg/kg/d, respectively), dilation of sinusoids/loss of hepatocytes (6/8 animals at 500 mg/kg/d), inflammatory cell infiltration (8/8 and 7/8 animals at 50 and 500 mg/kg/d, respectively) and an increased in pigmented centrilobular hepatocytes (8/8 and 8/8 at 50 and 500 mg/kg/d, respectively). The changes were associated with increased ALT activity in both sexes (152 - 207% in males and 82 - 122% in females), increased cholesterol (34%) and phospholipid (14 - 32%) levels in males and an increase in triglyceride levels in both sexes at week 26 (71 and 32%, respectively).

At the top dose only, changes in haematological parameters in both sexes included decreased PCV, Hb concentration and RBC count.

4.7.1.2 Repeated dose toxicity: inhalation

One guideline 28 day inhalation study in rats, carried out to GLP standards is available.

A deficiency in the study has been noted. The duration of exposure was 4 hours (the study conformed to US EPA 82-4), whereas the duration of exposure recommended in OECD 412 (1981) is 6 hours. However, this study is still considered relevant to the assessment of imiprothrin for the purpose of classification.

In this study, Sprague-Dawley rats (10/sex/group) were exposed (whole body) to generated mist aerosols of the test substance at 2.4, 22 and 186 mg/m^3 (0.0024, 0.022 and 0.186mg/L respectively) for 4 hours per day (28 days for males and 29 days for females). Additional animals (10/sex/group) were included as air or vehicle only controls. All doses were below the guidance value for classification (cat 1: C ≤ 0.06mg/L/6h/day; cat 2: 0.06 < C ≤ 0.6mg/L/6h/d), although the exposure times in the study was shorter than recommended.

No mortality was observed at any dose in this study.

In all exposure groups except the air control, wet fur, rough coat, localised scab (including bleeding) or localised loss of hair were observed. The incidence of loss of hair was slightly higher in the females of the 186 mg/m^3 dose group.

Compared with the vehicle control group, a reduction in the body weight was observed from the 8th exposure in males at the top dose. Throughout the dosage period the total weight gain in this group was significantly lower for both males (27%) and females (20%) compared with the vehicle control. At this dose level the terminal body weights were also lower in both males (14%) and females (7%).

Treatment-related toxicity was reported only in the highest exposure group. There were no mortalities; however, clinical signs of toxicity characteristic of neurotoxicity were observed, including decreased spontaneous activity, tiptoe gait, hypersensitivity and tremor. Irregular respiration, nasal discharge, salivation and urinary incontinence were also seen.

At the top dose, changes indicative of regenerative anaemia including less than 10% reduction in circulating red cell mass and increased reticulocyte numbers (27% and 87% in males and females, respectively) were observed.

There was a statistically significant decrease in the absolute weight of the thymus and an increase in the absolute weight of submandibular salivary gland at the top dose. The latter effect was associated with increased incidence of dense basophilic staining of the acinar cells of the salivary gland in 9 males and 10 females on histopathological examination. The relative weights of several organs were significantly increased compared to controls, including the liver, brain, salivary gland, adrenals, thyroid, testes and ovaries. In addition, dark livers were seen in 8/20 animals.

Clinical chemistry revealed an increase in total cholesterol (females, 20%; males, 22%) and a decrease in triglycerides (56%) in males.

4.7.1.3 Repeated dose toxicity: dermal

One guideline 21 day dermal study in rats, carried out to GLP standards, is available.

In this study, Sprague-Dawley rats (5/sex/group) were treated daily with imiprothrin in corn oil, administered at dose levels of 100, 300 and 1000mg/kg/d. The area of skin treated with imiprothrin was semi-occluded for 6 hours before the dressing was removed and the site was washed. The 100 and 300mg/kg/d doses were below the guidance value for classification (cat 1: ≤ 80mg/kg/d; cat 2 ≤ 800mg/kg/d (based on a 28 day rat study)).

No deaths, effects on food consumption, body weight gain, or clinical signs of toxicity were noted during the study. There were no abnormal findings noted following haematological or clinical chemistry analysis. No abnormal macropathological findings were observed.

Histomorphological alterations at the site of application were observed in all groups. However the incidence and severity of these changes in the low and mid-group were the same as those of the control (slight) and therefore not considered to be of toxicological significance. Compared to the controls, the incidence and severity of acanthosis (8/10) and hyperkeratosis (3/10) were increased in the high dose.

The salivary gland weight in treated males at the top dose was observed to be slightly higher than the control (15%) although this finding was not statistically significant.

4.7.1.4 Repeated dose toxicity: other routes

No data were provided for repeated dose toxicity by other routes of administration.

4.7.1.5 Human information

There were no human data.

4.7.1.6 Other relevant information

None.

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

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE

Six repeated dose oral toxicity studies were available; 2 in rats, 2 in mice and 2 in dogs. Of these studies, three were 90 days studies (1 in rats, 1 in mice and 1 in dogs), one was a 2 year dietary chronic toxicity study in rats, one was an 18 month study in mice and the final was a 1 year study in dogs. One guideline 28 inhalation study and one guideline 21 day dermal study (both in rats) were also available.

Mortality

Treatment-related deaths were reported only in the 18 month carcinogenicity study in mice at doses ≥ 3500ppm (m: 354mg/kg/d; f: 409mg/kg/d), which is above the guidance value for classification. No mortality was observed in the inhalation study in rats, but clinical signs of toxicity characteristic of neurotoxicity were observed; including decreased spontaneous activity, tiptoe gait, hypersensitivity and tremor.

Organ weights and pathology

An increase in liver weight was noted in all oral studies. Some of these observations were made at dose levels slightly below or at the guidance values for classification. These effects occurred from 10mg/kg/d (males only) in the 18 month mouse study and from 100mg/kg/d in the 90 day dog study. However, in other studies, the effects on liver weight occurred above the guidance values for classification. At the dose level below the relevant guidance value for classification there was no supporting histopathology and therefore, the effects in the liver are not considered to warrant classification.

An increase in the relative weight of the salivary submandibular gland was noted in both sexes in the 90 day dog study from 100mg/kg/d. An increased incidence in proliferation of the salivary submandibular gland was also observed in 7/8 animals at the top dose (1000 mg/kg/d) in this study. These findings were not seen in recovery animals. In the 1 year dog study, the increase in salivary submandibular gland weight was only observed in females and only from 500mg/kg/d. Increases in the weight of the salivary gland were also observed in the inhalation and dermal studies in rats (see below). In the inhalation study, the effect was associated with a test-related increased incidence of dense basophilic staining of the acinar cells of the salivary gland in 9 males and 10 females on histopathological examination. However, the PAS staining was described as slight, which suggests that the functional activity of the salivary gland was comparable between the high and vehicle control groups. Since there is no supporting histopathological evidence at doses below the guidance values, the changes to the weight of the salivary submandibular gland are not considered to warrant classification.

Changes to the weights of the uterus, prostate, testes or ovaries were noted in a number of studies. However, the only effects noted below the guidance values were increases in the weights of the ovaries (11%) and testes (19%) at the top dose in the inhalation study in rats. Decreases of 43% and 78% in the absolute weight of the uterus were observed in female dogs at 50mg/kg/d and 500mg/kg/d respectively in the 1 year study. At 500mg/kg/d in the same study, a 41% increase in the relative weight of the prostate was observed in males, along with an 18% decrease in the absolute weight of the testes. Since there were no accompanying histopathological findings in these organs and the effects on their weights were mostly observed at doses greatly above the guidance values, the

observed changes to the weights of the uterus, prostate, testes and ovaries are not considered to warrant classification.

Clinical Chemistry

In male dogs in the 90 day study, increases in cholesterol and ALP and a decrease in AST were observed at the top dose. Increases in LDH were noted in top dose females in the same study. In the 1 year dog study, a 24% decrease in AST activity was observed in females at the mid dose. At the top dose, increases in ALT and triglycerides (both sexes), phospholipids and cholesterol (males only), and a decrease in AST (females only) were observed. The only effects on clinical chemistry that occurred below the guidance values for classification were an increase in cholesterol levels and a decrease in triglycerides at the top dose in the inhalation study in rats. These effects alone are not considered severe enough to warrant classification.

Haematology

Haematological effects were not observed at doses below the guidance value for classification in rats or mice. In dogs, a decrease in red blood cell count and an increase in platelet count were observed at 1000mg/kg/d in the 90 day study. In the 1 year study, decreases in Hb level, red blood cell count and PCV (were observed at 500mg/kg/d. These effects are not considered sufficient to warrant classification.

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

The guidance value for classification with STOT RE is ≤ 100 mg/kg bw/d (based on a 90-day study in the rat). This value is adjusted accordingly to account for the duration of the available study.

Oral studies

There were few treatment related effects at doses below the guidance value for classification in the oral toxicity studies. At 100ppm (m: 10mg/kg/d; f: 12mg/kg/d) in the 18 month oral carcinogenicity study in mice, a 14% increase in absolute liver weight was observed in males. In dogs administered 100mg/kg/d imiprothrin in the 90-day study, increased salivation and incidence of loose and watery faeces were observed. In these animals, there were also increases in relative liver weight and salivary sub-mandibular gland weight.

Inhalation study

All doses in the 28-day inhalation study were below the guidance value for classification. Decreases in bodyweight and bodyweight gain, and changes in organ weights, haematological parameters (increased reticulocyte count, decreased prolongation of activated partial thromboplastin in females and clinical chemistry (increase in total cholesterol and decrease in triglyceride levels in males) were observed. Clinical signs of toxicity characteristic of neurotoxicity were observed in this study, including decreased spontaneous activity, tiptoe gait, hypersensitivity and tremor. No further information on duration or reversibility is available. Although these effects were observed at concentrations below the guidance value for classification, they are not considered severe enough for classification.

Dermal study

The dermal study provided no evidence to support classification of imiprothrin as STOT RE.

The liver, salivary gland and red blood cells were identified as the target organs for toxicity in the repeated dose studies. However, there were no consistent significant adverse effects at doses below the guidance values for classification. Section 3.9.2.8.1 of Annex 1 of the CLP Regulation lists effects that do not justify classification. The list includes *small changes in clinical biochemistry, haematology or urinanalysis parameters and/ or transient effects, when such changes are of doubtful or minimal toxicological importance'*. In the absence of confirmatory histopathology, the toxicological significance of the effects on haematology and clinical biochemistry parameters are uncertain. A STOT RE classification is therefore not warranted on the basis of these observations.

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

No classification, conclusive but not sufficient for classification

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

Six repeated dose oral toxicity studies (all under GLP and guideline complaint) were available; two in rats (for 90 days and 2 years), two in mice (for 90 days and 18 months) and two in dogs (for 90 days and 1 year). One GLP guideline 28 day inhalation study and one GLP guideline 21 day dermal study (both in rats) were also available. In addition, there was a GLP guideline 90 day oral repeated dose neurotoxicity study in rats. In the table below the effects in these studies at relevant doses for classification are presented.

Table: Summary of repeated dose toxicity studies with imiprothrin

Study	Dose levels	Target organ(s) NOAEL/C	Effects at relevant doses for classification
ORAL			
90 day (diet) SD rat (12/sex/group) OECD TG 408 GLP (Study SGT-20-0040, 1992)	0, **100**, 3000, 6000, 10000 ppm equivalent to m: 0, 5.9, 179, 350, 611 mg/kg bw/day f: 0, 7, 197, 399, 657 mg/kg bw/day Guidance value for classification **≤ 100** mg/kg bw/day	Salivary gland, liver, red blood cells NOAEL 100 ppm	No

90 day (diet) Neurotoxicity study SD rat (12/sex/group) US EPA 82-7 GLP (Study SGT-51-0074, 1995)	0, **1000**, 3000 and 10000 ppm equivalent to m: 0, 62, 191 and 648 mg/kg bw/day f: 0, 74, 219, 722 mg/kg bw/day Guidance value for classification **≤ 100** mg/ kg bw/day	None (only body weight affected) $NOAEL_{general\ tox}$ 1000 ppm $NOAEL_{neurotox}$ >10000 ppm	No	
2 year (diet) SD rat (64/sex/group; interim sacrifice of 14/sex/group after 52 weeks) OECD TG 453 GLP (Study SGT-50-0069, 1995)	0, **50, 250**, 2500, 5000 ppm equivalent to m: 0, 2, 9, 90 or 180 mg/kg bw/day f: 0, 2, 11, 109, 219 mg/kg bw/day Guidance value for classification **≤ 12.5** mg/ kg bw/day	Salivary gland, liver, red blood cells NOAEL 250 ppm	No	
90 day (diet) CD-1 Mouse (12/sex/group) OECD TG 408 GLP (Study SGT-20-0021, 1992)	0, 1000, 3000, 5000, 7000 ppm equivalent to m: 0, 130, 371, 643, 883 mg/kg bw/day f: 0, 150, 435, 803, 1239 mg/kg bw/day Guidance value for classification **≤ 100** mg/ kg bw/day)	Liver, red blood cells NOAEL 1000 ppm	No	
18 month (diet) CD-1 Mouse (66/sex/group; interim sacrifice of 15/sex/group after 52 weeks) US EPA 83-2 GLP (Study SGT-50-0070, 1994)	0, **100**, 3500, 7000 ppm equivalent to m: 0, 10, 354, 702 mg/kg bw/day f: 0, 12, 409, 814 mg/kg bw/day Guidance value for classification **≤ 16.7** mg/ kg bw/day	Liver, red blood cells NOAEL 100 ppm	No	
90 day (capsule) Beagle dog (4/sex/group; additional 2/sex in control and high dose groups for 6-week recovery period) OECD TG 409 GLP (Study SGT-20-0051, 1992)	0, **10, 100**, 1000 mg/kg bw/day Guidance value for classification **≤ 100** mg/ kg bw/day	Salivary gland, liver, red blood cells; no longer seen in recovery animals NOAEL 10 mg/kg bw/day	100 mg/kg bw/day: <u>Observations</u> ↑salivation, loose & watery faeces <u>Organ weights</u> ↑salivary gland: 15% f; 28% m (relative) ↑ liver: 11% f; 14% m (relative)	

1 year (capsule) Beagle dog (4/sex/group) OECD TG 452 GLP (Study SGT-41-0065, 1994)	0, **5**, 50, 500 mg/kg bw/day Guidance value for classification **≤ 25** mg/kg bw/day	Salivary gland, liver, red blood cells NOAEL 5 mg/kg bw/day	No
INHALATION			
28 day SD rat (10/sex/group) US EPA 82-4 GLP (Study SGT-20-0056, 1992)	0 (vehicle and air controls), **2.4, 22, 186** mg/m^3 (0.0024, 0.022, 0.186 mg/L) Whole body, 4h/day Guidance values for classification (dusts and mists) Cat. 1 **≤ 0.06** mg/L/6h/day Cat. 2 **0.06 < C ≤ 0.6** mg/L/6h/day	Salivary gland, liver, red blood cells NOAEC 22 mg/m^3	186 mg/m^3 (0.186 mg/L): Observations ↓ body weight (bw): 7% f; 14% m ↓ bw gain: 20% f; 27% m Clinical signs of toxicity characteristic of neurotoxicity including decreased spontaneous activity (1 to 9 m and f), tip toe gait (1 to 6 m and f), hypersensitivity (1 f) and tremor (1 f) Organ weights ↑salivary gland: 52% f; 58% m (relative) ↓ thymus: 17% m; 23% f (absolute) ↑ liver: 11% m; 21% f (relative) ↑ kidneys: 11% m; 16% f (relative) ↑ brain: 9% f; 13% m (relative) ↑ ovaries: 11% (relative) ↑ testes: 19% (relative) ↑ thyroid: 31% m (relative) ↑ adrenals: 19% f (relative) Haematology ↓(<10%) in Hb, Hc and erythrocyte numbers: m and f ↑ reticulocyte count: 27% m; 87% f ↓ prolongation of activated partial thromboplastin: 43% f Clinical Chemistry ↑ total cholesterol: 20% f; 22% m ↓ triglyceride: 56% m Histopathology ↑basophilic staining (slight) of acinar cells in salivary gland: 9 m and 10 f
DERMAL			
21 day SD rat (5/sex/group) US EPA 82-2 GLP (Study SGT-51-0072, 1995)	0, **100, 300**, 1000 mg/kg bw/day Semi-occluded, 6h/day Guidance value for classification **≤ 800** mg/kg bw/day	Skin, salivary gland $NOAEL_{systemic}$ 300 mg/kg bw/day $NOAEL_{local}$ 300 mg/kg bw/day	No

The liver, salivary sub-mandibular gland and red blood cells were identified by the DS as the target organs for toxicity in the repeated dose studies. However, it was concluded that there were no consistent significant adverse effects nor supporting histopathology at doses at or below the guidance values for classification. Therefore the DS concluded that a STOT RE classification is not warranted for imiprothrin.

Comments received during public consultation

No specific comments were received on this hazard class.

Assessment and comparison with the classification criteria

Following repeated oral administration, hepatotoxicity and haematotoxicity were reported across all three species, the mouse being less sensitive than the rat or the dog. In addition, the salivary gland was also a target organ for toxicity in the rat and dog. Upon repeated inhalation some clinical signs of neurotoxicity were observed in rats, as well as effects on liver, red blood cells and salivary gland. The latter organ was also affected in rats following repeated dermal administration.

In the available studies, the effects on the target organs were most consistently observed at doses that are above the guidance values for classification for STOT RE. Only in the 90 day oral study in dogs and the 28 day inhalation study in rats effects were observed at or below the guidance values for classification. In dogs, it concerned increases in weights of the liver and salivary sub-mandibular gland at 100 mg/kg bw/day, but as there were no supporting histopathological findings in these organs, these effects in the 90 day oral dog study do not warrant classification.

In rats, several effects were observed at 0.186 mg/L. The effects on the liver (increases in weight and total cholesterol, decrease in triglycerides) and red blood cells (indicative of regenerative anaemia) were however not supported by histopathological findings in the relevant organs. The increase in salivary gland weight at 0.186 mg/L was associated with an increased incidence of basophilic staining of the acinar cells, but the staining was described as only slight. Weights of some other organs were also affected, but without accompanying histopathological findings. Finally, some clinical signs of neurotoxicity were observed, but RAC notes that the degree of severity and the exact onset of these signs is not reported. They are likely to be acute in nature, as supported by the absence of histopathological or functional long term findings investigated through detailed examination and FOB in the 90-day oral neurotoxicity study in rats. Overall, RAC considers the effects observed at a dose below the guidance value in the 28 day inhalation rat study not to warrant classification.

In conclusion, RAC agrees with the Dossier Submitter proposal that **no classification for STOT RE is warranted**.

4.9 Germ cell mutagenicity (Mutagenicity)

Table 13: Summary table of relevant in vitro and in vivo mutagenicity studies

In Vitro Data			
Method	**Organism/strain**	**Concentrations tested**	**Result**
Bacterial reverse mutation (Ames test) (1992) Imiprothrin Purity 95.3% OECD 471 GLP CAR Doc IIIA A6.6.1 Kogiso (1992)	*S. typhimurium/* TA 98, TA 1535, TA 1537, TA100, TA 1538 *E coli*: WP2 uvr A	+S9/-S9: 0, 156, 313, 625, 1250, 2500, 5000 µg/plate	**±S9: Negative** No evidence of toxicity up to limit concentration. The number of revertants at all concentrations was similar to controls with or without metabolic activation.
Mammalian chromosome aberration test (1992) Imiprothrin Purity 95.3% US EPA guideline 84-2, comparable to OECD 473 GLP CAR Doc IIIA A6.6.2 Hara (1992)	Chinese hamster lung cells	with S9: 0, 25, 50, 75, 100 µg/ml without S9: 0, 75, 150, 225, 300 µg/ml	**+S9 : Positive** **-S9 : Negative** In the presence of S9, increased frequency of structurally aberrant cells observed at 75 and 100µg/ml Cells with aberrations (+S9) (excluding gaps): 1.5%, 1.0%, 2.5%, 7.5% and 34.0% at 0, 25, 50, 75 and 100 µg/ml A dose-related increase in the frequency of polyploidy was evident in all dose groups. Growth rate at the respective highest concentration was < 50 %.
Mammalian cell gene mutation test (1992) Imiprothrin Purity 95.3% OECD 476 GLP CAR Doc IIIA A.6.6.3 Hara (1992)	Chinese hamster lung fibroblasts (V79)	-S9: 0, 44.4, 66.7, 100, 150 µg/ml Expt 1 (+S9): 0, 50, 100, 150, 200 µg/ml Expt 2 (+S9): 0, 50, 100, 150, 175 µg/ml	**±S9: Negative** No increased mutant frequency was observed. Cytotoxicity (i.e. low relative survival ratio) was observed at the highest doses, precluding the determination of mutation frequency.

In vivo Data			
Method	**Organism/strain**	**Concentrations tested**	**Result**
Bone marrow micronucleus test (1992) Imiprothrin Purity 95.3% US-EPA guideline 84-4, comparable to OECD 474 GLP CAR Doc IIIA A6.6.4 Sumitomo Chemical Co., Ltd (1992)	Mouse/ CD-1 / 5m +5f per group	0, 19, 38, 75 mg/kg bw Single intraperitoneal injection in corn oil	**Negative** One 75 mg/kg treated male and female found dead. Signs of toxicity consistent with neurotoxicity (tremor, clonic convulsion, decrease spontaneous activity, ataxic gait, prone position and urinary incontinence) observed at ≥38 mg/kg No significant increased incidence of micronucleated PCEs
Unscheduled DNA synthesis (UDS) assay in rat hepatocytes (1992) Imiprothrin Purity 95.3% US-EPA guideline 84-4, comparable to OECD 486 GLP CAR Doc IIIA A6.6.5 Sumitomo Chemical Co., Ltd (1992)	Rat/ Sprague-Dawley/5m+5f per group.	0, 250, 500, 1000 mg/kg bw (dose-response study) Single oral gavage in corn oil	**Negative** No significant increase in net nuclear grain counts (NG) or in the number of UDS positive cells (%R, the cells having 5 NG or more) when compared with vehicle control group was observed.

4.9.1 Non-human information

4.9.1.1 In vitro data

Three guideline *in vitro* studies assessing the mutagenic potential of imiprothrin are available.

Clear negative results were observed *in vitro* in a bacterial reverse mutation test and in a mammalian cell gene mutation (*hprt)* assay conducted in Chinese hamster lung fibroblasts (V79).

In a chromosome aberration test in Chinese hamster lung cells, a dose-related increase in structural aberrations was noted with exogenous metabolic activation (+S9). An increased incidence of polyploidy cells was observed at all dose levels.

4.9.1.2 In vivo data

Two guideline studies assessing the mutagenic potential of imiprothrin *in vivo* are available.

Imiprothrin gave a clear negative result in the bone marrow micronucleus test, in which imiprothrin was administered once intraperitoneally to CD-1mice (5/sex/group). No significant increases in micronucleated polychromatic erythrocytes were seen in the bone marrow of mice treated by intraperitoneal injection. Although only a slight reduction in PCE/NCE ratio was observed, the dose level tested produced general systemic toxicity including mortality and the toxicokinetics data suggest that imiprothrin will have reached the bone marrow as it is widely distributed.

There was no evidence of DNA damage observed in the liver unscheduled DNA synthesis (UDS) assay in rats. The mean nuclear net grain counts (NG) and the number of UDS positive cells were not significantly different from vehicle control values.

4.9.2 Human information

There is no human information available.

4.9.3 Other relevant information

There is no other relevant information available.

4.9.4 Summary and discussion of mutagenicity

Although imiprothrin gave clear negative results in both a bacterial reverse mutation test and a mammalian cell gene mutation assay, a positive response was found in an *in vitro* chromosome aberration assay in cultured Chinese hamster lung cells. An increased frequency of structurally aberrant cells was observed at 75 and 100μg/mL. Additionally, an increased incidence of polyploidy was noted in all treated groups.

In contrast, no evidence of genotoxicity was found *in vivo* in either a well conducted mouse bone marrow micronucleus test or an Unscheduled DNA Synthesis (UDS) assay in rat hepatocytes.

4.9.5 Comparison with criteria

According to the criteria in the CLP Regulation, category 1 is reserved for, "*substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans."*

Category 2 is reserved for, *"substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans."*

Although the mammalian chromosome aberration test in Chinese hamster lung cells showed that imiprothrin has *in vitro* clastogenic activity, these effects were not expressed *in vivo* in a bone marrow micronucleus test in mice. Further reassurance for the absence of genotoxic effects *in vivo* is provided by the negative result in a rat liver Unscheduled DNA synthesis assay. Overall, it is considered that there is no evidence to suggest that imiprothrin is genotoxic *in vivo* and therefore, imiprothrin does not warrant classification for mutagenicity.

4.9.6 Conclusions on classification and labelling

No classification: conclusive but not sufficient for classification

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Three guideline/GLP *in vitro* studies assessing the mutagenic potential of imiprothrin are available. Clear negative results were observed *in vitro* in a bacterial reverse mutation test (Study SGT-20-0023, 1992) and in a mammalian cell gene mutation (hprt) assay conducted in Chinese hamster lung fibroblasts (V79) (Study SGT-20-0046, 1992). In a chromosome aberration test in Chinese hamster lung cells (Study SGT-20-0024, 1992), a dose-related increase in structural aberrations was noted with exogenous metabolic activation at the two highest concentrations tested (75 and 100 µg/mL). An increased incidence of polyploidy cells was observed at all dose levels. These effects were not observed in the absence of metabolic activation.

In two guideline/GLP studies assessing the mutagenic potential of imiprothrin *in vivo*, no evidence of genotoxicity was found in a mouse bone marrow micronucleus test following intraperitoneal administration (Study SGT-20-0041, 1992) and in an Unscheduled DNA Synthesis (UDS) assay in rat hepatocytes following oral administration (Study SGT-20-0045, 1992). Although in the micronucleus test only a slight reduction in PCE/NCE ratio was observed, general systemic toxicity including mortality (at the highest dose) was seen. Further, in view of toxicokinetic data suggesting wide distribution of imiprothrin, the DS presumed that imiprothrin would have reached the bone marrow, and therefore considered the result of the micronucleus test clearly negative.

The DS considered that the positive results obtained in the *in vitro* mammalian chromosome aberration test in Chinese hamster lung cells could be disregarded in face of the negative results obtained in both *in vivo* studies. Overall, the DS concluded that there is no evidence to suggest that imiprothrin is genotoxic *in vivo* and that classification is therefore not warranted.

Comments received during public consultation

2 MSCAs commented that a genotoxic effect in somatic cells cannot be ruled out in view of a positive *in vitro* chromosome aberration assay in lung cells following metabolic activation, and no *in vivo* clastogenicity study available in a metabolically active organ. One of these MSCAs argued that neither the *in vivo* micronucleus test in bone marrow nor the *in vivo* UDS test in liver could adequately negate the positive *in vitro* finding. This MSCA further pointed to a structural alert for *in vivo* clastogenicity within the imiprothrin structure, but concluded that, overall, the criteria for classification as Muta. 2 are not met.

The DS in response stated that isolated positive results are not unusual and that it could be a false positive. With evidence from radiolabelled imiprothrin studies that the substance is widely distributed to a wide range of organs and tissue, the DS considered it reasonable

to presume that also the bone marrow had been reached and therefore considered the available *in vivo* test data to be adequately reassuring.

Assessment and comparison with the classification criteria

Imiprothrin tested negative in a bacterial reverse mutation assay and a mammalian cell gene mutation assay, but showed *in vitro* clastogenic activity in a mammalian chromosome aberration test in Chinese hamster lung cells following metabolic activation. Although this effect was not expressed *in vivo* in a conventional bone marrow micronucleus test, and imiprothrin also tested negative in a rat liver UDS assay, RAC notes that these tests do not inform on the clastogenic potential in metabolically active organs like the liver or the lung. Whereas genotoxicity in somatic cells can therefore not be totally ruled out, RAC considers a conclusion for **no classification** justified given that the data available do not meet the criteria for classification.

4.10 Carcinogenicity

Table 14: Summary table of relevant carcinogenicity studies

<table>
<tr><th>Method</th><th>Dose levels</th><th>Observations and remarks
(effects of major toxicological significance)</th></tr>
<tr><td>2 year carcinogenicity study
Oral (diet)
Imiprothrin
Purity 92.9%
Rat/ (SD) 64/sex/dose
OECD 453
GLP
CAR Doc IIIA A6.7/01
Sumitomo Chemical Co., Ltd (1995)</td><td>0, 50, 250, 2500 or 5000 ppm equivalent to:

m: 0, 2, 9, 90 or 180 mg/kg/d

f: 0, 2, 11, 109 or 219 mg/kg/d</td><td>No clear substance-related increase in tumour incidence was observed.

<u>Liver</u>

<table>
<tr><td colspan="6"><u>Males</u> (50 animals in all dose groups)</td></tr>
<tr><td>Doses (mg/kg bw/d)</td><td>0</td><td>2</td><td>9</td><td>90</td><td>180</td></tr>
<tr><td>Adenoma</td><td>1</td><td>1</td><td>1</td><td>0</td><td>4</td></tr>
<tr><td>Haemangioma</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Carcinoma</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td colspan="6"><u>Females</u> (50 animals in all dose groups)</td></tr>
<tr><td>Doses (mg/kg bw/d)</td><td>0</td><td>2</td><td>11</td><td>109</td><td>219</td></tr>
<tr><td>Adenoma</td><td>0</td><td>1</td><td>0</td><td>3</td><td>1</td></tr>
<tr><td>Carcinoma</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
</table>
No historical control data are available

<u>Lung</u>

<table>
<tr><td colspan="6"><u>Males</u> (50 animals in all dose groups)</td></tr>
<tr><td>Doses (mg/kg bw/d)</td><td>0</td><td>2</td><td>9</td><td>90</td><td>180</td></tr>
<tr><td>Adenoma</td><td>0</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td colspan="6"><u>Females</u> (50 animals in all dose groups)</td></tr>
<tr><td>Doses (mg/kg bw/d)</td><td>0</td><td>2</td><td>11</td><td>109</td><td>219</td></tr>
<tr><td>Adenocarcinoma</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
</table>
No historical control data are available

Non-neoplastic adverse effects on the submandibular salivary gland and the liver (reported in the repeated dose section)</td></tr>
</table>

18 month carcinogenicity study Oral (diet) Imiprothrin Purity 92.9%Mouse/CD-1/ 66/sex/dose OECD 451 GLP CAR Doc IIIA A6.7/02 Sumitomo Chemical Co. Ltd (1994)	0, 100, 3500 or 7000 ppm equivalent to: m: 0, 10, 354 or 702 mg/kg/d f: 0, 12, 409 or 814 mg/kg/d	Lung adenocarcinoma (males): 6/51, 5/51, 7/51, 13/50 at 0, 10, 354, 702 mg/kg bw/d Lung adenoma (females): 9/51, 7/51, 11/51, 15/49 at 0, 12, 409, 814 mg/kg bw/d ***Historical control data provided below (refer to tables 19 and 20).*** Liver adenoma: (males): 14/51, 13/51, 13/51, 21/50 at 0, 10, 354, 702 mg/kg bw/d Liver adenoma (females): 0/51, 0/51, 2/51, 1/51 at 0, 12, 409, 814 mg/kg bw/d ***No historical control data for the incidence of liver tumours in mice are available*** Mortality in females and haematological and liver effects in both sexes (reported in the repeated dose section) were observed. Female survival: 86.3%, 80.4%, 72.5% and 54.9% at 0, 12, 409 and 814mg/kg bw/d

Non-human information

4.10.1.1 Carcinogenicity: oral

Two oral chronic toxicity and carcinogenicity studies are available, one in rats and one in mice.

2 year rat study

Imiprothrin was administered to Sprague Dawley rats (50/sex/dose) at 0, 50, 250, 2500 or 5000 ppm (m: 0, 2, 9, 90 or 180 mg/kg/d; f: 0, 2, 11, 109 or 219 mg/kg/d) in the diet for 2 years. A satellite group of animals (14/sex/dose) was maintained on the same regimen and was sacrificed after 52 weeks.

This study conformed to OECD 453, with a minor deviation. The guideline requires 20 animals in the high dose satellite group for evaluation of pathology, whereas only 14 animals were used. This is not considered to have affected the overall conclusions of the study.
Non-neoplastic effects seen in this study are discussed in section 4.7.

Neoplastic findings in the liver

Table 15: Summary of neoplastic findings in the livers of rats

Males (50 animals in all dose groups)					
Doses (mg/kg bw/d)	**0**	**2**	**9**	**90**	**180**
Adenoma	1	1	1	0	4
Haemangioma	0	0	0	0	1
Carcinoma	1	0	0	0	0
Females (50 animals in all dose groups)					
Doses (mg/kg bw/d)	**0**	**2**	**11**	**109**	**219**
Adenoma	0	1	0	3	1
Carcinoma	0	0	0	0	1

No historical control data for the incidence of liver tumours in rats are available

Under the conditions of this study, single incidences of hepatocellular adenoma and carcinoma were found in control males. No liver tumours were seen in control females. In animals receiving imiprothrin, a higher frequency of benign liver tumours was seen in top dose males and in the second highest female dose group only. Individual incidences of adenoma were also seen in males at the lower two dose levels and in females at the lowest and highest doses only. No hepatocellular carcinoma was seen in treated males, but one animal with carcinoma was observed amongst the high dose females. Additionally, there was one isolated case of haemangioma in the top dose group males. Given the low numbers of tumours observed in the treated animals, the presence of both

benign and malignant tumours in control males, and the absence generally of any clear dose-response, it seems unlikely that the tumour findings were treatment-related.

Neoplastic findings in the lung

Table 16: Summary of neoplastic findings in the lungs of rats

Males (50 animals in all dose groups)					
Doses (mg/kg bw/d)	**0**	**2**	**9**	**90**	**180**
Adenoma	0	0	0	0	2
Females (50 animals in all dose groups)					
Doses (mg/kg bw/d)	**0**	**2**	**11**	**109**	**219**
Adenocarcinoma	0	1	0	0	0

No historical control data for the incidence of lung tumours in rats are available

Lung adenocarcinoma was observed in females in the low dose group only. In males, there was an increase in lung adenoma at the top dose only (4%) against a 0% incidence in controls and all other treatment groups. These very limited tumour findings are not considered to indicate that imiprothrin is carcinogenic.

18 month mouse study

Imiprothrin was administered to CD1 mice (51/sex/dose) at 0, 100, 3500 or 7000ppm in the diet (m: 0, 10, 354 or 702 mg/kg/d; f: 0, 12, 409 or 814 mg/kg/d*)* for 78 weeks. A satellite group of animals (15/sex/dose) were maintained on the same regimen and were sacrificed after 52 weeks.

Administration of imiprothrin resulted in a significant increase in mortality rate in females at ≥ 409mg/kg bw/d. Female survival rates were: 86.3%, 80.4%, 72.5% and 54.9% at 0, 12, 409 and 814mg/kg bw/d. Treatment did not affect the mortality rate in males.

The non-neoplastic effects seen in this study have been discussed in section 4.7.

Liver

Hepatocyte hypertrophy was observed in both sexes (m: ≥ 354mg/kg bw/d; f: ≥ 409mg/kg bw/d). Additional hepatic changes in the main group were clear cell foci in males at ≥354mg/kg bw/d and an increase in foci of cellular alterations in females at the top dose.

There were no statistically significant differences in the incidence of any type of focal proliferative hepatocytic lesion between control and treated groups.

Table 17: Incidences of proliferative hepatocytic lesions in all mice of main group

FINDINGS	**Male**				**Female**			
Dose (mg/kg bw/d)	0	10	354	702	0	12	409	814
No. of mice	51	51	51	50[a]	51	51	51	51
Foci of cellular alteration	6	4	10	12	1	0	4	6
Adenoma	14	13	13	21	0	0	2	1
Carcinoma	5	7	1	6	0	0	0	0

[a] One animal which died accidentally was excluded from the analysis.

No historical control data for the incidence of liver tumours in mice are available

Both liver adenoma and carcinoma were evident in control males but not females. In males, although malignant lesions were seen in treated animals, the findings were not dose-related and of very similar frequency to the control observations. There was an increase in hepatocellular adenoma at the top dose in males (14/51, 13/51, 13/51, 21/50 at 0, 10, 354 and 702 mg/kg bw/d, respectively). It is noted that there was a relatively high frequency of benign tumours in concurrent controls and therefore the significance of this apparent dose-related effect is unclear. In contrast, very few liver tumours were observed in female mice and no dose response was evident (liver adenoma: 0/51, 0/51, 2/51, 1/51 at 0, 12, 409 and 814 mg/kg bw/d, respectively). According to the study report, no statistical significance was present for males or females. On the basis of these data, it is considered that imiprothrin has not been found to produce a clear hepatocarcinogenic effect in mice.

Lung

Sections from the left lobe of the lung and other lobes bearing macroscopic lesions underwent histopathological examination. The findings from these original lung sections are presented in the table below.

Table 18: Incidence of alveologenic tumours in mice

FINDINGS		Male				Female			
	Dose (mg/kg bw/d)	0	10	354	702	0	12	409	814
(In original lung sections)									
Number of mice		51	50[a]	51	50[b]	50[a]	51	51	49[c]
Adenoma (%)		5.9	14.0	7.8	6.0	6.0	3.9	7.8	16.3
Adenocarcinoma (%)		9.8	8.0	11.8	26.0*	6.0	3.9	9.8	8.2

[a] The autolysed lung specimen from one animal was excluded from the analysis.
[b] One animal which died accidentally was excluded from the analysis.
[c] The lung tissues from 2 animals were lost due to cannibalism.
* Significantly different from control group at P < 0.05hcd = laboratory historical control data

Table 19: Laboratory historical control data for neoplastic findings in the lungs of mice (made available by the applicant)

Study ID Study Year	Total	1 1988-1992	2 1989-1992	3 1989-1993	4[a)] 1991-1994	5 1992-1994	6 1997-1999
Treatment period (weeks)	78	78	78	78	78	78	78
Male (n)	403	145	51	51	51	54	51
Adenoma	(12.2%)	(14.5%)	(3.9%)	(21.6%)	(5.9%)	(14.8%)	(7.8%)
Adenocarcinoma	(5.9%)	(2.8%)	(7.8%)	(5.9%)	(9.8%)	(7.4%)	(7.8%)
Female (n)	406	150	51	50	50	54	51
Adenoma	(5.4%)	(4.7%)	(13.7%)	(0.0%)	(6.0%)	(5.6%)	(3.9%)
Adenocarcinoma	(4.4%)	(5.3%)	(3.9%)	(2.0%)	(6.0%)	(1.9%)	(5.9%)

[a)] Study ID number 4 is the imiprothrin study (original incidence data, not the including the incidences from additional sections).

Table 20: Historical control data from the supplier for neoplastic findings in the lungs of mice

	Total	Minimum	Maximum
Male (n)	2945		
Adenoma	421 (14.3%)	2.00%	42.00%
Adenocarcinoma	217 (7.37%)	1.43%	26.00%
Female (n)	3143		
Adenoma	299 (9.51%)	1.67%	26.67%

Adenocarcinoma	145 (4.61%)	0.77%	18.37%

The incidences of benign and malignant tumours in female mice were highest at the top dose. However tumours were also observed in females in the control, low and mid-dose groups. The incidences of both adenoma and adenocarcinoma in concurrent control females fell within the historical control data range. Increased incidence of lung adenoma was observed in females in the top dose group at the end of the treatment period (2/44, 1/41, 4/37 and 6/28 at 0, 12, 409 and 814mg/kg bw/d, respectively, in surviving females). When analysed in combination with findings in dead and moribund sacrificed animals, the incidence of this neoplastic change was not statistically significantly different from controls (3/50, 2/51, 4/51 and 8/49 at 0, 12, 409 and 814mg/kg bw/d, respectively). The incidence of lung adenoma in females at the top dose (16.3%) was above the incidence for historical controls in this test laboratory (0.0 - 13.7%) but within the broader historical control data range from the animal supplier (1.67-26.67%).

In males, a statistically significant increase in adenocarcinoma was observed at the top dose (9.8%, 8%, 11.8% and 26% at 0, 10, 354 and 702 mg/kg bw/d). Of the historical control incidences from the laboratory, the highest incidence of adenocarcinoma in males was recorded in the imiprothrin study (i.e. Study No. 4: control incidence of adenocarcinoma was 9.8%). Thus, both the incidences at the mid and high doses of imiprothrin exceeded the historical control incidence for lung adenocarcinoma in male mice in this test laboratory. The statistically significant incidence of 26% at the top dose is at the upper limit of the historical control data range from the animal supplier (1.43 - 26%). Benign lung tumours were seen in all treatment groups and the incidence of adenoma in males did not show a dose response relationship. As the highest incidence of adenoma in males was observed in the low dose group, the carcinogenic findings in male mice cannot be ascribed unequivocally to treatment with imiprothrin.

Overall, this tumour profile may at most indicate a slight carcinogenic effect of imiprothrin in mice. However, the magnitudes observed are very small and the overall picture is uncertain.

As a follow-up to this first examination, the carcinogenicity study was extended to allow further analysis. An additional examination was performed to evaluate alveolar proliferating lesions in all lobes. Step sections were produced from the remaining lung tissues. The largest lung section was stained and examined for alveolar proliferative lesions only. The table below indicates the incidences of lung adenoma and adenocarcinoma in the original and additional sections combined.

Table 21: Incidence of alveologenic tumours in mice (including main study and additional histopathological investigation)

FINDINGS		Male				Female			
Dose (mg/kg bw/d)		0	10	354	702	0	12	409	814
(Combined: Original + additional lung sections)									
Number of mice		51	51	51	50[a]	51	51	51	49[b]
Adenoma (%)		19.6	21.6	19.6	18.0	17.6	13.7	21.6	30.6
Adenocarcinoma (%)		11.8	9.8	13.7	26.0	9.8	5.9	11.8	12.2

[a] One male which died accidentally was excluded from the analysis.

[b] The lung tissues from 2 animals were lost due to cannibalism.

No historical control data for the incidence of tumours in step sections in mice are available

According to the test laboratory, there was no longer any statistical significance seen using Fisher's exact test because more tumours were found in the additional examination.

In high dose males, an increased incidence of lung adenocarcinoma was again observed at the top dose (11.8%, 9.8%, 13.7%, 26% at 0, 10, 354 and 702mg/kg bw/d). According to the study author, the increased incidence lacked statistical significance when compared to controls. The neoplastic changes occurred only at the top dose and there was a high background incidence 11.8%. The incidence in the combined original and additional sections at the top dose was the same as in the original lung sections (26%). An increase in lung adenocarcinoma was not seen in females. However the absence of increased adenocarcinoma in females might be related to the increased mortality rate in females at ≥ 409mg/kg bw/d (survival rates were: 86.3%, 80.4%, 72.5% and 54.9% at 0, 12, 409 and 814mg/kg bw/d).

In males, further incidences of benign lesions were observed in the additional sections in all dose groups. In females, further incidences of benign and malignant tumours were observed in all dose groups in the additional sections. However, as in the main study, there were no statistically significant responses evident.

The interpretation of these findings in mice is not straightforward. Although an increase with dose was found for lung adenocarcinoma in male mice, a similar increase was not seen in females. It is unclear whether the reduced survival of females at the top dose(s) as a factor in this apparent difference in sensitivity between the sexes. Similarly, in the absence of any other information suggesting a sex-specific response of the mouse lung to imiprothrin, the malignant tumours may not have been treatment-related. Further doubt about the significance of the tumour findings is cast by the observation of benign lung tumours control and in all dose groups in both sexes. Adenocarcinoma was also observed in control animals.

Overall, the observed profile of tumours in the livers and lungs of control and treated male and female mice does not show a clear carcinogenic response to imiprothrin in this species.

4.10.1.2 Carcinogenicity: inhalation

There are no available data.

4.10.1.3 Carcinogenicity: dermal

There are no available data.

4.10.2 Human information

There is no human information available.

4.10.3 Other relevant information

There is no other relevant information.

4.10.4 Summary and discussion of carcinogenicity

Two carcinogenicity studies were available; one in rats and one in mice.

Rats

In a 2-year oral carcinogenicity study, the liver and the submandibular salivary gland were identified as target organs for toxicity.

A small increase in the incidence of adenoma was observed at the top dose in the lung and liver in male rats. However, these small incidences may have occurred by chance. A clear carcinogenic effect has not been seen in rats.

Mice

In an 18-month oral carcinogenicity study, administration of imiprothrin resulted in a significant increase in female mortality at the top two doses. At the top dose, the erythrocyte count, haemoglobin concentration and haematocrit value decreased, accompanied by increases in the reticulocyte count.

The liver was also a target organ with increased weight, dark discolouration, hepatocellular hypertrophy, and with clear cell change and altered hepatic foci.

An increase in hepatocellular adenoma was observed in males at the top dose only. However, the relatively small increase in tumours is not considered to show clear evidence of a carcinogenic effect.

An increased incidence of lung adenocarcinoma was observed in high dose males (5/51, 4/50, 6/51, 13/50) and lung adenoma (but not adenocarcinoma) was increased in females (3/50, 2/51, 4/51 and 8/49).

Overall, no clear treatment-related findings were observed in rats or mice, although an increased incidence of malignant tumours was evident in the lungs of top dose male mice (compared to concurrent and historical control rates).

4.10.5 Comparison with criteria

As there is no evidence of the carcinogenicity of imiprothrin to humans, classification in Category 1A would be inappropriate. Similarly, given the absence of a clear carcinogenic response in laboratory animals, and no evidence of mutagenicity in target tissues, Category 1B classification for carcinogenicity is not warranted. However, careful consideration needs to be given as to whether Category 2 or no classification is the most appropriate. In accordance with the guidance to the CLP criteria, the key factors are considered in the table below.

Table 22: Key factors to consider in the evaluation of carcinogenicity

Factor to consider	**Analysis**	**Level of concern**
Tumour type and background incidence	Tumour types are relevant to humans. However the incidences were relatively high in controls.	↑/↓
Multi-site responses	No	↓
Progression of lesions to malignancy	Yes	↑
Reduced tumour latency	No information	-
Whether responses are in single or both sexes	Prominent in males only	↓
Whether responses are in a single species or several species	Prominent in mice only	↓
Structural similarity to a substance(s) for which there is good evidence of carcinogenicity	No indication	-
Routes of exposure	Oral exposure is relevant to humans	↑
Comparison of absorption, distribution, metabolism and excretion between test animals and humans	No data available	-
The possibility of a confounding effect of excessive toxicity at test doses	No indication that toxicity was a factor	-
Mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity	No mechanistic basis is available to suggest a carcinogenic effect of imiprothrin	↓

As summarised in the table, the concern for a carcinogenic potential of imiprothrin is lowered by the relatively high background incidence of tumours and the lack of a mechanistic basis for the findings. Furthermore, a prominent effect was only seen in the lungs of male mice at the top dose. On the basis of both the strength and weight of evidence, it is considered that imiprothrin does not warrant classification for carcinogenicity.

4.10.6 Conclusions on classification and labelling

No classification: conclusive but not sufficient for classification

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

Two carcinogenicity studies were available; one in rats and one in mice.

2 year rat study

In a 2 year carcinogenicity study (Study SGT-50-0069, 1995) conducted under GLP and conform to OECD TG 453 guideline, imiprothrin was administered to SD rats (50/sex/dose) at 0, 50, 250, 2500 or 5000 ppm (males: 0, 2, 9, 90, 180 mg/kg bw/day; females: 0, 2, 11, 109, 219 mg/kg bw/day) in the diet for 2 years. A satellite group of animals (14/sex/dose) was maintained on the same regimen and was sacrificed after 52 weeks. Neoplastic lesions were observed in the liver and the lungs, as shown in the table below.

Table: Summary of neoplastic findings (incidence) in the 2 year rat study

	Males (50 animals in all dose groups)					**Females** (50 animals in all dose groups)				
Doses (mg/kg bw/day)	**0**	**2**	**9**	**90**	**180**	**0**	**2**	**11**	**109**	**219**
LIVER										
Adenoma	1	1	1	0	4	0	1	0	3	1
Haemangioma	0	0	0	0	1	0	0	0	0	0
Carcinoma	1	0	0	0	0	0	0	0	0	1
LUNG										
Adenoma	0	0	0	0	2	0	0	0	0	0
Adenocarcinoma	0	0	0	0	0	0	1	0	0	0

No historical control data available

As to the findings in the liver, the DS considered that, given the low numbers of tumours observed in the treated animals, the presence of both benign and malignant tumours in control males, and the absence of any clear dose-response, it is unlikely that the tumour findings were treatment-related. The DS further considered that the limited number of tumour findings in the lung (lung adenocarcinoma in females at the low dose and lung adenoma in males at the top dose) do not indicate that imiprothrin is carcinogenic.

18 month mice study

In an 18 month carcinogenicity study (Study SGT-50-0070, 1994) conducted under GLP and conform to OECD TG 451 guideline, imiprothrin was administered to CD-1 mice (51/sex/dose) at 0, 100, 3500 or 7000 ppm (males: 0, 10, 354, 702 mg/kg bw/day; females: 0, 12, 409 or 814 mg/kg bw/day) in the diet for 18 months. A satellite group of animals (15/sex/dose) was maintained on the same regimen and was sacrificed after 52 weeks. Similar to rats, neoplastic lesions were observed in the liver and the lungs, as shown in the table below.

Table: Summary of neoplastic findings in the 18 month mouse study

	Males					Females				
Doses (mg/kg bw/day)	**0**	**10**	**354**	**702**	**HCD**	**0**	**12**	**409**	**814**	**HCD**
LIVER (incidence)					n/a					n/a
No. of mice	51	51	51	50[a]		51	51	51	51	
Foci of cellular alteration	6	4	10	12		1	0	4	6	
Adenoma	14	13	13	21		0	0	2	1	
Carcinoma	5	7	1	6		0	0	0	0	
LUNG (%)										
No. of mice	51	50[b]	51	50[a]		50[b]	51	51	49[c]	
Adenoma	5.9	14.0	7.8	6.0	12.2 (3.9-21.6)	6.0	3.9	7.8	16.3	5.4 (0-13.7)
Adenocarcinoma	9.8	8.0	11.8	26.0*	5.9 (2.8-9.8)	6.0	3.9	9.8	8.2	4.4 (1.9-6)

[a] One animal which died accidentally was excluded from the analysis
[b] The autolysed lung specimen from one animal was excluded from the analysis
[c] The lung tissues from 2 animals were lost due to cannibalism
* Significantly different from control group at P < 0.05
HCD = laboratory historical control data; mean (range) from 6 studies (1988-1999), one of which was the imiprothrin study
n/a = no historical control data available

Liver adenoma and carcinoma were observed in the male, but not the female, control group. The malignant liver lesions in males were not dose-related and averaged the same frequency as seen in the control group. In the top dose males an increase in adenoma was seen, but with a relatively high frequency of these benign tumours in concurrent controls the DS considered the significance of this apparent dose-related effect unclear. In the female mice there were very few liver tumours observed and no dose-response was evident. According to the study report, no statistical significance was present for males or females. On the basis of these data, the DS considered that imiprothrin has not been found to produce a clear hepatocarcinogenic effect in mice.

In female mice, an increase (not statistically significant) in lung adenoma was seen at the top dose. The incidence at this dose (16.3%) was outside the laboratory historical control range (0-13.7%) but within the broader historical control range from the animal supplier (1.67-26.67%; not considered relevant by RAC). No increase in lung adenocarcinoma was seen, possibly due to the increased mortality rate in females at the higher doses (survival rates were 86.3, 80.4, 72.5 and 54.9% at 0, 12, 409 and 814 mg/kg bw/day, respectively).

In male mice, a statistically significant increase in lung adenocarcinoma was observed at the top dose. The incidence at this dose (26%) (as well as the 11.8% incidence at the mid dose) exceeded the laboratory historical control range (2.8-9.8%), and was at the upper limit of the animal supplier historical control range (1.43-26%; not considered relevant by RAC). Benign lung tumours were reported in all treatment groups, but the incidence of adenoma did not show a dose-response relationship.

As the lung tumour profile indicated an uncertain picture of the carcinogenic effects of imiprothrin in mice, an additional examination was performed to evaluate alveolar proliferating lesions in all lobes (the original examination concerned sections from the left lobe of the lung and other lobes bearing macroscopic lesions). When looking at the

incidences of lung adenoma and adenocarcinoma in the combination of original and additional lung sections (see table below), further incidences of both benign and malignant lung tumours were observed in the additional sections in all dose groups (except for adenocarcinoma in males at the top dose), but there was no longer statistical significance seen.

Table: Lung tumour incidences in the original and additional lung sections combined

	Males					**Females**				
Doses (mg/kg bw/day)	**0**	**10**	**354**	**702**	**HCD**	**0**	**12**	**409**	**814**	**HCD**
LUNG (%)					n/a					n/a
No. of mice	*51*	*51*	*51*	*50*[a]		51	51	51	49[b]	
Adenoma	19.6	21.6	19.6	18.0		17.6	13.7	21.6	30.6	
Adenocarcinoma	11.8	9.8	13.7	26.0		9.8	5.9	11.8	12.2	

[a] One animal which died accidentally was excluded from the analysis
[b] The lung tissues from 2 animals were lost due to cannibalism
HCD = laboratory historical control data; mean (range)
n/a = no historical control data available

According to the DS, the interpretation of the lung findings in mice is not straightforward. Although an increase with dose was found for lung adenocarcinoma in male mice, a similar increase was not seen in females. It is unclear whether the reduced survival of females at the top dose was a factor in this apparent difference in sensitivity between the sexes. Similarly, in the absence of any other information suggesting a sex-specific response of the mouse lung to imiprothrin, the malignant tumours may not have been treatment-related. Further doubts about the significance of the tumour findings is cast by the observation of benign lung tumours in control and all dose groups in both sexes. Adenocarcinoma was also observed in control animals.

Overall, the DS considered that no clear treatment-related findings were observed in rats or mice, although an increased incidence of malignant tumours was evident in lungs of top dose male mice (compared to concurrent and historical control rates). In deciding on whether classification is warranted or not, the DS took into account that there was no evidence of mutagenicity, and that a prominent effect was only seen in the lungs of male mice at the top dose. Furthermore, the DS considered that the concern for a carcinogenic potential of imiprothrin is lowered by the relatively high background incidence of tumours and the lack of a mechanistic basis for the findings. On the basis of both the strength and weight of evidence, the DS concluded that imiprothrin does not warrant classification for carcinogenicity.

Comments received during public consultation

Two MSCA's commented that classification for carcinogenicity category 2 should be considered, one MSCA in view of the lung tumours in male mice, the other MSCA in light of significant treatment-related increases in lung adenocarcinoma in male mice (positive trend), supported by related findings in rats and indications for neoplastic change in livers of rats and mice (positive trends). Both MSCA's highlighted the relevance of comparing the incidence of lung tumours to the laboratory historical control data (HCD) rather than to the supplier HCD (as done in the CLH report). The MSCA's also highlighted that a mutagenic effect cannot be excluded (in view of the positive *in vitro* chromosomal aberration with

metabolic activation and the structural alert identified). One of the MSCA's finally pointed to structural similarities with another pyrethroid insecticide acting on the sodium channel and classified as a carcinogen as a potential basis for read-across.

The DS in response indicated that, to their opinion, a prominent effect was only seen in lungs of male mice at the top dose, but that the data are not sufficiently convincing to classify imiprothrin for carcinogenicity, given the relatively high background incidence of the tumours and the lack of a mechanistic basis for the findings. Given that the available data on imiprothrin were sufficient to conclude on 'no classification', read-across to data on other substances was not considered necessary by the DS.

Assessment and comparison with the classification criteria

In the two oral bioassays available (one in rats, one in mice), imiprothrin slightly increased the incidences of lung and liver tumours at the highest dose levels in rats and mice, in male animals in particular.

Rat study

Slightly increased incidences (not statistically significant; HCD not available) of lung adenoma (2/50 vs 0/50 in controls) and liver adenoma (4/50 vs 1/50 in controls) were observed in male rats at the highest dietary dose of 5000 ppm, at which there was in addition one isolated case of haemangioma. No increase in lung or liver carcinoma was observed in males, and aside from an increase in pitted foci of the liver no treatment-related histopathological findings were noted in the liver or lungs. Lung and liver tumour incidences were not increased in female rats, and these organs did not show abnormal histopathological findings, aside from an increase in pitted foci of the liver at the top dose. Based on these results, there is very limited evidence for carcinogenicity of imiprothrin in rats, with only a slight, not statistically significant increase in benign tumours in one sex only. These findings do not warrant classification.

Mouse study

Male mice at the highest dietary dose of 7000 ppm showed increased incidences of liver adenoma and lung adenocarcinoma. As to the liver adenoma, the increase (21/50 vs 14/51 in controls) was not statistically significant (HCD not available). Males at this dose did not show an increased incidence of liver carcinoma (6/50 vs 5/51 in controls). In contrast to males, very few liver tumours were observed in females (no carcinoma in any dose group or in controls, 0/51, 0/51, 2/51 and 1/51 adenoma at 0, 100, 3500 and 7000 ppm, respectively). Females did show an increase (not statistically significant) in foci of cellular alteration though, as did males. Non-neoplastic liver changes upon imiprothrin treatment included increases in liver weight and hepatocellular hypertrophy in males and females of the mid and high dose groups.

As to the lung adenocarcinoma, the increase in male mice at the high dose (26% vs 9.8% in controls) was statistically significant and outside the laboratory HCD (mean 5.9%, range 2.8-9.8%). No increase in lung adenoma was seen in male mice (6% vs 5.9% in controls). Female mice at the high dose did not show an increased incidence of lung adenocarcinoma (8.2% vs 6% in controls), but the incidence of lung adenoma was increased (16.3% vs 6%

in controls). The difference with the control females was not statistically significant, but the incidence was slightly above the HCD (mean 5.4%, range 0-13.7%).

RAC considers the slight, not statistically significant increase in benign liver tumours in one sex in one species (male mice only) does not warrant classification.

The interpretation of the malignant lung tumour findings in one sex at the top dose only is more difficult. RAC notes that at the mid dose the incidence of lung adenocarcinoma in male mice also exceeded the laboratory historical control range and that the increase was dose-related (positive trend). RAC further notes that survival of male mice was not affected by treatment and was well above the test guideline value of 25%. Males at the high (and mid) dose did show a marked decrease in body weight gain though over the whole treatment period (approximately 40% (and 20%) of control body weight gain), associated with a significant reduction in food consumption. This could point to these dose levels being above the maximum tolerated dose (MTD). A similar effect on body weight gain and food consumption was seen in females at the high dose, where, in contrast to males, treatment did result in reduced survival (54.9% vs 86.3% in controls; yet, well above 25%) but not in increased incidences of lung adenocarcinoma. However, according to information from Industry, for mice, changes in body weight are more suitable for the evaluation of systemic effects of a tested chemical than changes in body weight gain, given that in mice variation in body weight gain is normally more noticeable than variation in body weight. When looking at the final body weights, the reductions, as compared to controls, were indeed much less marked (for males at the mid and high dose the decrease was approximately 9 and 15%, respectively; for females this was approximately 10 and 22%, respectively), indicating that the mid and high dose levels were not clearly above the MTD. Whether the increased mortality in females may have been a factor in the apparent sex difference is difficult to say; it may not have been too much of a confounding factor, given that the higher mortality was mainly observed towards the end of the study (after 69 weeks of treatment at the high dose). Besides, females did show increases in lung adenoma and in lung adenoma and adenocarcinoma combined (positive trends). RAC finally notes that, aside from genotoxicity data, other mechanistic data as to the possible mode of action of lung tumour formation by imiprothrin is lacking.

All in all, the increase in lung adenocarcinoma constitutes limited evidence for carcinogenicity of imiprothrin in mice. Since:

- the increase is marked and dose-related;
- it has not been convincingly shown that the elevated lung tumour incidences at the highest dose level are linked to a bad health status of the exposed males, in view of the relatively moderate reductions in body weight;
- a contribution of genotoxicity cannot totally be excluded, given that *in vitro,* imiprothrin was shown to be clastogenic in lung cells, with no *in vivo* studies in metabolically active tissues available to counteract this;
- the available data do not convincingly indicate that the lung tumours are not relevant for humans,

RAC considers the lung tumours to warrant classification in category 2. This category is considered appropriate in view of the experimental data indicating a weak carcinogenic potential of imiprothrin, expressed in one species and one sex only.

RAC therefore concludes that **classification as Carc. 2; H351 is warranted**.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

Table 23: Summary table of relevant reproductive toxicity studies - Fertility

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Two generation study in rats Rat, SD /30/sex/grp Oral (diet) Purity 92.9% OECD 416 GLP CAR Doc IIIA A6.8.2 Argus Research Laboratories, Inc.(1994)	0, 200, 2000, 6000 ppm Equivalent to: **200ppm** P1 males: 9-20mg/kg bw/d P1 females: 12-31mg/kg bw/d F1 males: 11-30mg/kg bw/d F1 females: 12-29mg/kg bw/d **2000ppm** P1 males: 96-179mg/kg bw/d P1 females: 110-325mg/kg bw/d F1 males: 115-149mg/kg bw/d F1 females: 117-297mg/kg bw/d **6000ppm** P1 males: 288-542mg/kg bw/d P1 females: 346-909mg/kg bw/d F1 males:	No adverse effects on fertility parameters including mating, gestational indices and length, pup viability and lactation performance **P1 males** 200ppm (9-20mg/kg bw/d) 1 death on Day 113 – not considered to be test substance related 2000ppm (96-179mg/kg bw/d) One male sacrificed moribund on Day 113. Moribund condition not considered to be test substance related. 6000ppm (288-542mg/kg bw/d) ↓ food consumption, bodyweight gain and bodyweight ↓ terminal bodyweight (↓ 12.5%) ↑ absolute weight of the liver (↑11%) ↑ liver weight relative to brain weight ↑ haemosiderosis in the spleen **P1 females** 2000ppm (110-325mg/kg bw/d) ↑ haemosiderosis in the spleen 6000ppm (346-909mg/kg bw/d) ↓ bodyweight gain for the entire premating period (Days 1 to 80) and food consumption ↓ terminal bodyweight (↓ 5.7%) ↑ bodyweight gain during lactation in dams – attributed to normal variation for lactating rats ↑ absolute weight of the liver (↑12%)

	360-420mg/kg bw/d F1 females: 366-883mg/kg bw/da Exposure Period: P1 males: 147 - 148 days P1 females: 152 - 154 days F1 males: 95 - 114 days F1 females: 104 - 128 days (dams without litter) / 107 - 140 days (dams with litter)	↑ liver weight relative to brain weight ↑ haemosiderosis in the spleen **F1 males** 2000ppm (115-149mg/kg bw/d) 1 death (not test substance related) ↓ Bodyweight on Days 1-36 post weaning. 6000ppm (360-420mg/kg bw/day) Three rats failed to thrive (not test substance related) ↑ incidence of splenic haemosiderosis ↓ food consumption, mean bodyweight gain and bodyweight ↓ terminal bodyweight (↓ 14.2%) ↓ absolute brain weight (↓ 5.5%) **F1 females** 2000ppm (117-297mg/kg bw/d) ↓ food consumption, average bodyweight and average bodyweight gain ↓ terminal bodyweight (↓5.2%) 6000ppm (366-883mg/kg bw/d) ↑ incidence of splenic haemosiderosis ↓ food consumption average bodyweight, average bodyweight gain and bodyweight gain ↓ terminal bodyweight (↓ 10.7%) ↓ absolute ovary weights (left ↓19.7%; right ↓ 23%) ↑ liver weight (↑ 16%) **F2 males and females** ↓ average pup weight (Days 4-21) (significant) at 6000ppm Minor skeletal abnormalities, indicative of disturbed ossification, were noted (predominantly in the high dose group); unilateral or bilateral 14th ribs, ↑ average number of thoracic vertebrae and rib pairs and ↓ average number of lumbar vertebrates. Unilateral or bilateral 14th ribs:

Dose (mg/kg bw)	0	200	2000	6000
Postnatal day 4				
Fetal incidence (%)	26.9	22.6	48.1**	50.3**
Litter incidence (%)	65.2	55	90.5*	91.7**
Postnatal day 21				

Fetal incidence (%)	0.6	0.7	2.8	15.2**
Litter incidence (%)	4.3	5.0	9.5	50**

* Significantly different from vehicle control group value (P≤0.05)
** Significantly different from vehicle control group value (P≤0.01)

Dose (mg/kg bw)	0	200	2000	6000
Thoracic vertebrae (ossification sites per pup per litter)				
PND 4[a,b]	13.28 ± 0.30	13.20 ± 0.27	13.54 ± 0.31**	13.47 ± 0.27
PND 21	13.00 ± 0.02	13.00 ± 0.02	13.02 ± 0.09	13.13 ± 0.21**
Lumbar vertebrae (ossification sites per pup per litter)				
PND 4[b]	5.72 ± 0.30	5.79 ± 0.27	5.45 ± 0.32**	5.52 ± 0.29*
PND 21	6.00 ± 0.02	5.99 ± 0.05	5.98 ± 0.09	5.87 ± 0.19**
Ribs, pairs (ossification sites per pup per litter)				
PND 4[b]	13.21 ± 0.24	13.15 ± 0.23	13.41 ± 0.27*	13.75 ± 1.67*
PND 21	13.00 ± 0.02	13.00 ± 0.02	13.02 ± 0.07	13.12 ± 0.20**

a) PND = Post natal day
b) PND 4 data includes pups that were stillborn, uncertain viability or sacrificed on day 4 postpartum
* Significantly different from vehicle control group value (P≤0.05)
** Significantly different from vehicle control group value (P≤0.01)

NOAEL: Parental: 200 ppm in female equivalent to 12 - 31 mg/kg/d and 2000 ppm in male equivalent to 96 - 179 mg/kg bw/d for toxicity; and > 6000 ppm (288 - 909 mg/kg bw/d) for reproductive performance*

NOAEL: F1: 200 ppm equivalent to 11 - 30 mg/kg d for toxicity; and > 6000 ppm equivalent to 360 - 883 mg/kg bw/d for reproductive performance*

NOAEL: F2: 2000 ppm for toxicity*

*As given in the Competent Authority Report

4.11.1.1 Non-human information

One guideline two generation study investigating the fertility effects of imiprothrin in rats is available.

Sprague-Dawley rats (30/sex/group) were exposed to imiprothrin (92.9%) in feed for two generations at dietary levels of 0, 200, 2000 and 6000 ppm. The achieved test material intakes for P1 parental animals were 9-20, 96-179 and 288-542 mg/kg bw/day (males) and 12-31, 110-325 and 346-909

mg/kg bw/day (females) at 200, 2000 and 6000 ppm respectively. F1 animals received 11-30, 115-149 and 360-420 mg/kg bw/day (males) and 12-29, 117-297 and 366-883 mg/kg bw/day (females) at 200, 2000 and 6000 ppm respectively. P1 animals were treated for 80 days, mated and exposure continued through cohabitation and until scheduled sacrifice. All litters (F1 pups) were reduced to comprise 8 animals, where possible 4 males and 4 females, on Day 4 *post-partum*, and nursed for 3 weeks. Those animals not selected were sacrificed. The F1 generation also comprised 30 rats per sex and received test substance for a maximum of 84 days, were mated and test substance administration continued through cohabitation and until scheduled sacrifice. Offspring from the F1 animals (F2 pups) were retained until Day 21 *post-partum*, at which time they were sacrificed and skeletal examination was conducted.

There were no specific compound-related clinical signs. Deaths in the P1 and F1 generation males were not considered compound-related.

The significant pathological finding for the P1 generation was increased liver weight in both sexes (10-20%), although no pathological evidence of effects in the liver was found. An increase in the incidence of splenic haemosiderosis was seen in both sexes of the P1 and F1 generations, consistent with the regenerative anaemia observed in the repeat dose studies.

Body weight gains or average body weights were significantly reduced for P1 and F1 generation rats in the 6000 ppm group.

A significant decrease in pup weight/litter was noted for 6000 ppm group. At this dose, the average pup weight was significantly lower from Day 1 (9%) to Day 21 (21%) of lactation.

There were no gross abnormalities, however a few minor skeletal abnormalities (unilateral/bilateral 14^{th} rib, decreased number of lumbar vertebrae, increased number of thoracic vertebrae and rib pairs), indicative of disturbed ossification, were observed in the F2 litters at 2000ppm and 6000ppm. The incidences were more prominent at the high dose (6000ppm). These were considered most likely to have been due to the poor nutritional state of the dams.

No adverse effects on fertility parameters including mating, gestational indices and length, pup viability and lactation performance were observed at doses up to 6000 ppm (equivalent to 288 - 909 mg/kg bw/d), the highest dose tested.

4.11.1.2 Human information

There is no human information available.

4.11.2 Developmental toxicity

Two developmental toxicity studies are available; one extended study in rats, with a method similar to OECD 414, and one guideline study in rabbits. There is also an additional rabbit study, which was conducted to further investigate one of the findings in the developmental study.

Table 24: Summary table of relevant reproductive toxicity studies - Development

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Developmental toxicity study in rats Rat/ (SD) Females: 36 per group Oral (gavage) Purity 92.9% OECD 414, **(extended to produce F1 litter from some parental animals)** GLP CAR Doc IIIA A6.8.1/01 Panapharm Laboratories Co. Ltd (1992)	0, 50, 200 or 600 mg/kg/d (vehicle: corn oil) Exposure period: Gestation days 6-17	No effect on gestation, litter size, lactation, viability index or weaning index for any dose group. **Dams** <u>50mg/kg/d</u> No adverse effects reported <u>200mg/kg/d</u> Minor signs of toxicity immediately after dosing ↓ bodyweight gain 20-106% (Days 8 and 10-12) <u>600mg/kg/d</u> Mortality (3/36) with signs of toxicity (tremor, clonic convulsion and staggering gait) ↓ bodyweight at (Day 8 of gestation), ↓ bodyweight gain 22-180% (Days 8-13 and 15 of gestation) ↓ food consumption (Days 7-10 of gestation) **Fetuses** <u>50mg/kg/d</u> ↑ incidence of unilateral dilatation of the renal pelvis (6/125 vs 0/119 in control) <u>200mg/kg/d</u> ↑ incidence of minor skeletal abnormalities ↑ incidence of lumbar rib (incidence of 48% vs 16% in controls) <u>600mg/kg/d</u> ↓ fetal weight (6%) ↑ incidence of minor skeletal abnormalities ↑ incidence of lumbar rib (incidence of 68% vs. 16% in controls), ↑ incidence of pre-sacral vertebrae (12% vs 1% in controls) ↑ incidence of splitting of the vertebral body (14% vs. 1% in controls) ↑ number of fetuses with thymic remnants in the neck (22% vs. 3% in controls) reduced ossification of 5th and 6th stern brae *NOAEL*: 50mg/kg/d (Maternal toxicity)*

		NOAEL: 50mg/kg/d (Developmental toxicity)*
Developmental toxicity study in rabbits Rabbit/JW-NIBS Female: 15 per group Oral (gavage) Purity 92.9% OECD 414 GLP CAR Doc IIIA A6.8.1/02 Sumitomo Chemical Co. Ltd (1992)	0, 30, 100 or 300mg/kg/d (vehicle: corn oil) Exposure period: Gestation days 6-18	**Dams** <u>100mg/kg/d</u> 1 abortion or premature labour ↓ bodyweight gain and food consumption Tremor in one animal immediately after administration of test article on Day 8 of gestation. <u>300mg/kg/d</u> 2 deaths (Days 17&26) 1 moribund animal (Day 18) 5 abortions or premature labours (1 of which was the dead animal) ↓ food consumption (29-78%), bodyweight gain (68-200%) and bodyweight (7-8% on days 15-18 of gestation) Pale red urine **Fetuses** <u>30mg/kg/d</u> 27 pre-sacral vertebrae (6 fetuses vs. 1 in controls) <u>100mg/kg/d</u> ↓ bodyweight Fusion of the nasal bone (1 animal vs. 1 in controls) Hypoplasia of the frontal bone (2 animals vs. 0 in controls) 27 pre-sacral vertebrae (7 fetuses vs. 1 in controls) <u>300mg/kg/d</u> ↓ bodyweight (males:15%; females:16%: correlated to ↓ food consumption) ↑ incidence of fusion in the nasal bone (9 animals vs 1 in controls) ↑ incidence of hypoplasia of the frontal bone (10 animals vs. 0 in controls) 27 pre-sacral vertebrae (11 fetuses vs 1 in controls) *NOAEL*: 30mg/kg/d (Maternal toxicity)* *NOAEL*: 30mg/kg/d (Developmental toxicity)*

Additional study in rabbits (1992) Rabbits/JW-NIBS (20 females/ group) Oral (gavage) Imiprothrin Purity 92.2% U.S. EPA-FIFRA Guideline 83-3 GLP Sumitomo Chemical Co. Ltd (1992)	0, 3, 10 or 30mg/kg/d Once daily - days 6 -18	*Dams* <u>Control</u> Vesicle point(s) in kidney (3 dams) Blackish spot in liver (1 dam) <u>3mg/kg/d</u> Tremor in one dam – death 4 minutes later – At necropsy of this dam, an oily substance was observed in the lung, suggesting a gavage error. Abortion/premature labour on d27 of gestation (1 dam) Abnormal lobulation of lung (1 dam) Whitish spot in kidney (1 dam) Whitish point(s) in liver (1 dam) <u>10mg/kg/d</u> Abortion/premature labour in one dam on d28 gestation Vesicle point(s) in kidney (1 dam) Deformed spleen (1 dam) Diverticulum of the gallbladder (1 dam) Yellowish material in yolk sac (1 dam) <u>30mg/kg/d</u> Vesicle point(s) in kidney (1 dam) Linear scar in the kidney (1 dam) Blackish spot on duodenal mucosa (1 dam) Liver showed whitish point(s) (3 dams) *Fetuses* <u>Control</u> 27 pre-sacral vertebrae (2 fetuses) <u>3mg/kg/d</u> 27 pre-sacral vertebrae (6 fetuses) <u>10mg/kg/d</u> Asymmetry of the cervical vertebral arch (1 fetus) (malformation) 27 pre-sacral vertebrae (5 fetuses) <u>30mg/kg/d</u> ↑ number of ossified middle phalanges of finger (females) 27 pre-sacral vertebrae (6 fetuses) Various minor anomalies and skeletal variations in addition to 27 pre-sacral vertebrae were observed. However, the incidences were not different between the treated and control groups.

*As given in the Competent Authority Report Doc IIA

4.11.2.1 Non-human information

The potential of imiprothrin to cause adverse developmental effects has been investigated in rats and rabbits.

Study in rats

The extended developmental toxicity study in rats was similar to OECD guideline 414. Imiprothrin (92.9%) was administered to Sprague Dawley rats (36/dose) at 0, 50, 200 and 600mg/kg bw/d in corn oil, by gavage, on Days 6-17 of gestation. Two thirds of dams were sacrificed on day 20 and the fetuses were examined for developmental toxicity, with the remaining third of dams allowed to deliver offspring to produce the F1 generation. The dosing period was extended when the test guidelines were revised. The OECD 414 guideline recommends that the substance is administered daily from implantation (day 5 post mating) until the day prior to scheduled kill. If available preliminary studies are not indicative of a high potential for preimplantation loss, treatment may be extended; beginning from mating until the day prior to scheduled caesarean section. The shorter dosing period used in the available study for imiprothrin is not considered to have affected the reliability of the results.

On day 4 postpartum, the number of new-born pups was adjusted to 8 per litter. Three males and females per litter were selected for behavioural testing and a further two males and females per litter, at 12-13 weeks of age, were selected for assessment of toxic effects. The behavioural testing included a motor co-ordination test, a water-maze test and an open field test. The F1 animals used in the behaviour tests were sacrificed at 12 weeks of age and histopathology was conducted.

Maternal toxicity

Deaths (3/36) and clear signs of toxicity (tremor, clonic convulsion and staggering gait) were noted at 600 mg/kg/d: two showed soiled perinaris, loose stools, salivation, lateral position, hypoactivity and bradypnea and died on Days 9 and 12 of gestation. The death of the third animal was attributed to a dosing error. No gross abnormalities were observed on necropsy.

In the 600 mg/kg/d group, body weight was reduced on Day 8 of gestation and body weight gain reduced on Days 8-13 and 15 of gestation. Food consumption was reduced on Days 7-10 of gestation.

In the 200 mg/kg/d dose group there were minor signs of toxicity immediately after dosing. There was no effect on body weight although body weight gain was reduced on Days 8 and 10-12.

No effects were observed on gestation, litter size, lactation, viability index or weaning index for any dose group.

No adverse effects were observed on mating, fertility and gestation of F1 parental animals. There were no differences in viability index after birth in the treated groups. No abnormalities were observed following necropsy of F1 parental animals and fetuses from F1 dams.

Developmental effects

At 600 mg/kg/d, fetal weights of both sexes were reduced. On necropsy, there were no gross fetal abnormalities.

An increased incidence of unilateral dilatation of the renal pelvis (6/125 vs 0/119 in controls) was observed in fetuses of the 50mg/kg dose group. However, this observation was considered to be an incidental finding because it was not observed at higher doses.

No treatment-related cranio-facial or other skeletal malformations were observed. However there was a statistically significant increased incidence of skeletal variations. Higher incidences of lumbar rib were observed at the mid- and high- doses (16%, 20%, 48% and 68% at 0, 50, 200 and 600 mg/kg/d, respectively). The dose-dependent increase in the incidence of lumbar rib raises a possible cause for concern for developmental toxicity. Splitting of the vertebral body (32 (14%) compared to 2 (1%) in control) and increase pre-sacral vertebrae (12% vs. 1% in control) were observed together with reduced ossification of 5^{th} and 6^{th} stenebrae in fetuses at 600 mg/kg/d.

In addition, a significant increase in number of fetuses with visceral anomalies mainly thymic remnants in the neck was seen at 600mg/kg/d (0/119, 2/125, 0/119 and 24/127 at 0, 50, 200 and 600mg/kg/d, respectively).

Since considerable overt signs of toxicity including mortality were evident in dams at the dose levels at which skeletal and visceral variations were observed, it is possible that the fetal effects could be considered as secondary consequences of maternal toxicity.

<u>*Study in rabbits*</u>

Imiprothrin (92.9%) was administered to JW-NIBS rabbits (15-17/dose) at 0, 30, 100 and 300mg/kg bw/d in corn oil, by gavage on days 6-18 of gestation.

Maternal toxicity

In the 300 mg/kg/d dose group, 1 death (day 26), 1 moribund animal (day 18) and 5 abortions or premature labour (1 of which was the dead animal) occurred. In addition, one animal had a tremor immediately after test article administration on day 17 and died shortly afterwards (this may have been due to a gavage error). Body weight gain (↓ 68-200%) and food consumption were reduced and body weight (↓ 7-8% on days 15-18 of gestation) was statistically reduced in the late phase of the administration period. Pale red urine was found for all animals of this dose group. This is likely to have been related to the spontaneous abortions. Abnormalities of the digestive system, such as blackish points or depression on gastric or duodenal mucosa, gas retention in the digestive tract,

muddy content in cecum, yellowish points on the gall bladder mucosa and pale colouration of heart and kidney were found and considered to be treatment-related.

At 100mg/kg/d, 1 animal had an abortion or premature labour. However as this also occurred for one control animal and few abnormal necropsy findings were present for both animals, the abortion or premature labour in these two animals was considered spontaneous. Body weights were not different from the control group, although body weight gain and food consumption tended to be reduced (not statistically different from control). Tremor was noted in one animal immediately after administration of the test article on Day 8 of gestation and in another animal a red fluid was vomited from the mouth during administration. These were considered to be due to gavage error.

Developmental effects

There were no differences between each group and the control group with respect to number of corpora lutea, number of implantations, implantation index, gestation, mortality of fetuses and embryos, number of live fetuses and sex ratio. No fetus showed any abnormal external characteristics. Visceral examination showed minor abnormalities and variations in each treated group, which were not different from the control group.

At 100mg/kg/d, there was a tendency towards lower fetal body weight. At 300mg/kg/d, body weights of live fetuses were significantly lower for both sexes (males: 15%; females: 16%). Low fetal weight was correlated to suppression of food consumption.

A number of dams were excluded from the analysis for various reasons including gavage error, decreased bodyweight and food consumption and emesis of red liquid. Excluding those dams, the developmental effects observed in this study are summarised in the table below. One type of malformation was observed (fusion of the nasal bone) in addition to 2 types of skeletal variation (hypoplasia of the frontal bone and 27 pre-sacral vertebrae).

Table 25: Incidences of effects observed in the rabbit developmental toxicity study

	Dose (mg/kg bw/d)				
	0	30	100	300	hcd
Hypoplasia of the frontal bone					
Number of pups with effect	**0/74 (0%)**	**0/75 (0%)**	**2/70 (2.9%)**	**10/64 (15.6%)**	**Mean: 0.1% Range: 0.0-1.4%**
Litter incidence	0/12 (0%)	0/11 (0%)	1/10 (10%)	2/8 (25%)	
Fetal incidences within affected litters	N/A	N/A	2/8	4/8 6/10	
Fusion of the nasal bone					
Number of pups with effect	**1/74 (1.4%)**	**0/75 (0%)**	**1/70 (1.4%)**	**9/64 (14.1%)**	**Mean: 0.1% Range: 0.0-1.4%**
Litter incidence	1/12 (8.3%)	0/11 (0%)	1/10 (10%)	4/8 (50%)	
Fetal incidences within affected litters	1/7	N/A	1/9	3/8 1/8 3/8 2/10	
27 Pre-sacral vertebrae					
Number of pups with effect	**1/74 (1.4%)**	**6/75 (8.0%)**	**7/70 (10.0%)**	**11/64 (17.2%)**	**Mean: 3.4% Range: 0.0-8.6%**
Litter incidence	1/12 (8.3%)	4/11 (36.4%)	3/10 (30%)	3/8 (37.5%)	
Fetal incidences within affected litters	1/7	1/5 3/8 1/8 1/4	3/6 1/5 3/7	6/10 1/8 4/6	

hcd: historical control data from 11 studies (1989-1992); one of which was the main oral study in rabbits and one of which was the additional study in rabbits.

Full historical control data for skeletal anomaly and variation in JW-NIBS rabbits were provided by the applicant.

Table 26: Historical control data for skeletal anomaly and variation in JW-NIBS rabbits

Study ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a)]**	**9**	**10**	**11[b)]**		
Study Year	**1989**	**1989**	**1989**	**1989**	**1990**	**1990**	**1991**	**1991**	**1991**	**1991**	**1992**		
No. of dams	**14**	**13**	**2**	**13**	**14**	**12**	**14**	**12**	**14**	**15**	**17**		
No. of fetuses	**81**	**84**	**15**	**82**	**78**	**71**	**96**	**74**	**81**	**101**	**113**	**Mean**	**Range**
Fusion of the nasal bone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	**0.1 (0.1)**	**0 - 1 (0.0-1.4)**
Hypoplasia of the frontal bone	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0.1 (0.1)**	**0 - 1 (0.0-1.4)**
27 Pre-sacral vertebrae	2 (2.5)	1 (1.2)	0 (0.0)	3 (3.7)	0 (0.0)	2 (2.8)	7 (7.3)	1 (1.4)	7 (8.6)	8 (7.9)	2 (1.8)	**2.7 (3.4)**	**0 - 8 (0.0-8.6)**

Numbers in brackets are frequencies

[a)] Study ID no. 8 is 1st study of imiprothrin

[b)] Study ID no. 11 is 2nd study of imiprothrin

Fusion of the nasal bone

Fusion of the nasal bone, which is regarded as a malformation, was observed at incidences of 1.4%, 0%, 1.4% and 14.1% in the control, 30, 100 and 300mg/kg bw/d dose groups respectively. The significantly increased incidence at the top dose greatly exceeded the historical control data range (0-1.4%) and is considered to be treatment-related.

At 100mg/kg bw/d, dam numbers 312 and 313 received gavage error. Tremor was noted immediately after administration on day 8 of gestation in animal no. 312. The tremor, which the study author attributed to gavage error, disappeared in approximately 15 minutes. Emesia of red liquid at administration on day 12 of gestation was noted in dam no. 313. The study author excluded these animals from the statistical analysis from the time of gavage error.

Hypoplasia of the frontal bone

Hypoplasia of the frontal bone was observed in treated animals at incidences of 0%, 0%, 2.9% and 15.6% at 0, 30, 100 and 300mg/kg bw/d, respectively. At 100mg/kg bw/d, the effect was observed in 2 pups in 1 of the 10 litters. However this hypoplastic effect was also noted at this dose in 3/7 pups of dam no. 312, which was excluded from analysis after day 8 of gestation due to gavage error on that day. At 300mg/kg/d, hypoplasia of the frontal bone was observed in 10 fetuses (2/8 litters; with a fetal incidence of 4/8 and 6/10 pups). The former of these two litters was the same litter in which 1/8 pups showed fusion in the nasal bone at 300mg/kg/d, indicating a possible cause for concern for craniofacial development. It is unclear from the available data whether the two effects occurred in the same animal; only that they were observed in the same litter. It was postulated by the study author

that the hypoplasia may have been a retarded ossification related to lower fetal body weights (and thus suppression of food consumption in the dams).

27 Pre sacral vertebrae

The finding of 27 pre-sacral vertebrae, which is regarded as a skeletal variation, was observed in all groups with fetal incidences of 1.4%, 8.0%, 10.0% and 17.2% at 0, 30, 100 and 300mg/kg bw/d, respectively. According to the study author, the incidence in the treated groups was not statistically different to the control group although the incidence tended to increase dose-dependently. Additionally, 27 PSV was observed in one pup of the dam in the 100mg/kg bw/d group which was excluded from the analysis due to gavage error. The incidence at the top dose (17.2%) was higher than the spontaneous incidence for the test laboratory at the time of the imiprothrin study (0 – 7.3%: study numbers 1 - 8 in table 26). However it was stated by the study author that the incidence at 30 mg/kg/d (8%) also exceeded the upper limit of spontaneous incidence in the laboratory, although not greatly, and was not significantly different from the control group in this study. n Thus no definite conclusion was reached regarding treatment-relationship.

Following on from the observation of 27 pre-sacral vertebrae, an additional study was conducted, in which animals (20/group) were dosed at 0, 3, 10 or 30 mg/kg/d. 27 pre-sacral vertebrae was observed in 2, 6, 5 and 6 fetuses (1.8, 5.2, 3.9 and 4.8%) in the control, 3, 10 and 30mg/kg/d groups respectively, suggesting no dose-relationship or any significance between treated and control groups. The study authors concluded that there was no tendency for 27 pre-sacral vertebrae to increase in a dose dependant manner, as it had done in the previous study. Various minor anomalies and skeletal variations in addition to 27 pre-sacral vertebrae were observed. However, the incidences were not different between the treated and control groups.

Table 27: Incidence of 27 Pre-sacral vertebrae in rabbits

	Fetal incidence of 27 Pre-sacral vertebrae					
Dose (mg/kg/d)	0	3	10	30	100	300
Main study	1.35%			8%	10.0%	17.2%
Additional study	1.8%	5.2%	3.9%	4.8%		

The results of the two rabbit studies are presented in the table above. Although the study authors concluded that there was no significance between the incidence of 27 pre-sacral vertebrae in the treated and control groups in the additional study, the overall picture from the 2 studies could be interpreted as showing a dose dependent increase in the incidence of 27 pre-sacral vertebrae in rabbits from 3mg/kg/d. However, the 8% incidence of 27 pre-sacral vertebrae observed in the first study was not reproduced in the second study. When the spontaneous incidence data was amended to include further studies conducted shortly after the imiprothrin study, the incidence at 30mg/kg bw/d (8%) fell within the newly updated historical data range (0 - 8.6%: Study numbers 1 – 11 in table 26). There was certainly an effect at the top dose of the first study. However, the relevance of this finding is not clear because maternal toxicity was noted at this dose. Therefore there is some uncertainty surrounding these observations. Since the observations at ≤ 30mg/kg bw/d are equivocal, it is considered most reasonable to conclude from these studies that imiprothrin caused an increased incidence of 27 pre-sacral vertebrae at ≥ 100mg/kg bw/d. Therefore there is a *possible* cause for concern for developmental toxicity.

From the results of the rabbit study, it appears that imiprothrin does have the potential to induce adverse developmental effects in fetuses including fusion of the nasal bone, hypoplasia of the frontal

bone and 27 pre-sacral vertebrae. However, the effects were mainly seen at maternally toxic doses and therefore require further consideration in relation to classification.

4.11.2.2 Human information

There is no human information available.

4.11.3 Other relevant information

4.11.4 Summary and discussion of reproductive toxicity

Effects on fertility

A two-generation study in the rat found no adverse effects on fertility parameters including mating, gestational indices and length, pup viability and lactation performance at doses up to 6000 ppm in the diet (equivalent to 288 - 909 mg/kg bw/d). Therefore, imiprothrin does not cause any adverse effects on fertility at doses of up to 288-909 mg/kg/day, the highest dose tested.

Supporting evidence for a lack of effect is available from the repeated dose studies. Whilst the absolute weight of the uterus decreased significantly in dogs exposed to ≥50 mg imiprothrin/kg/d for 1 year, there were no accompanying histopathological findings. Changes in the weights of other reproductive organs (prostate, testes and ovaries) were also observed in repeated dose studies, but their magnitudes did not raise concern for significant treatment-related toxicity.

Developmental toxicity

Two developmental toxicity studies are available; one in rats and one in rabbits, plus an additional study in the rabbit to investigate an effect observed in the main study.

Rabbit

Maternal toxicity was clearly evident at 300 mg/kg bw/day (two treated animals died and five suffered abortion or premature labours, maternal bodyweight was significantly reduced in the last phase of the dosing period and bodyweight gain was suppressed throughout the study period). At 100 mg/kg bw/day, body weight was not different from the control group, although body weight gain and food consumption tended to be reduced (not statistically different from control).

A statistically significant and dose-related reduction in fetal bodyweight was observed at 300 mg/kg/d.

Skeletal variations were observed from doses of 100mg/kg bw/day and skeletal malformations were seen at the top dose.

An increased incidence of fusion of the nasal bone was observed at 300mg/kg/day (9 animals vs. 1 in controls). The applicant characterised the effect as a minor anomaly because the fused site was observed only in the proximal portion of the nasal structure. However, fusion of skull bones is considered to be of a high level of concern, as noted in the ECETOC Guidance on Evaluation of Reproductive Toxicity Data.

Hypoplasia of the frontal bone was also seen in groups treated with 100 and 300 mg/kg bw/day; although it is noted that the mean fetal weight in the litters exhibiting this effect was lower than the overall average. In addition, the dam giving birth to the litter at 100 mg/kg bw/day was found to have

lower bodyweight, decreased body weight gain and reduced food consumption when compared to the group average. However, similar findings were noted in another dam at this does level without further consequences.

Increased incidence of 27 pre-sacral vertebrae (a skeletal variation) was observed in all treated groups and exceeded historical control values from 100mg/kg bw/d. In an additional rabbit study, conducted to further investigate the observation of 27 pre-sacral vertebrae in the first study, this skeletal variation was observed at fetal incidences of 1.8%, 5.2%, 3.9% and 4.8% at 0, 3, 10 and 30mg/kg bw/d, respectively. Although the study authors concluded from this study that there was no tendency for 27 pre-sacral vertebrae to increase in a dose-dependent manner, the results from the first study showing that imiprothrin caused an increase in the incidence of 27 pre-sacral vertebrae at doses ≥ 100mg/kg bw/d cannot be dismissed.

Overall, the results indicate that imiprothrin has the potential to induce developmental toxicity in rabbits under the conditions of this study. However, the possibility that the developmental toxicity was secondary to maternal toxicity should be taken into consideration.

Rat

In the rat developmental toxicity study, no treatment-related cranio-facial or other skeletal malformations were observed. However, increases in skeletal variations were noted at 200 mg/kg/d and above. There was a higher incidence of lumbar rib at the mid and high dose levels and an increased incidence of pre-sacral vertebrae and splitting of the vertebral body were observed at 600 mg/kg/d. An increase in the number of fetuses with thymic remnants in the neck was observed at 600 mg/kg/d.

As in the rabbit study, adverse developmental effects in rats occurred in combination with maternal toxicity. Therefore adverse developmental effects may have been secondary to the state of the dams. The increased incidence of skeletal variations and thymic remnants occurred in groups showing maternal toxicity. Following oral administration of 600mg/kg/d of imiprothrin, three dams died and signs of toxicity (tremor, clonic convulsion and staggering gait) were evident. Bodyweight gain from gestation days 8-12/13 was significantly reduced at ≥200 mg/kg/d (by 20-180%). Fetal bodyweights in the 600mg/kg/d group were 6% lower than controls.

In the rat two-generation study, increased incidences of minor skeletal abnormalities (unilateral/bilateral 14th rib, decreased number of lumbar vertebrae, increased number of thoracic vertebrae and rib pairs) were observed at ≥2000ppm. However, the incidences were more prominent at 6000ppm and may have resulted from the suppression of body weight associated with reduced food consumption in the parent animals (i.e. F1 dams).

In summary, no malformations were observed in rat fetuses at any dose. However, skeletal and visceral variations were noted. Comparison with criteria

4.11.5 Comparison with criteria

Fertility

In a standard two generation study, there were no adverse effects on reproductive performance, fertility and parturition in rats fed imiprothrin at dietary concentration of up to 6000ppm (equivalent to 288-909 mg/kg bw/d). Therefore imiprothrin does not warrant classification for fertility.

Development

In rats and rabbits, maternal toxicity was evident at the top dose (600 and 300 mg/kg bw/day in rats and rabbits respectively). At the mid-dose (200 and 100 mg/kg bw/day in rats and rabbits respectively) only minor effects on maternal bodyweight or bodyweight gain and food consumption were noted.

A skeletal malformation (fusion of the nasal bone) was observed at the top dose in rabbits, but no malformations were noted in rats at any dose. Fusion of skull bones is considered to be of a high level of concern (ECETOC Guidance on Evaluation of Reproductive Toxicity Data).

Skeletal variations were observed in both species from lower doses, in addition to visceral variations in rats.

The apparent dose-dependent increase in 27 pre-sacral vertebrae in the first rabbit developmental toxicity study (1.4%, 8%, 10.0% and 17.2% at 0, 30, 100 and 300mg/kg bw/d) is difficult to interpret. Maternal toxicity was clearly evident at 300 mg/kg bw/d, but was less apparent at 100 mg/kg bw/d where only body weight gain and food consumption tended to be reduced (but without statistical significance compared to controls). The incidence at the low dose (8%) was found to be within the range of the updated historical control data (0-8.6%) and the results of the additional study (conducted with 3, 10 and 30 mg/kg bw/day imiprothrin) did not confirm the findings at 30 mg/kg bw/day in the original study. However, overall, it is considered that the observation of increased 27 pre-sacral vertebrae at 100 mg/kg bw/day cannot be dismissed completely.

Hypoplasia of the frontal bone was seen in rabbits at 100 and 300 mg/kg bw/day. Whilst there is evidence that this was associated with lower fetal body weight and reduced body weight gain and food consumption in the dams, the findings in 2 fetuses from 1 litter at 100mg/kg/d in rabbits cannot be dismissed completely.

It is possible that the increased incidences of lumbar rib, pre-sacral vertebrae and splitting of the vertebral body seen at the top-dose level of 600 mg/kg bw/day in the rat developmental toxicity study, together with the increase in the number of fetuses with thymic remnants in the neck, could be due to maternal toxicity. However, the increased incidence of minor skeletal abnormalities and lumbar rib in fetuses at 200mg/kg/day cannot be discounted on account of maternal toxicity since dams at this dose level showed only minor signs of toxicity immediately after dosing and a decrease in bodyweight gain on days 8 and 10-12.

The increased incidence of abortion/premature labour observed in rabbits may be a non-specific secondary consequence of toxicity in the dams as depicted by the reduction in body weight gain (68-200%) and food consumption (29-78%).

The ECETOC Guidance on Evaluation of Reproductive Toxicity Data supports the designation of supernumerary ribs and small (hypoplastic) skull bones as variations/retardations of a low-moderate level of concern. Consequently, these effects observed in rats and rabbits could be considered insufficient to support classification for developmental toxicity. However, the malformation observed in rabbits (fusion of the nasal bones) supports classification of imiprothrin for developmental toxicity because it is considered to be of a high level of concern (ECETOC Guidance). Adding to the weight of evidence for classification is the fact that the incidence of lumbar rib in the rat and the observations of 27 pre-sacral vertebrae, fusion of the nasal bone, and hypoplasia of the frontal bone in rabbits showed clear dose-response relationships. Also, the effects occurred in more

than one litter, at least at the top dose. The fetal and litter incidences of the abnormalities give rise to a cause for concern for craniofacial development.

Category 1A is reserved for known human reproductive toxicants. As no human data are available, classification of imiprothrin in category 1A is not warranted.

Categories 1B and 2 are reserved for presumed and suspected human reproductive toxicants respectively. According to table 3.7.1(a) in Annex I of the CLP Regulation:

> *"Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1…Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects."*
>
> *Section 3.7.1.4.2 of Annex I of CLP also states that "Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity.*

Had the fusion of the nasal bone and hypoplasia occurred in the absence of maternal toxicity, it is considered that a classification for reproductive toxicity in Category 1B could have been justified. Taking the maternal toxicity into consideration reduces the level of concern, but it is considered that it cannot *be unequivocally demonstrated that the developmental effects were secondary to maternal toxicity.* Therefore, these effects are considered to present evidence of developmental toxicity and classification in Category 2 is considered appropriate.

Lactation

Classification for effects on or via lactation is based on the following criteria, laid out in Section 3.7.2.1.1 of Annex I of the CLP Regulation:

(a) Human evidence indicating a hazard to babies during the lactation period;

No human evidence is available.

(b) Results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk;

There is no such evidence.

(c) Absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

The ability of imiprothrin to partition into the breast milk has not been investigated.

On this basis, imiprothrin does not meet the criteria in the CLP Regulation and therefore no classification for effects on or via lactation is proposed.

4.11.6 Conclusions on classification and labelling

Repr. 2- H361d; Suspected of damaging the unborn child

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

For the endpoint reproductive toxicity, one two-generation study in rats is available, as well as two developmental toxicity studies (one in rats, one in rabbits).

Fertility

In a two-generation study (Study SGT-41-0067, 1994) conducted under GLP and conform to OECD TG 416, imiprothrin was administered to SD rats (30/sex/group) at 0, 200, 2000 or 6000 ppm in the diet for two generations. The achieved test material intakes for P1 parental animals were 9-20, 95-179 and 288-543 mg/kg bw/day (males) and 12-31, 110-325 and 346-909 mg/kg bw/day (females) at 200, 2000 and 6000 ppm, respectively. F1 animals received 11-30, 115-300 and 350-972 mg/kg bw/day (males) and 12-29, 117-297 and 366-883 mg/kg bw/day (females) at 200, 2000 and 6000 ppm, respectively. The main effects observed in the parental generations included decreased food consumption, body weight and body weight gain (at 6000 ppm in males and females of P1 and F1, and at 2000 ppm in F1 females), increased incidences of splenic haemosiderosis (at 6000 ppm in males and females of P1 and F1, and at 2000 ppm in P1 females), and increased liver weights without histopathology findings (at 6000 ppm in P1 males and females and F1 females). In pups at the top dose, a significant decrease in pup weight was seen from day 1 (9%) to day 21 (21%) of lactation. Pups showed no gross abnormalities, but a few minor skeletal abnormalities (increased number of unilateral/bilateral 14th rib, thoracic vertebrae and rib pairs, decreased number of lumbar vertebrae), indicative of disturbed ossification, were observed in F2 litters at 2000 and (more prominently) 6000 ppm. These were considered most likely to have been due to the poor nutritional state of the dams. There were no adverse effects on fertility parameters including mating, gestational indices and length, pup viability and lactation performance.

Given the lack of adverse effects on fertility, the DS concluded that imiprothrin does not warrant classification for fertility.

Developmental toxicity

<u>Rats</u>

In an extended developmental toxicity study (Study SGT-21-0048, 1992) conducted under GLP and with a method similar to OECD TG 414, imiprothrin was administered to female SD rats (36/dose) at 0, 50, 200 and 600 mg/kg bw/day in corn oil, by gavage, on days 6-17 of gestation. Two thirds of dams were sacrificed on day 20 and the foetuses were examined for developmental toxicity, with the remaining one third of dams allowed to deliver offspring to produce the F1 generation.

Maternal toxicity was evident at the top dose, with clear signs of toxicity (such as tremor, clonic convulsions and staggering gate), death (3/36, with 1/3 due to a dosing error) and reductions in food consumption, body weight and body weight gain on several gestation days (but no longer at the end of gestation). The latter reductions were, to a more limited degree, also seen at the mid dose, as well as minor signs of toxicity immediately after dosing.

Foetal weights at 600 mg/kg bw/day were slightly (not statistically significantly) decreased (6%). There was a significant increase in number of foetuses with visceral anomalies, mainly thymic remnants in the neck seen at 600 mg/kg bw/day (22% compared to 3% in control). An increased incidence of unilateral dilatation of the renal pelvis was observed at 50 mg/kg bw/day (6/125 vs 0/119 in control), but this was considered an incidental finding since the effect was not seen at higher dose levels. No treatment-related skeletal anomalies were observed. However, increased incidences of skeletal variations were seen: higher incidences of lumbar rib were found at 200 and 600 mg/kg bw/day (16%, 20%, 48% and 68% at 0, 50, 200 and 600 mg/kg bw/day, respectively). Foetuses at 600 mg/kg bw/day additionally showed pre-sacral vertebrae (12% vs 1% in control), splitting of the vertebral body (14% compared to 1%), and reduced ossification of 5^{th} and 6^{th} vertebrae.

In this extended study no abnormal effects were observed on mating, fertility and gestation of F1 parental animals, neither were there differences in viability index after birth in the treated groups, or abnormalities following necropsy of F1 parental animals and foetuses from F1 dams. There were also no differences in any F1 groups in the motor coordination, learning ability and emotional behaviour tests.

Since considerable overt signs of toxicity including mortality were evident in dams at the high dose, the DS considered it possible that the foetal effects could be considered as secondary consequences of maternal toxicity. At the mid dose, however, the maternal toxicity was limited to transient reductions in body weight gain.

Rabbits

In a developmental toxicity study (Study SGT-20-0025, 1992) conducted under GLP and conform OECD TG 414, imiprothrin was administered to female JW-NIBS rabbits (15/dose) at 0, 30, 100 and 300 mg/kg bw/day in corn oil, by gavage, on days 6-18 of gestation. In a follow-up study, additional animals (20/group) were dosed at 0, 3, 10 or 30 mg/kg bw/day on days 6-18 of gestation, to further investigate some of the findings in the main study.

The top dose of 300 mg/kg bw/day was clearly maternally toxic with clinical signs, death (2 animals, 1 of which may have been due to a gavage error, plus 1 moribund animal), abortions or premature labour (5 animals, 1 of which was a dead animal), and statistically significantly reduced body weight gain (by 68-200%, throughout gestation), food consumption (by 29-78%, throughout treatment period) and body weight (by 7-8% on days 15-18 of gestation). Abortion or premature labour was also seen in 1 animal at 100 mg/kg bw/day, but as this also occurred in 1 control animal, the finding was considered spontaneous. Body weight gain and food consumption were also reduced at 100 mg/kg bw/day throughout gestation and treatment period, respectively, but the differences with controls were not statistically significant. No maternal toxicity was seen at 30 mg/kg bw/day.

A statistically significant reduction in foetal body weight was observed at 300 mg/kg bw/day (15-16%). Also at 100 mg/kg bw/day the foetal bodyweight tended to be reduced (4.3-4.9%; not statistically significant). No foetus showed any abnormal external characteristics. Visceral examination showed minor abnormalities and variations in each treated group, which were not different from the control group. One type of skeletal malformation was observed (fusion of the nasal bone) in addition to two types of skeletal variation (hypoplasia of the frontal bone and 27 pre-sacral vertebrae). The incidences are shown in the table below.

Table: Incidences of skeletal malformations and variations observed in the rabbit developmental toxicity study

	Dose (mg/kg bw/day)				
	0	30	100	300	HCD
Fusion of the nasal bone					
Number of pups with effect	**1/74 (1.4%)**	**0/75 (0%)**	**1/70 (1.4%)**	**9/64* (14.1%)**	**Mean: 0.1% Range: 0.0-1.4%**
Litter incidence	1/12 (8.3%)	0/11 (0%)	1/10 (10%)	4/8 (50%)	
Foetal incidences within affected litters	1/7	N/A	1/9	3/8 1/8 3/8 2/10	
Hypoplasia of the frontal bone					
Number of pups with effect	**0/74 (0%)**	**0/75 (0%)**	**2/70 (2.9%)**	**10/64 (15.6%)**	**Mean: 0.1% Range: 0.0-1.4%**
Litter incidence	0/12 (0%)	0/11 (0%)	1/10 (10%)	2/8 (25%)	
Foetal incidences within affected litters	N/A	N/A	2/8	4/8 6/10	
27 Pre-sacral vertebrae					
Number of pups with effect	**1/74 (1.4%)**	**6/75 (8.0%)**	**7/70 (10.0%)**	**11/64 (17.2%)**	**Mean: 3.4% Range: 0.0-8.6%**
Litter incidence	1/12 (8.3%)	4/11 (36.4%)	3/10 (30%)	3/8 (37.5%)	
Foetal incidences within affected litters	1/7	1/5 3/8 1/8 1/4	3/6 1/5 3/7	6/10 1/8 4/6	

HCD: historical control data from 11 studies (1989-1992); one of which was the main oral study in rabbits and one of which was the additional study in rabbits.
* Significantly different from control group at $P < 0.05$

Fusion of the nasal bone, which the DS considered to be a malformation, was observed at the top dose in 50% of the litters with an incidence (14.1%) greatly exceeding the historical control range (0-1.4%). Hypoplasia of the frontal bone was observed at the top dose (in 2/8 litters, one litter being the same litter in which 1/8 pups showed fusion in the nasal bone, indicating a possible cause for concern for craniofacial development) and the mid dose (in 1/10 litters; however, it was also noted in 3/7 pups of a dam that was excluded from analysis due to gavage error). The incidences at the mid (2.9%) and high

dose (15.6%) exceeded the historical control range (0-1.4%). It was postulated by the study author that the hypoplasia (which is considered a variation) may have been a retarded ossification related to lower foetal body weights (and thus suppression of food consumption in the dams).

A dose-related (but not statistically significant) increase in 27 pre-sacral vertebrae (regarded as a skeletal variation) was observed in all groups, with statistical significant foetal incidences at the mid dose (10.0%) and high dose (17.2%) exceeding the historical control range (0-8.6%). This effect was additionally observed in one pup of a mid-dose dam that was excluded from the analysis due to gavage error. Given that no definite conclusion could be reached regarding treatment-relationship, a follow-up study was conducted in rabbits to further investigate the 27 pre-sacral vertebrae findings.

In the follow-up study, 27 pre-sacral vertebrae was observed in 2, 6, 5 and 6 foetuses (1.8, 5.2, 3.9 and 4.8%) in the control, 3, 10 and 30 mg/kg bw/day groups respectively. The study authors concluded that there was no tendency for 27 pre-sacral vertebrae to increase in a dose dependant manner, as it had done in the main study. Various minor anomalies and skeletal variations in addition to 27 pre-sacral vertebrae were also observed, but the incidences were not different between the treated and control groups.

The DS considered the results of the rabbit study to indicate a potential for imiprothrin to induce adverse developmental effects in foetuses, including fusion of the nasal bone, hypoplasia of the frontal bone and 27 pre-sacral vertebrae. However, the DS also noted that the effects were mainly seen at maternally toxic doses.

Conclusion

Some of the developmental findings at the top dose levels in rats and rabbits (600 and 300 mg/kg bw/day, respectively) might be related to the high level of maternal toxicity. However, the DS considered that the secondary nature of all the developmental effects has not been unequivocally demonstrated, as supported by some developmental effects being seen at dose levels where maternal toxicity was limited (200 and 100 mg/kg bw/day in rats and rabbits, respectively) or absent. According to the DS, effects that cannot be dismissed completely and may form a possible cause for concern for developmental toxicity are the malformation (fusion of the nasal bone) in rabbits at 300 mg/kg bw/day, the dose-related increase in hypoplasia of the frontal bone and 27 pre-sacral vertebrae at 100 and 300 mg/kg bw/day in rabbits, and the dose-related increase in lumbar rib in the rat at 200 and 600 mg/kg bw/day. With reference to the ECETOC Guidance on Evaluation of Reproductive Toxicity Data, the DS considered that the increase in supernumery ribs and small (hypoplastic) skull bones as observed in the rat and rabbit studies could be insufficient to support classification, since these findings are designated a low-moderate level of concern. However, with reference to the same ECETOC Guidance, the DS considered the malformation in rabbits to support classification as this finding has a high level of concern. Adding to the weight of evidence are the dose-response observed for most findings, and the effects occurring in more than one litter, at least at the top dose. Had the hypoplasia and fusion of the nasal bone occurred in the absence of maternal toxicity, the DS considered that a classification for developmental toxicity in category 1B could have been warranted. Given however that the maternal toxicity reduces somewhat the level of concern, the DS considered category 2 more appropriate.

Lactation

The DS did not propose classification for effects on or via lactation because imiprothirid does not meet the criteria, for two out of three criteria due to lack of data (i.e., there is no human evidence available indicating a hazard to babies, and the ability of imiprothrin to partition into the breast milk has not been investigated). For the third criterion, the two-generation study in rats showed no evidence for an effect of imiprothrin on lactation performance.

Comments received during public consultation

One MSCA agreed to the proposal for classification in reproductive toxicity category 2 (H361d), based on the skeletal malformations in the rabbit but not the rat study.

Industry provided five expert statements (four confidential and one public), all in support of no classification for developmental toxicity. The main arguments given for no classification are:

- Fusion of the nasal bone in rabbits was only observed at the severely maternally toxic dose of 300 mg/kg bw/day (above MTD).
- Fusion of the nasal bone as observed in the rabbit study was observed only in the proximal part of the nasal suture. Because the bridge of the nasal region does not experience the radial expansion that occurs in the dome of the skull, partial joining of nasal bones across the midline will not result in anatomical malformations similar to craniosynostosis. Such nasal bone fusions would likely remodel over time, and should therefore be considered a skeletal variation rather than a malformation.
- In the rabbit study there was indeed no evidence of fusion between the nasal bones and the adjacent bones comprising the facial skeleton nor any indication of dysmorphology of the anterior part of the cranium or palate.
- Hypoplasia of the frontal bone as observed in rabbits at doses of 100 and 300 mg/kg bw/day was due to delayed ossification as a consequence of a lower foetal body weight derived from dams that were strongly affected by the treatment (reduced food consumption and body weight loss).
- Delayed ossification is a more appropriate descriptor than hypoplasia, since the overall shape of the frontal bone, as well as of the dome of the skull, was reported to be normal.
- 27 pre-sacral vertebrae is a common skeletal variation in rabbits, often in conjunction with 13th rib; they are not mechanistic precursors to malformations.
- Pre-sacral vertebrae and lumbar (or supernumery) ribs are also a common finding in rodents. The sensitive period for the induction of additional ribs/vertebra is early in the gestation period (GD 8-12), when axial specification is being established. Maternal toxicity during this period has been shown to be associated with the induction of supernumery ribs.
- The rib and vertebrae findings in rats showed substantial post-natal resolution, indicating they signify delayed ossification rather than a structural alteration in development.
- The increases in 27 pre-sacral vertebrae in the rabbit study at 100 and 300 mg/kg bw/day and in lumbar ribs/pre-sacral vertebrae in rats at 200 and 600 mg/kg

bw/day can be explained as a consequence of maternal toxicity, that was already evident in both species in the early stages of embryonic development.

Two individuals did not support the proposed classification based on the findings at the top dose in the rabbit study because at this dose there was extensive maternal toxicity. One individual additionally noted that the study authors described the fusion of nasal bones only as a minor finding that was not accompanied by further evidence of fusion or abnormality of any other cranial bones.

The DS in response indicated that the proposed classification is primarily based on the findings in rabbits. According to the DS, it is the finding of fusion of the nasal bone (which with reference to the ECETOC Guidance on Evaluation of Reproductive Toxicity Data is to be considered a malformation) in this species, in combination with hypoplasia of the frontal bone, that gives rise to a cause for concern for craniofacial development. The DS acknowledged that the maternal toxicity may have contributed to the findings in rabbit foetuses (otherwise category 1B could have been justified), but still did not consider this to be unequivocal evidence that the observed effects were a secondary non-specific consequence of lower foetal bodyweight. Consequently, the DS stood by their proposal for category 2.

Assessment and comparison with the classification criteria

Fertility

In view of the absence of findings on fertility parameters in the two-generation study in rats, RAC supports the DS conclusion that imiprothrin does not need to be classified for effects on fertility and sexual development.

Developmental toxicity

In the rat developmental toxicity study, increases in a number of skeletal variations and a visceral finding (thymic remnants in the neck) were observed. These effects are indicative of delayed ossification or a manifestation of developmental delay, and showed partial or complete post-natal resolution. With the exception of lumbar ribs, all other effects were only observed at the highest dose of 600 mg/kg bw/day, a dose that was clearly maternally toxic. An increase in lumbar ribs was additionally observed at the mid dose of 200 mg/kg bw/day, but also at this dose there was maternal toxicity, with decreased food consumption and body weight gain (in particular during gestation days 9-18). Delayed ossification was also seen in the rat two-generation study at maternally toxic dose levels. RAC considers the effects observed in rats not to constitute a high level of concern; they are considered insufficient to warrant classification.

In the rabbit developmental toxicity study, effects observed included increases in 27 pre-sacral vertebrae and in hypoplasia of frontal bone (both skeletal variations), and in fusion of nasal bone. Similar to the rats, RAC does not consider the skeletal variations, which occurred at maternally toxic dose levels of 100 and 300 mg/kg bw/day, to constitute a high level of concern; they are considered insufficient to warrant classification. As to the fusion of the nasal bone, the DS considered this to be a malformation. RAC however notes that apparently it was a partial fusion, not a full-length fusion/hypoplasia. According to the DS it is the finding of the malformation in combination with the hypoplasia of the

frontal bone that gives rise to a cause for concern for craniofacial development. RAC however notes that there was no indication of fusion of other cranial bones, and that the overall shape of the frontal bone, as well as of the dome of the skull, was apparently normal. It is moreover noted that an increase in fusion of the nasal bone was only observed at a dose that was clearly above the MTD (with clinical signs of toxicity, 2/15 dams dying, 5/15 dams having abortions, and consistently lower food consumption and body weight gain during organogenesis). Normally effects observed at dose levels above the MTD should be carefully taken into consideration as they could be secondary non-specific consequences of maternal toxicity.

Given the total weight of evidence, RAC considers that **classification for developmental toxicity is not warranted**.

Lactation

RAC supports the conclusion of the DS that imiprothrin does not meet the criteria in the CLP Regulation and therefore does not need to be classified for effects on or via lactation.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Table 28: Summary of relevant neurotoxicity studies

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Repeated dose neurotoxicity study Rat, Crl:CD® (SD) BR/ m+f/12/sex/group Oral (diet) 90 days US-EPA 82-7 GLP CAR Doc IIIA A6.6/02	0, 1000, 3000 and 10000 ppm equivalent to: M: 0, 62, 191 and 648 mg/kg/d F: 0, 74, 219, 722 mg/kg/d	**3000ppm (m: 191mg/kg/d; f: 219mg/kg/d)** ↓ bodyweight (females at ≥ 3000 ppm 10-12%) **10000ppm (m: 648mg/kg/d; f : 722mg/kg/d)** ↓ bodyweight (males: 5-18%) ↓ food consumption (7-16%) Significant reduction in hind limb grip strength on Day 86 in males

4.12.2 Summary and discussion

Mortality

There were no mortalities in either the oral repeated dose neurotoxicity study or in the 28 day inhalation study.

Neurotoxic effects

In the oral repeated dose study, the major effects of treatment with imiprothrin were on bodyweight and food consumption. The observed reduction in hindlimb grip strength for 10,000ppm group males was considered to be possibly due to the reduced bodyweight in this group.

Clinical signs characteristic of neurotoxicity were observed in the inhalation study at 186mg/m^3, including decreased spontaneous activity, tip toe gait, hypersensitivity, tremor, jumping and urinary incontinence.

4.12.3 Comparison with criteria

The repeated dose study provided no indication of a neurotoxic effect of imiprothrin. No information about the duration or reversibility of the clinical signs observed at the top dose in the inhalation study was available. The effects are not sufficient to warrant classification for neurotoxicity.

4.12.4 Conclusions on classification and labelling

Available data do not support classification of imiprothrin for neurotoxicity under CLP.

5 ENVIRONMENTAL HAZARD ASSESSMENT

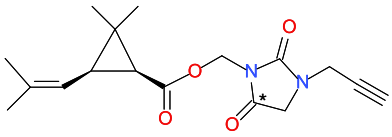
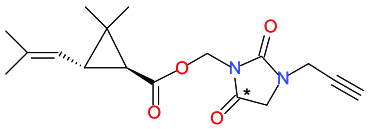
Imiprothrin (referred to in test reports as S-41311) is a synthetic pyrethroid insecticide for the control of arthropods such as cockroaches and other crawling insects. As with other pyrethroids, it acts on the sodium channel in the nerve membranes of the invertebrate nervous system. They affect the nervous system resulting in tremors, paralysis and death.

Available environmental fate and hazard studies have been reviewed under Regulation EU/528/2012 and considered valid. Details are included in the Competent Authority Report, 2016. Unless otherwise stated, these studies were conducted in accordance with GLP and the validity criteria of the respective test guideline. They are considered reliable and suitable for use in hazard classification. Further details are presented below for studies conducted on the active substance imiprothrin but not for its degradants. Limited degradant ecotoxicity data is presented in Annex II. There are no data to indicate that degradants are more toxic than imiprothrin and so degradants are not considered further for classification of imiprothrin.

Imiprothrin is a racemic mixture of 4 isomers although there are 2 main isomers (see Section 1). Environmental testing was conducted using imiprothrin active substance as either the *trans* or *cis* isomer (both in the R-configuration) which together comprise approximately 90% purity (see section 1) in an approximate ratio of *trans*:*cis* of c.a., 80:20.

Table 29 presents the compounds used in the studies, and shows the position of [^{14}C] radiolabel used.

Table 29: Structure of imiprothrin indicating positions of the ^{14}C labels.

Name	Structure
(1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin	
1R)-*trans*-[imidazolidinyl-5-^{14}C]imiprothrin, or [alc-^{14}C]imiprothrin, or S-41311	

The measured water solubility of imiprothrin 93.5 mg/l at 25 ^{o}C and pH6.5 following the shake flask method (Lorence, 1994b).

Imiprothrin is not anticipated to dissociate (Furuta, 1995).

5.1 Degradation

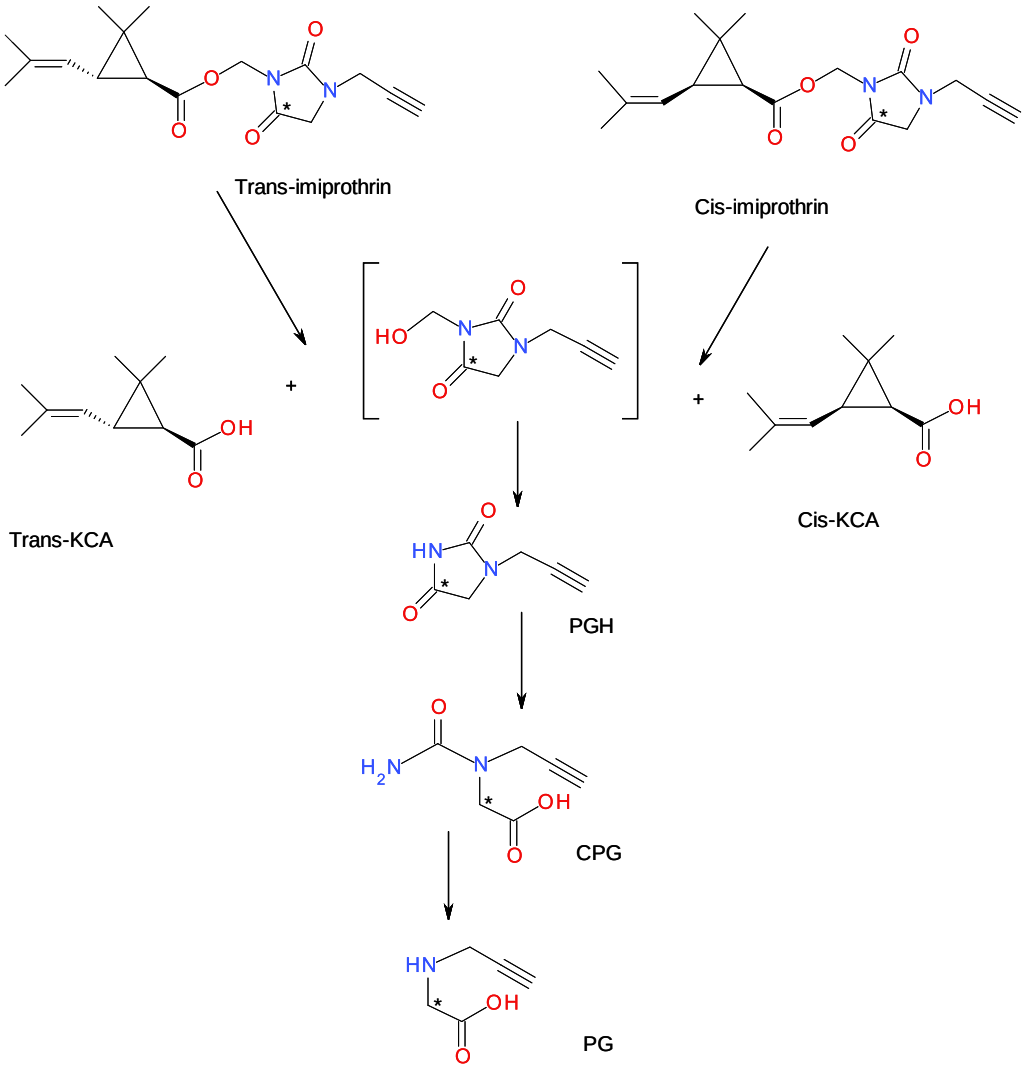
A summary of available valid information on the fate of imiprothrin is presented in Table 30 below.

Table 30: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Aquatic hydrolysis US EPA Subdivision N, guideline 161-1, similar to OECD Test Guideline 111, GLP, purity: 98.5%	pH 5: stable pH 7: DT_{50} 58.6 days at 25 °C pH 7: DT_{50} 166 days at 12 °C pH 9: DT_{50} 0.746 days at 25 °C pH 9: DT_{50} 2.11 days at 12 °C	Valid	Shah, 1995
MITI-I test comparable to OECD Test Guideline 301C, purity: 99.5%	2% mineralisation (oxygen consumption) 58% imiprothrin remaining at day 28 (HPLC analysis)	Valid	Ryoichi and Satoru, 1993
Water/sediment simulation OECD Test Guideline 308, GLP, purity: 98.4% for *cis* isomer and 99.2% for *trans* isomer	$DT_{50\ total\ system}$ 1.1-5.9 days at 20 °C $DT_{50\ total\ system}$ 2.1-11.2 days at 12 °C 39-52% AR CO_2 mineralisation after 101 days	Valid	Hiler and Lomax, 2016
UK CA recalculated values following Ordinary Least Square (OLS) following FOCUS	$DT_{50\ total\ system}$ 1.37-5.4 days at 20 °C $DT_{50\ total\ system}$ 2.6-10.2 days at 12 °C		CAR (2016)

Based on the CAR, the proposed degradation pathway in water-sediment systems is presented in Figure 1.

Figure 1: Proposed degradation pathway in water-sediment systems



PGH: 1-propargylimidazolidine-2,4-dione
CPG: N-carbamoyl-N-propargylglycine
KCA: chrysanthemic acid
PG: propargylglycine

5.1.1 Stability

Aqueous hydrolysis

An aqueous hydrolysis study (Shah, 1995) is available using radiolabelled [Alc-^{14}C]-*trans*-imiprothrin. The study followed US EPA Subdivision N guideline 161-1 which is comparable to OECD Test Guideline 111. Aqueous buffered solutions at pH 5, 7 and 9 were prepared with ~1 mg/l imiprothrin and samples were incubated in the dark, under sterile conditions at 25 ± 1 ºC for 30 days. Analysis was performed by radio-high performance liquid chromatography (radio-HPLC) with radioactivity determined by Liquid Scintillation Counting (LSC).

Imiprothrin was hydrolytically stable at pH 5 while hydrolysis was observed at pH 7 and 9, increasing with alkalinity. At the study temperature (25 ºC), the half-lives were 58.6 days at pH 7 and 0.746 days at pH 9. Converting these values to 12 ºC results in half-lives of 166 days at pH 7 and 2.11 days at pH 9.

The hydrolysis reaction created one major [^{14}C] labelled product, N-carbamoyl-N-propargylglycine (CPG), which was itself formed as a result of hydrolysis of an intermediate product, namely 1-propargylimidazolidine-2,4-dione (PGH). This reaction was observed in both the pH 7 and pH 9 test solutions. CPG reached a maximum of 26.5% at pH 7, 30 days and 89.8 at pH 9, 122 hours. PGH reached a maximum of 2% at pH 7, 30 days and 4.61 at pH 9, 122 hours.

A further reaction product was identified but this compound only reached 4.9 % at pH 9 at 122 h and 1.8 % at pH 7 on day 30.

As the hydrolysis of imiprothrin was carried out using [^{14}C]- alcohol radiolabelled trans-imiprothrin, only hydrolysis products containing the imidazolidine ring were identifiable using radio- HPLC. Structurally similar pyrethroids are considered to include chrysanthemic acid (KCA) as degradant. Therefore, in the absence of further information the assessment under Regulation EU/528/2012 considers that KCA was probably also produced during the hydrolysis of imiprothrin.

Aqueous photolysis

No data are available on the photodegradation of imiprothrin.

Assessment under Regulation EU/528/2012 considered photodegradation of structurally relevant analogues. This indicated that photodegradation was likely to occur under experimental conditions with the formation of degradants such as chrysanthemic acid and imidazolidone. Experimental photodegradation half-lives were 1.92 to 6.9 days at 12 ºC for structurally similar substances Prallethrin and Bioallethrin.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

No data available.

5.1.2.2 Screening tests

A ready biodegradation study (Ryoichi and Satoru, 1993) is available using racemic imiprothrin (purity 99.5%) following the Japanese MITI-I method (similar to OECD Test Guideline 301C). This study was not conducted to GLP although Japanese standards were followed and the study was considered valid under Regulation EU/528/2012. The study was run using 100 mg/l imiprothrin and a closed test system at 25 ^{o}C, pH 7. The inoculum was from the Chemicals Inspection and Testing Institute in Japan although further details of the source are not available.

The biodegradation rate based on oxygen consumption was 2%.

The residual imiprothrin amount analysed by HPLC was 58%. Degradation products PGH and KCA were detected at 50% and 45% yield respectively. This suggests that while imiprothrin underwent primary degradation, minimal mineralisation occurred.

5.1.2.3 Simulation tests

An aerobic waster-sediment simulation study (Hiler and Lomax, 2016) is available following OECD Test Guideline 308 and GLP. The study used radiolabelled *cis* and *trans* isomers of imiprothrin: (1*R*)-*cis*-[cyclopropyl-1-^{14}C]-imiprothrin and (1*R*)-*trans*-[cyclopropyl-1-^{14}C]-imiprothrin. Two freshwater systems were employed at a ratio of 3:1 water:sediment, Goose River (GR) and Golden Lake (GL), with characteristics presented in Table 31.

Table 31: Characteristics for GR and GL water/ sediment systems

Criteria	Goose river (GR)	Golden Lake (GL)
Sediment properties	31% sand 38% silt 11% clay Organic matter 5.9% Clay loam CEC 22.3 (meq/100 g soil) 7.8 pH 1:1 soil: water ratio	85% sand 12% silt 3% clay Organic matter 2.1% Loamy sand CEC 9.5 (meq/100 g soil) 8.1 pH 1:1 soil: water ratio
Water properties	pH: 8.5	pH: 8.7
Dissolved oxygen (average value over 101 days), ppm	6.34 *cis* 8.47 *trans*	6.93 *cis* 8.97 *trans*

Test systems were dosed with nominally 0.123 µg/g sediment via direct addition after a 31day equilibration period. The study was run at 20 ^{o}C ±2 ^{o}C, in the dark under aerobic conditions for 101 days.

The test item and degradants were analysed by High Performance Liquid Chromatography (HPLC) and radioactivity confirmed by Liquid Scintillation Counting (LSC). Mean AR recoveries were acceptable. The test item was analysed by normal-phase HPLC to determine isomer ratio and any changes. Further isomerisation of the test item was not observed over the study period.

During the study, AR was observed to dissipate from the water phase to sediment and mineralise to carbon dioxide. By day 31, 34.6 and 52.2% AR was observed in the water phase for *cis*-^{14}C-imiprothrin. In the *trans*-^{14}C-imiprothrin systems this was 40.1 and 50.3% AR. The level of AR in sediment peaked on day 6 in *cis*-^{14}C-imiprothrin systems with 25-43.2% AR. In *trans*-^{14}C-imiprothrin systems the maximum occurred on day 13 with 17-31.1% AR.

The imiprothrin profile over the study period declined significantly with 0.5-0.7% AR observed in the *cis*-^{14}C-imiprothrin systems by day 101 and <LOD AR in the *trans*-^{14}C-imiprothrin systems on day 101.

The concentration of ^{14}C-carbon dioxide increased over the study period to termination on day 101. A maximum of 39.6 and 44.5% AR was observed in the *cis*-^{14}C-imiprothrin systems with 52.3 and 39.9% AR observed in the *trans*-^{14}C-imiprothrin systems. At day 31 CO_2 measurements were 7.5 to 12.2 %AR.

Three major degradants were observed in both systems; PGH, CPG and PG – the maximum levels (% AR) are presented in Table 32. In general higher AR values were observed for the *trans* isomer. Due to the position of the radiolabel, it was not possible to measure concentrations of the degradant KCA, although this was predicted to occur based on information on similar pyrethroid substances.

Table 32: Major degradants and maximum levels in GR and GL water/ sediment systems

Degradant	Max %	
	Water	Sediment
PGH	38.8	13.9
CPG	49.2	14.2
PG	-	16.7

The study calculated single first order (SFO) DT_{50} values which are considered to reflect primary degradation not mineralisation. These are presented in Table 33 along with temperature adjusted DT_{50} values at 12 ^{o}C. During the Biocides review, the UK CA recalculated dissipation following SFO kinetics as it was felt statistical details were not sufficient to ensure FOCUS guidance had been followed. DT_{50} values were recalculated using SFO following the Ordinary Least Square (OLS) method as recommended in FOCUS guidance. These values are also presented in Table 33 along with temperature adjusted DT_{50} values at 12 ^{o}C. Where possible the UK CA also calculated SFO DT_{50} values for degradation products. These values are included in Table 33 along with temperature adjusted DT_{50} values at 12 ^{o}C.

Table 33: Whole System DT_{50} values in GR and GL water/ sediment systems

Compound	DT_{50} whole system (days) at study temperature, 20 °C	DT_{50} whole system (days) at 12 °C
Study values for: *cis*-^{14}C-imiprothrin	5.7-5.9	9.9-11.2
Study values for: *trans*-^{14}C-imiprothrin	1.6-2.4	3-4.6
UK CA values for: *cis*-^{14}C-imiprothrin	1.44-5.4	2.7-10.2
UK CA values for: *trans*-^{14}C-imiprothrin	1.37-1.59	2.6-3.0
PGH	3.99-7.94	7.4-15.1
CPG	23.3-43.6	44.2-82.7
PG	51.5-42.7	97.7-81

Overall, imiprothrin (1R-*cis* and 1R-*trans*) was observed to dissipate from the water phase to sediment and mineralise to carbon dioxide. Primary degradation was rapid with imiprothrin $DT_{50\ total\ system}$ values between 2.6 and 10.2 days at 12 °C (UK CA values). Ultimate degradation was slower with mineralisation at 7.5 to 11.2 % AR on day 31 and 39.6 to 52.3% AR by study termination on day 101. $DT_{50\ total\ system}$ values for major degradants indicate they have longer half-lives than the imiprothrin parent.

5.1.3 Summary and discussion of degradation

Imiprothrin is considered hydrolytically stable at pH 5. Hydrolysis was observed at pH 7 and 9, increasing with alkalinity. At 25 °C, half-lives were 58.6 days at pH 7 and 0.746 days at pH 9. Converting these values to 12 °C results in half-lives of 166 days at pH 7 and 2.11 days at pH 9.

The hydrolysis reaction created one major [^{14}C] labelled product, N-carbamoyl-N-propargylglycine (CPG), which was itself formed as a result of hydrolysis of an intermediate product, namely 1-propargylimidazolidine-2,4-dione (PGH). Based on structural similarity to other pyrethroids, chrysanthemic acid (KCA) is also considered a relevant hydrolysis degradant.

No data are available on the photodegradation of imiprothrin. Consideration of structurally similar pyrethroids indicates photodegradation may occur under experimental conditions with the formation of degradants such as chrysanthemic acid and imidazolidone. However, it is noted that the actual degree of photodegradation in the aquatic environment depends on local conditions and seasons and is difficult to quantify. Given the available data, there is insufficient information to evaluate photodegradation in the European environment in terms of mineralisation or transformation to non-classifiable substances. Therefore it is not considered possible to meet the criteria for rapid degradation through information on aquatic photolysis alone.

In a ready biodegradation study minimal (2%) mineralisation was observed although primary degradation did occur given the residual amount of imiprothrin at day 28 was 58%.

In an aerobic water-sediment study, imiprothrin 1R-*cis* and 1R-*trans* isomers were observed to dissipate from the water column to sediment and undergo mineralisation via transformation products PGH, CPG and PG. While it was not possible to analysis for KCA, it is also considered a relevant degradant based on read-across to similar pyrethroid substances.

Reflecting primary degradation, UK CA calculated whole system DT_{50} values for imiprothrin are considered to range between were 2.6 and 10.2 days at 12 ºC. Evolution of CO_2 indicating mineralisation was observed with 7.5-11.2% AR remaining by day 31 and 39-52% AR by day 101. On this basis imiprothrin does not have an ultimate degradation half-life <16 days.

Total System DT_{50} values were calculated for the three principle degradants. The DT_{50} for PGH is less than 16 days but it is unclear if this reflects mineralisation or degradation to CPG and further degradation to PG which have longer half-lives. In addition, the ecotoxicity profile for degradants is unclear due to a lack of data.

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

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

One adsorption/desorption study is available using imiprothrin and following OECD Test Guideline 121, HPLC method (Betteley, 1996). The mean K_{oc} value was 268 resulting in a log K_{oc} of 2.43 indicating imiprothrin is likely to be moderately mobile in soil.

5.2.2 Volatilisation

Experimental data (Lorence, 1996a) indicate the vapour pressure for imiprothrin is low at 1.86×10^{-6} Pa at 25 °C.

The Henry's Law Constant (Okada, 2000) was calculated to be 6.33×10^{-6} Pa m^3 mol^{-1} indicating imiprothrin is unlikely to partition significantly from the water phase to air.

5.2.3 Distribution modelling

5.3 Aquatic Bioaccumulation

Table 34: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Partition coefficient *n*-octanol/water (shake flask method)	Log K_{ow} 2.9 at 25 °C pH 6.2-6.6 No evidence of pH dependence		Lorence, 1994d
Experimental aquatic BCF OECD 305, GLP, purity: 98.6 to 99.3%	Whole fish $BCF_{lipid\ normalised}$: 124 - 144 l/kg wet weight based on total radioactive residues (TRR)	Flow through, 28 days exposure, 7 days depuration	2014

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

No reliable data available.

QSARs were presented in the draft assessment under Regulation EU/528/2012. Given the uncertainty associated with QSAR predictions for surface active substance (imiprothrin is considered surface active: surface tension value of 46.6 mN/m at 21 °C), these were not considered reliable estimates.

5.3.1.2 Measured bioaccumulation data

An experimental aquatic BCF study for imiprothrin is available following GLP and OECD 305 (2014). It was reviewed under Regulation EU/528/2012 and considered suitable to fulfil the bioaccumulation in fish endpoint.

The study used two radio labels: (1R)-*cis*-[cyclopropyl-1-^{14}C]-imiprothrin (98.6 % purity) and (1R)-*trans*-[cyclopropyl-1-^{14}C]-imiprothrin (99.3% purity) in a ratio of 1:4. A flow-through system with Bluegill Sunfish (*Lepomis macrochirus*) was employed with two exposure concentrations; nominally 0.07 and 0.7 µg/l. Exposure solutions were prepared with the aid of a solvent (acetone) equivalent to 0.0125 ml/l and a solvent control was included. The exposure period ran for 28 days followed by a 7 day depuration period.

Based on total radioactive residues (TRR), kinetic whole fish BCFs were 97.7-138 l/kg. Based on [^{14}C]-imiprothrin whole fish BCFs were 4.41-7.96 l/kg.

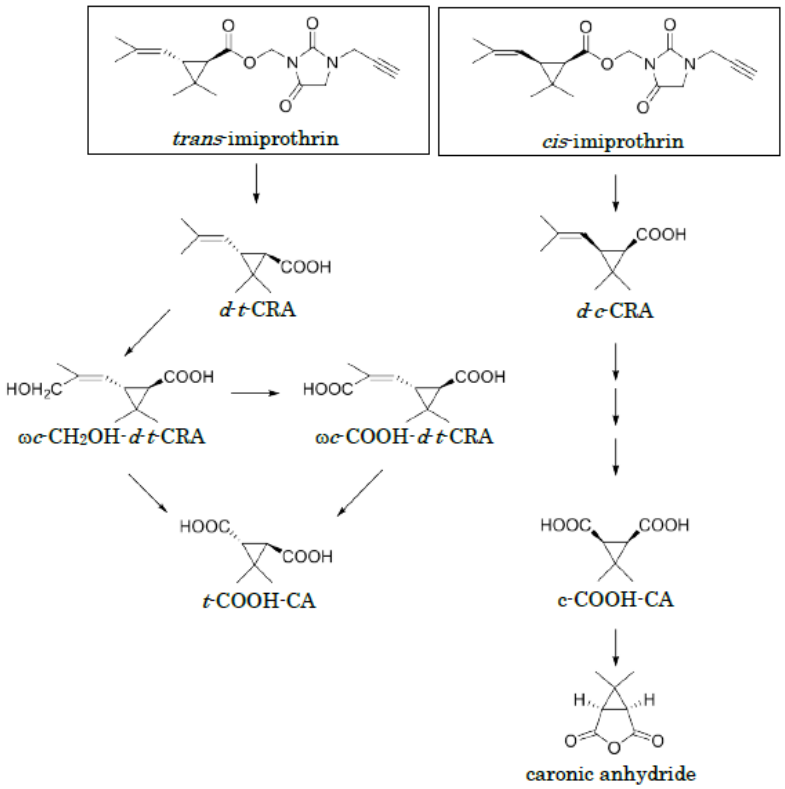
Steady state whole fish BCFs based on TRR were 96.4-114 l/kg. Steady state whole fish BCFs based on [^{14}C]-imiprothrin were 3.55-4.58 l/kg.

Lipid normalised whole fish BCFs based on TRR were 124-144 l/kg. Lipid normalised whole fish BCFs based on [^{14}C]-imiprothrin were 4.57-5.8 l/kg.

During the depuration period, levels of ^{14}C-residues fell with depuration half-lives of 0.442-0.514 days for TRR and 0.173-0.303 days for [^{14}C]-imiprothrin.

During the study [^{14}C]-imiprothrin was observed to rapidly metabolise as illustrated in Figure 2 below.

Figure 2: Proposed metabolic pathway in Bluegill sunfish



5.3.2 Summary and discussion of aquatic bioaccumulation

The experimental logK_{ow} for imiprothrin is 2.9 at 25 °C pH 6.2-6.6 (no pH dependence).

An experimental whole fish $BCF_{lipid\ normalised}$ was 124 to 144 l/kg based on ^{14}C-residues.

Overall, the logK_{ow} is considered to be below the CLP logK_{ow} trigger value of ≥ 4 and the whole fish BCF for imiprothrin (or TRR) is below the CLP trigger of ≥ 500 intended to identify substances with a potential to bioaccumulate.

5.4 Aquatic toxicity

A summary of available valid information on the aquatic toxicity of imiprothrin is presented in Table 35. A summary of information for degradants is also included in Annex II, Table 1. This is limited and overall the ecotoxicity profile of degradants is unclear.

Table 35: Summary of relevant information on aquatic toxicity for imiprothrin

Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg/l)	
Acute toxicity to fish US EPA FIFRA 72-1, GLP, purity: 92.9%	Bluegill Sunfish (*Lepomis macrochirus*)	Mortality	Flow-through	96 hours	LC_{50}	0.07 (mm)	ABC Laboratories, Inc, USA (1993a)
Acute toxicity to fish US EPA FIFRA 72-1, GLP, purity: 92.9%	Rainbow Trout (*Oncorhynchus mykiss*)	Mortality	Flow-through	96 hours	LC_{50}	**0.038** (mm)	ABC Laboratories, Inc, USA (1993b)
Daphnia sp Acute Immobilisation US EPA FIFRA 72-2, GLP, purity: 92.9%	*Daphnia magna*	Acute immobilisation	Flow-through	48 hours	EC_{50}	0.051 (mm)	Bowman and Stuerman, 1993c
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity: 91.6%	*Pseudo-kirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	>7.8 (mm) **1.3** (mm)	Bell, 1996a

Notes:
mm refers to the endpoint being based on mean measured test concentrations
*formerly *Selenastrum capricornutum*
Bold values indicate most sensitive acute and chronic endpoints

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Two reliable acute toxicity to fish studies are available using imiprothrin. Both were conducted in accordance with GLP following US EPA FIFRA guideline 72-1 which is considered comparable to OECD Test Guideline 203.

Study 1 (1993a)
The flow-through study used Bluegill Sunfish (*Leopmis macrochirus*) the nominal exposure range was 0.012, 0.019, 0.032, 0.054, and 0.090 mg/l. Exposure solutions were prepared with the aid of the solvent dimethylformamide (DMF) at 0.1 ml/l and a solvent control was included. Study conditions were considered acceptable. Measured concentrations at 0 hours were 89 to 110% of nominal. Measured concentrations at 96 hours were 97 to 119% of nominal. Results were based on mean measured concentrations. The 96-h LC_{50} was 0.07 mg/l (95% confidence intervals 0.063 to 0.079 mg/l) based on mean measured concentrations.

Study 2 (1993b)

The flow-through study used Rainbow Trout (*Oncorhynchus mykiss*) the nominal exposure range was 0.012, 0.019, 0.032, 0.054 and 0.09 mg/l. Exposure solutions were prepared with the aid of the solvent dimethylformamide (DMF) at 0.1 ml/l and a solvent control was included. Study conditions were considered acceptable. Measured concentrations at 0 hours were 93 to 120% of nominal and 106 to 133% of nominal at 96 hours. Results were based on mean measured concentrations. The 96-h LC_{50} was 0.038 mg/l (95% confidence intervals 0.021 to 0.062 mg/l) based on mean measured concentrations.

5.4.1.2 Long-term toxicity to fish

No data available.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Study 1 (Bowman and Stuerman, 1993c)

A flow-through acute toxicity to *Daphnia magna* study using imiprothrin is available following US EPA FIFRA guideline 72-2 and GLP. This was considered comparable to OECD Test Guideline 102 – the only difference was that 2 instead of 4 replicates were employed although this is not considered to have affect study validity. Exposure solutions were prepared with the aid of the solvent DMF at 0.1 ml/l and a solvent control was included. The nominal exposure range was 0.02, 0.03, 0.05, 0.09 and 0.15 mg/l. Measured concentrations at 0 hours were 67 to 104% of nominal. Measured concentrations at 48 hours were 66 to 115% of nominal. Results were based on mean measured concentrations: 0.013, 0.03, 0.049, 0.082 and 0.160 mg/l.

The 48-h LC_{50} was 0.051 mg/l (95% confidence intervals 0.03 to 0.082 mg/l) based on mean measured concentrations.

5.4.2.2 Long-term toxicity to aquatic invertebrates

No data available.

5.4.3 Algae and aquatic plants

Study 1 (Bell, 1996a)

A static algal growth inhibition test using *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) is available following GLP and OECD Test Guideline 201. A saturated stock solution was prepared but dissolving the test material in acetone which was subsequently evaporated off by heating at 40 ^{o}C. Algal medium and 10% Tween 80 DMF was added before ultrasoncation for 1.5 hours. The resulting exposure solutions were considered to have a maximum of 0.1 ml/l solvent and a solvent control was included. The nominal exposure range was 0.46, 1.0, 2.2, 4.6 and 10 mg/l. Analysis by HPLC-UV at 0 hours was 86 to 104% of nominal. Analysis at 72 hours was 27 to 70% of nominal. Geometric mean measured concentrations were 0.33, 0.53, 1.3, 3.2 and 7.8 mg/l. The study was run under constant illumination at 24 ^{o}C ±1 ^{o}C and study validity criteria were met. The study pH ranged from 7.5 to 8.2.

At the highest treatment 36% growth inhibition was observed between 0 and 72 hours compared to the solvent control. On this basis, the 72-h E_rC_{50} was considered >7.8 mg/l based on mean measured concentrations. The 72-hour NOE_rC was 1.3 mg/l based on mean measured concentrations.

It was noted during review under Regulation EU/582/2012 that greater inhibition was observed at 48 hours. For the highest two exposure concentrations this was approximately 25 and 70% indicating the 48-hour E_rC_{50} lies between 3.2 and 7.8 mg/l based on measured concentrations. The recovery effect was considered due to the decrease in imiprothrin in exposure solutions over time.

For the purpose of classification and labelling, a 72 or 96 hour endpoint is preferred. Therefore the 72-hour E_rC_{50} of >7.8 mg/l and NOE_rC of 1.3 mg/l are considered valid endpoints.

5.4.4 Other aquatic organisms (including sediment)

No data available.

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

Imiprothrin is considered hydrolytically stable at pH 5. Hydrolysis was observed at pH 7 and 9, increasing with alkalinity. Half-lives at 12 ºC were 166 days at pH 7 and 2.11 days at pH 9.

In a ready biodegradation study minimal (2%) mineralisation was observed although primary degradation did occur given the residual amount of imiprothrin at day 28 was 58%.

In an aerobic water-sediment study imiprothrin was observed to dissipate from the water column to sediment and undergo mineralisation via various transformation products. Reflecting primary degradation, whole system DT_{50} values for imiprothrin are considered to range between were 2.6 and 10.2 days at 12 ºC. Evolution of CO_2 indicating mineralisation was observed with 7.5-11.2 % AR by day 31 and 39-52 % AR by day 101. On this basis imiprothrin does not have an ultimate degradation half-life less than 16 days.

Total System DT_{50} values were calculated for the three principle degradants. The $DT_{50\ total\ system}$ for PGH is <16 days but it is unclear if this reflects mineralisation or degradation to transformation products with longer half-lives. The ecotoxicity profile for these degradants is unclear due to a lack of data.

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

The experimental $logK_{ow}$ for imiprothrin is 2.9 at 25 ºC pH 6.2-6.6 (no pH dependence).

An experimental whole fish $BCF_{lipid\ normalised}$ was 124 to 144 l/kg based on ^{14}C-residues.

Overall, the $logK_{ow}$ is considered to be below the CLP $logK_{ow}$ trigger value of ≥ 4 and the whole fish BCF for imiprothrin (or TRR) is below the CLP trigger of ≥ 500 intended to identify substances with a potential to bioaccumulate.

Due to a lack of data, the ecotoxicity profile and classification of degradants is unclear (see Annex I). Degradants are not considered further in relation to the hazard classification of imiprothrin.

Aquatic acute toxicity data on imiprothrin are available for fish, invertebrates and algae. Acute endpoints for fish and invertebrates lie in the range 0.01 to 0.1 mg/l. The lowest acute value is a 96-h LC_{50} of 0.038 mg/l for Rainbow trout. On this basis imiprothrin should be classified as Aquatic Acute 1 with an acute M-factor of 10.

Chronic toxicity data on imiprothrin for fish and invertebrates are not available. A chronic 72-h NOE_rC of 1.3 mg/l for algae would not result in an Aquatic Chronic classification. However, algae are not the most acutely sensitive trophic level. Adopting the surrogate approach using available acute fish and invertebrate data for a non-rapidly degradable substance would result in imiprothrin being classified as Aquatic Chronic 1 with a chronic M-factor of 10.

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 = 10

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

Chronic M-factor = 10

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Imiprothrin is a biocidal active substance in the scope of the Biocidal Products Regulation (Regulation (EU) No 528/2012) and is currently classified as Aquatic Acute 1 (H400) and Chronic 1 (H410) in Annex VI to the CLP Regulation (added at the 1st ATP).

Environmental testing was conducted using imiprothrin active substance as either *trans* or *cis* isomer (both in R-configuration) which together comprise approximately 90% purity in an approximate ratio of *trans*:*cis* of 80:20.

The DS proposed to revise the existing harmonised entry by adding M-factors of 10 for both acute and chronic hazards. Aquatic acute toxicity data are available for fish, invertebrates and algae. The lowest acute value is a 96-hrs LC_{50} of 0.038 mg/L for Rainbow trout (*Oncorhynchus mykiss*) resulting in a classification as Aquatic Acute 1 (H400) with an acute M-factor of 10. Chronic aquatic toxicity data on imiprothrin for fish and invertebrates are not available and a chronic 72-hrs NOErC of 1.3 mg/L for algae would not result in an Aquatic Chronic classification. However, algae are not the most acutely sensitive trophic level. Due to the lack of a full chronic dataset, the surrogate approach was applied by the DS using available acute fish and invertebrate toxicity data. Imiprothrin is not considered rapidly degradable for classification purposes, consequently the chronic hazard classification would result in Aquatic Chronic 1 (H410) with a chronic M-factor of 10.

Degradation

Hydrolysis of imiprothrin was tested according to US EPA Subdivision N guideline 161-1 (similar to OECD TG 111) following GLP principles. The substance was hydrolytically stable at pH 5, while hydrolysis was observed at pHs 7 and 9, increasing with alkalinity (half-lives of 58.6 days at pH 7 and 0.746 days at pH 9 at a study temperature of 25°C, respectively). Converting these values to 12°C results in half-lives of 166 days at pH 7 and 2.11 days at pH 9. One major hydrolysis product was formed, CPG (N-carbamoyl-N-propargylglycine; formed as a result of hydrolysis of the intermediate product PGH (1-propargylimidazolidine-2,4-dione)) reaching a maximum of 26.5 and 89.8% at pH 7 and 9, respectively. Based on structural similarity to other pyrethroids, KCA (chrysanthemic acid) was also considered as a relevant hydrolysis product.

Photodegradation of imiprothrin was not tested. However, consideration of structurally similar pyrethroids indicates that photodegradation may occur under experimental conditions with the formation of degradants such as KCA and imidazolidone.

Ready biodegradation was tested following the Japanese MITI-I method (similar to OECD TG 301 C). Despite the study not being conducted according to GLP principles, it was considered valid under Regulation (EU) No 528/2012. The study was run using 100 mg/L imiprothrin and a closed system at 25°C and pH 7. While primary degradation did occur with a residual amount of imiprothrin of 58% at day 28, the biodegradation rate based on oxygen consumption was 2% indicating minimal mineralisation. The main primary degradation products were PGH and KCA, amounting to 50 and 45%, respectively.

In an aerobic water/sediment simulation study conducted according to OECD TG 308 and following GLP principles, radiolabelled 1R-cis and 1R-trans isomers of imiprothrin were used. The study was run at 20°C±2°C in the dark for 101 days. The test item was observed to dissipate from the water column to sediment. Primary degradation was rapid with imiprothrin DT_{50} total system values between 1.37 and 5.4 days at 20°C (2.6 and 10.2 days at 12°C; recalculated by the DS). Ultimate degradation was slower with mineralisation at 7.5 to 11.2% applied radioactivity (% AR) on day 31 and 39.6 to 52.3% AR by study termination on day 101, indicating that imiprothrin does not have an ultimate degradation half-life of <16 days. The DT_{50} total system values for the three major degradants (PGH, CPG and PG (propargylglycine)) showed that they have longer half-lives than imiprothrin.

Overall, the DS concluded that the available information on degradation of imiprothrin was not sufficient to show that the substance is ultimately degraded within 28 days (equivalent to a half-life of <16 days) or transformed to non-classifiable degradants. As a result imiprothrin was considered non-rapidly degradable for classification purposes.

Bioaccumulation

A Log Kow of 2.9 (at 25°C and pH 6.2–6.6) was measured for imiprothrin following the EC method A.8. (Shake flask method). An experimental aquatic BCF study in Bluegill Sunfish (*L. macrochirus*) following OECD TG 305 and GLP principles showed a lipid normalised whole fish BCF of 124 to 144 L/kg (based on total ^{14}C-residues) and of 4.6-5.8 L/kg (based on ^{14}C-imiprothrin). The DS concluded that imiprothrin does not meet the CLP criteria for bioaccumulation, given both the Log Kow and the experimentally derived BCF were below the CLP trigger values of ≥ 4 (for Log Kow) and ≥500 (for BCF), respectively.

Aquatic toxicity

Valid aquatic acute toxicity data are available for fish, invertebrates and algae with fish being the most sensitive trophic level. Valid aquatic chronic toxicity data are available for algae only, while data for fish and aquatic invertebrates are lacking. All values were based on mean measured concentrations. A summary of the relevant information on aquatic toxicity is presented in Table 7.

Table 7. Summary of relevant information from aquatic toxicity studies on imiprothrin

Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg/L)	
Acute toxicity to fish US EPA FIFRA 72-1, GLP, purity: 92.9%	Bluegill Sunfish (*Lepomis macrochirus*)	Mortality	Flow-through	96 hours	LC_{50}	0.07 (mm)	ABC Laboratori Inc, USA (1993a)
Acute toxicity to fish US EPA FIFRA 72-1, GLP, purity: 92.9%	Rainbow Trout (*Oncorhynchus mykiss*)	Mortality	Flow-through	96 hours	LC_{50}	**0.038** (mm)	ABC Laboratori Inc, USA (1993b)
Daphnia sp Acute Immobilisation US EPA FIFRA 72-2, GLP, purity: 92.9%	*Daphnia magna*	Acute immobili-sation	Flow-through	48 hours	EC_{50}	0.051 (mm)	Bowman and Stuerman, 1993c
Freshwater Algal Growth Inhibition OECD TG 201, GLP, purity: 91.6%	*Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*)	Cell multipli-cation inhibition	Static	72 hours	ErC_{50} NOErC	>7.8 (mm) **1.3** (mm)	Bell, 1996a

Two acute fish studies (following US EPA FIFRA 72-1 guideline and according to GLP principles) were conducted using Bluegill Sunfish (*L. macrochirus*) and Rainbow trout (*O. mykiss*) under flow-through conditions over a period of 96 hours. In both studies exposure concentrations were prepared using the solvent dimethylformamide (DMF; 0.1 mL/L)) and a solvent control was included. The reported 96-hrs LC_{50} values were 0.07 mg/L (mm) in the first test and 0.038 mg/L (mm) in the second test. The measured concentrations of imiprothrin remained within 80–120% for all measured samples in the first test and increased up to 133% at 96 hours in the second test.

An acute study with *D. magna* was conducted under flow-through conditions following US EPA FIFRA 72-2 guideline and according to GLP principles, resulting in a 48-hrs EC_{50} of 0.051 mg/L (mm).

A static algal growth inhibition study was conducted following OECD TG 201 and according to GLP principles. The 72-hrs ErC_{50} was reported to be >7.8 mg/L (mm) and the 72-hrs NOErC 1.3 mg/L (mm). It was noted that greater inhibition was observed at 48 hours, indicating that the 48-hrs ErC_{50} would be between 3.2 and 7.8 mg/L based on mean

measured concentrations. The DS concluded that for the purpose of classification, endpoints based on an exposure of 72 or 96 hours are preferred. Therefore, the reported endpoints at 72 hours are used for classification purposes.

Based on the available information for aquatic acute toxicity, the DS concluded that imiprothrin meets the classification criteria as Aquatic Acute 1 with an M-factor of 10 based on the lowest 96-hrs LC_{50} of 0.038 mg/L for rainbow trout. Due to the lack of reliable chronic toxicity data for the acutely most sensitive trophic level, the DS applied the surrogate approach. Considering that imiprothrin is non-rapidly degradable, this resulted in a classification as Aquatic Chronic 1 with an M-factor of 10.

Comments received during public consultation

Two MSCAs supported the environmental classification as proposed by the DS.

Assessment and comparison with the classification criteria

The measured water solubility of imiprothrin is 93.5 mg/L at 25°C and pH 6.5. Imiprothrin is not anticipated to dissociate. Experimental data indicate the vapour pressure is low at 1.86×10^{-6} Pa at 25°C. The Henry's Law Constant of 6.33 x 10-6 Pa m^3 mol^{-1} indicates that imiprothrin is unlikely to partition significantly from the water phase to air. Imiprothrin is also surface active (surface tension 46.6 mN/m at 21°C). Measured data indicate that imiprothrin is likely to be moderately mobile in soil, Log K_{oc} of 2.43.

Degradation

Imiprothrin is hydrolytically stable at pH 5 and it undergoes hydrolysis with increasing alkalinity. Hydrolysis DT_{50} values at 12°C are 166 days at pH 7 and 2.11 days at pH 9, at 25°C 58.6 days at pH 7 and 0.746 days at pH 9. Two hydrolysis products were considered relevant, CPG (N-carbamoyl-N-propargylglycine) and KCA (chrysanthemic acid). Data on hydrolysis might be considered for classification purposes only when the longest half-life determined within the pH range 4-9 is less than 16 days (corresponding to a degradation of >70% within 28 days). Accordingly, imiprothrin is hydrolytically stable.

In a 28-day ready biodegradability study 2% mineralisation was observed, while primary degradation amounted to 42%. Imiprothrin is considered not readily biodegradable.

In an aerobic water/sediment simulation study, whole system DT_{50}s for imiprothrin were between 2.6 and 10.2 days at 12°C. Mineralisation was observed with 7.5 to 11.2 % AR on day 31 and 39.6 to 52.3% AR by day 101. Total system DT_{50}s for three principal degradants were between 7.4 and 97.7 days. The degradation data does not support that imiprothrin would fulfil the criteria for ultimate degradation in the aquatic environment with a half-life of <16 days (corresponding to a degradation of >70% within 28 days) or that it is transformed to non-classifiable products in that period.

Overall conclusion on degradation: RAC agrees with the DS's proposal to consider imiprothrin as not rapidly degradable for the purpose of classification and labelling.

Aquatic Bioaccumulation

Lipid normalised whole fish BCFs based on total ^{14}C-residues were 124-144 L/kg, and 4.6-5.8 L/kg based on ^{14}C-imiprothrin. The measured BCFs values are below the CLP criterion of BCF ≥500. The low bioaccumulation potential of imiprothrin is also supported by the experimental (shake-method flask) Log K_{ow} of 2.9, which is below the CLP trigger value of Log K_{ow} ≥4. It is noted that for surface-active substances, the shake-flask method is not the most suitable experimental method to determine the Log K_{ow} due to micelle/emulsion formation. According to the REACH Guidance (Chapter R.7a section 7.1.8.5), in many cases a calculated K_{ow} value based on the octanol and water solubilities will be the first choice for surfactants. In this regard, a Log K_{ow} value of 2.98 was calculated by RAC using KOWIN (v1.68 estimate). This value is in the same range as the experimental Log K_{ow} value of 2.90 for imiprothrin. It is considered that at best the experimental Log K_{ow} value could be used as supportive data since experimental BCF values are available. Therefore, RAC agrees with the DS proposal to consider imiprothrin as a substance with a low potential to bioaccumulate.

Aquatic toxicity

Aquatic acute toxicity data on imiprothrin are available for fish, invertebrates and algae (table above). Acute endpoints for fish and invertebrates lie in the range of 0.01 to 0.1 mg/L. The lowest acute aquatic toxicity value is a 96-h LC_{50} of 0.038 mg/L for the fish rainbow trout. According to Tables 4.1.0(a) and 4.1.3 of the CLP guidance, imiprothrin should be classified as Aquatic Acute 1 with an acute M-factor of 10.

Aquatic chronic toxicity data on imiprothrin is available for one trophic level, algae. In the absence of adequate long-term toxicity data for fish and aquatic invertebrates, the surrogate method is applied as recommended in CLP guidance section 4.1.3.3 and Table 4.1.0. The substance is considered not rapidly degradable and does not fulfil the criteria for bioaccumulation.

- Classification based on adequate chronic toxicity data. Algae long-term testing provide a 72-h NOErC of 1.3 mg/L. The NOErC is above 1 mg/L and the substance is not rapidly degradable. Imiprothrin does not fulfil the criteria for chronic classification, based on Table 4.1.0 (b)(i).
- Classification based on surrogate data for fish and aquatic invertebrates. The lowest acute toxicity value is a 96-h LC_{50} of 0.038 mg/L for rainbow trout. The 96-h LC_{50} is ≤1 mg/L and the substance is not rapidly degradable. Imiprothrin fulfils the criteria of category Chronic 1, based on Table 4.1.0(b)(iii).
- Overall conclusion: category Chronic 1 applies following the most stringent outcome.
- The M-factor is based on the acute aquatic toxicity between 0.01 and 0.1 mg/L.

<u>Conclusion on Classification</u>

RAC concludes that imiprothrin fulfils the CLP criteria for classification as **Aquatic Acute 1** with an **M-factor of 10** and **Aquatic Chronic 1** with an **M-factor of 10**.

6 OTHER INFORMATION

None

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8 ANNEXES

Annex I – Confidential information on substance identity (provided as a separate attachment)

Annex II - Aquatic toxicity data for imiprothrin degradants.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON IMIPROTHRIN (ISO); REACTION MASS OF: [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

Annex I – Confidential. See separate document attached to IUCLID.

ANNEX II – Aquatic toxicity data for imiprothrin degradants.

Table 1: Summary of relevant information on aquatic toxicity for imiprothrin degradants

Degradant / Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg/l)	
PGH							
Acute toxicity to fish Japanese Guideline, not GLP, purity 97.1%	Japanese Rice Fish (*Oryzias latipes*)	Mortality	Semi-static	48 hours	LC_{50}	>484 nominal	Sumitomo Chemical Co. Ltd (1992)

The above study was not conducted to GLP or for the standard endpoint duration. Various study details are unclear and analytical support is not available to support the use of nominal concentrations. Overall, it is considered only as supporting information that the degradant PGH is likely to be less toxic than the parent imiprothrin.

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