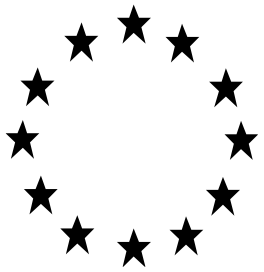
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Imiprothrin

Product-type 18
(Insecticides, acaricides and products to control other arthropods)

July 2017

UK

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the active substance imiprothrin as product-type 18 (insecticides, acaricides and products to control other arthropods), carried out in the context of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

On 30 April 2006, the UK competent authority received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 3 August 2006.

On 20 July 2016 the Rapporteur Member State submitted to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report (CAR).

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of imiprothrin for product-type 18, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency website, shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

Imiprothrin is the common name for a reaction mass of; 2,5-dioxo-3-prop-2-ynylimidazolidin-1-ylmethyl (1*R*)-*cis*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; 2,5-dioxo-3-prop-2-ynylimidazolidin-1-ylmethyl (1*R*)-*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate (ca 20:80). Imiprothrin is a viscous amber liquid with a molecular mass of 318.37 $gmol^{-1}$. It has a low volatility at room temperature and decomposes at 128 °C. It has a water solubility of 93.5 mg/l at 25 °C, relative density of 1.12 and vapour pressure 1.86 x 10^{-6} Pa. The octanol-water partition coefficient ($LogP_{ow}$ 2.9 at 25 °C) makes imiprothrin a moderately fat soluble compound. Imiprothrin is stable to hydrolysis under acidic conditions, hydrolyses slowly under neutral conditions (t½ = 58.6 days at pH 7) and readily hydrolyses under basic conditions (t½ = 17.9 hours at pH 9).

Validated analytical methods are available for the active substance as manufactured and for the relevant and significant impurities. Monitoring methods for soil, body fluids and tissues and food and feed are not required. The validation data provided for the monitoring of residues in air, surface and drinking water are not complete and will be required before the date of approval of the active substance.

Additional data to address the droplet size of the Pralle® 0.5 % aerosol formulation are required at product authorisation. These data must be conducted using the proposed formulation.

2.1.2. Intended Uses and Efficacy

The representative product for imiprothrin is Pralle®, a pre-pressurised handheld aerosol insecticide spray containing 0.5 % active substance.

The product is for indoor use only and may be used for treatments in domestic or restaurant kitchens and other areas in buildings where small infestations and harbourages of crawling insects may occur. For the control of cockroaches – *Periplaneta americana* (American cockroaches), *Blattella germanica* (German cockroaches) and *Blatta orientalis* (Oriental cockroaches) and other crawling insects – *Cimex lectularius* (bed bugs) and *Ctenocephalides felis* (cat fleas).

The discharge rate is 1.3 g s^{-1} and treatment is recommended using 1 - 2 s bursts, with 15 - 20 s total spray per treated area. This is equivalent to 97.5 - 130 mg imiprothrin.

The applicant has provided the following statement on mode of action:
'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. This action is demonstrated by the rapid knockdown action caused by pyrethroid compounds, such as imiprothrin, against target insects.'

The applicant has also provided the following statement on resistance:
'Although the development of resistance to pyrethroid insecticides is well documented, imiprothrin is not considered to have a high selection pressure for the development of resistance under the intended usage pattern. No incidence of resistance to imiprothrin in cockroaches (or other arthropods) has been recorded under the Resistant Pest Management Arthropod Database as compiled by Michigan State University (MSU) in conjunction with the Insecticide Resistance Action Committee (IRAC). When imiprothrin-containing formulations are used according to the label recommendations, they are not considered to have a high selection pressure for resistance.

However, as resistance to pyrethroids has been reported in the UK, the UK CA suggests that the issue of resistance be addressed at product authorisation stage for all imiprothrin-containing products.'

Further product specific efficacy data will be required in support of imiprothrin-containing insecticide products at the product authorisation stage.

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of innate efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.3. Classification and Labelling

2.1.3.1. Current active substance classification

The current harmonised classification of the active substance imiprothrin according to Regulation EC 1272/2008 is shown in Table 2.1.

Table 2.1 Current harmonised classification of imiprothrin according to Regulation EC 1272/2008

Pictogram:	
Signal WORD:	WARNING
Hazard class and category:	Acute Tox 4 ; Aquatic Acute 1 ; Aquatic Chronic 1
Hazard statements:	H302: Harmful if swallowed H400: very toxic to aquatic life H410: very toxic to aquatic life with long lasting effects

2.1.3.2. Proposed active substance classification

On the basis of a review of the data submitted, the UK CA proposes the following classification for imiprothrin. A CLH report has been prepared and submitted to ECHA and a RAC opinion is expected to be adopted in 2017.

Table 2.2 Proposed classification of imiprothrin according to Regulation EC 1272/2008

Pictogram:	
Signal WORD:	WARNING#
Hazard class and category:	Acute Tox 4 – Inhalation ; Acute Tox 4 – Oral ; Repro Tox 2 ; Aquatic acute 1 ; Aquatic chronic 1
H-statements:	H332: Harmful if inhaled. H302: Harmful if swallowed H361d: Suspected of damaging the unborn child H410: Very toxic to aquatic life with long lasting effects##
Ecotox M-Factor:	Acute M-factor: 10 Chronic M-factor: 10

Where the signal word 'Danger' is used on the label due to classification into another hazard class(es), the signal word 'Warning' shall not appear on the label.

In line with Article 27 of CLP, to avoid unnecessary duplication of hazard statements, for labelling purposes where the criteria H400 applies in addition to H410, the appropriate hazard statement for inclusion on the label is 'H410' – together with its associated pictogram and 'signal word'.

The Applicant does not agree with the proposal to classify imiprothrin with H332 (harmful if inhaled). A justification for their position was provided but it was concluded at WGI 2017 that no agreement on inhalation classification was required.

Precautionary statements required from an ecotoxicological perspective:

P273: 'Avoid release to the environment'
P391: 'Collect spillage'
P501: 'Dispose of contents/container to …' (in accordance with local / regional / national / international regulation – to be specified).

2.1.3.3. Current classification of the representative product

The classification of the biocidal product Pralle® according to Regulation (EC)1272/2008 is as follows:

PICTOGRAM:	
SIGNAL WORD	Not required
Classification	Flam Liq 1 Aquatic Chronic 2
H-Statements	H224: Extremely flammable liquid and vapour H411: Toxic to aquatic life with long lasting effects

There is a separate hazard class in CLP for flammable aerosols and also for receptacles containing compressed or liquefied gases.

SIGNAL WORD	DANGER
Classification	Aquatic Chronic 2
H-Statements	H222: Extremely flammable aerosol H280: Contains gas under pressure ; may explode if heated H411: Toxic to aquatic life with long lasting effects

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

Imiprothrin is a synthetic pyrethroid insecticide acting on the sodium channels of the insect nervous system. The PT18 product is a solvent based aerosol (Pralle® 0.5 % aerosol) intended solely for non-professional use which contains the active ingredient imiprothrin at a concentration of 0.5 % w/w. It will be formulated as a ready-for-use oil-based aerosol spray containing 300 ml (208 g) of the preparation, 1 g of imiprothrin. It will be sold as a surface spray for spot, crack and crevice treatment for indoor use only and may be used for treatments in domestic or restaurant kitchens and other areas in buildings where small infestations and harbourages of crawling insects may occur.

Full details of the exposure scenarios and modelling are presented in Document II-B (Section 3.2). The risk characterisation follows the principles agreed by the Biocides Technical Meeting, described in Technical Guidance Documents for Risk Characterisation of Systemic Effects[1]. The risk characterisation for systemic effects is conducted by comparison of the exposure with the appropriate Acceptable Exposure Limit (AEL). In this approach, the systemic exposure estimates are compared with the determined systemic AEL = N(L)OAEL (mg/kg bw/day)/overall Assessment Factor (AF). Risks are considered acceptable if the Exposure/AEL ratio x 100 % is < 100 %.

[1] http://ec.europa.eu/environment/biocides/pdf/tnsg_4_1.pdf

2.2.1.1. Hazard identification

2.2.1.1.1. *Toxicology hazard summary*

The toxicity of imiprothrin has been studied in experimental animals via the oral, inhalation and dermal routes. Repeat dose studies were performed with technical imiprothrin, with some of the acute toxicity and irritation studies performed with a 'manufacturing use product' (MUP).

Toxicokinetics

In rodents, imiprothrin is extensively absorbed following oral and inhalation exposure and it is concluded that absorption values of 100 % are derived for these routes for use in the human health risk characterisation. Following absorption, extensive metabolism occurs in rodents and imiprothrin and/or its metabolites are predicted to be widely distributed, although no data were available on tissue or blood levels prior to extensive excretion. Although there is no specific information to establish whether or not imiprothrin undergoes first pass metabolism, the speed of clearance (90 % in urine at 24 hours), 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, indicate that significant first pass metabolism can be assumed. In rodents, elimination is rapid and occurs predominantly via the urine. The ability of imiprothrin to partition into the breast milk and to cross the blood-placenta barrier has not been investigated.

Dermal absorption values

The only dermal absorption data available are for an ethanolic formulation containing 1 % (w/v) imiprothrin for which a value of 5 % was measured for human skin *in vitro*. Pralle® 0.5 % aerosol is an aromatic solvent based aerosol, which is different to an ethanolic product, and important given the low water solubility of imiprothrin (0.1g/L; log Kow 2.9). The content of imiprothrin is also lower. A value of 75 % is proposed for the dermal absorption of imiprothrin from Pralle® 0.5 % aerosol.

These values of 5 % for absorption from an ethanolic solution and 75 % for Pralle® were agreed at WGI 2017.

Inhalation absorption values

No data available, 100 % is assumed.

Acute toxicity, irritancy and sensitisation

Imiprothrin is of moderate acute toxicity in both rats (LD_{50} values of 1800 and 900 mg/kg in males and females, respectively) and mice (LD_{50} values of 724 and 550 mg/kg reported in males and females, respectively) by the oral route; the mouse appearing to be the more sensitive species. Clinical signs of toxicity suggestive of neurotoxic effects were seen in both species with changes in functional observational battery (FOB) occurring in rats treated with 300 mg/kg in an acute neurotoxicity study. However, no neuropathological changes were seen in the acute and sub-chronic neurotoxicity studies. Imiprothrin aerosol is also of moderate toxicity in rats. No mortality was observed at the maximum achievable concentration (by the experimental device) of 1.2 mg/l. However, LC_{50} values of 3.6 - 4.4 mg/l in male and 2.8 - 3.6 mg/l in female rats were reported for single inhalation exposure to the Manufacturing Use Product aerosol (S-41311 MUP), which is 50 % imiprothrin in isopropyl myristate. These data suggest classification of S-41311 MUP with H332 is appropriate[2]. It is noteworthy that these LC_{50} values expressed as concentration of imiprothrin in the formulation (i.e. 50 %) would be

[2] The Applicant does not agree with this proposal by the UK CA. It is noted that the final decision with regard to this proposal will be made by the Risk Assessment Committee of the European Chemicals Agency.

approximately 1.8 - 2.2 mg/l and 1.4 - 1.8 mg/l, respectively, above the concentration tested in the inhalation study with technical imiprothrin. Given that the other component of S-41311 MUP (isopropyl myristate) is of low acute inhalation toxicity (LC_{50} > 33 - 41 mg/l), it is considered that classification of imiprothrin as harmful by the inhalation and oral routes (Acute Tox 4 – Inhalation and Oral [H332 and H302]) is appropriate. The available data indicate that imiprothrin is not acutely toxic by the dermal route and no classification is considered appropriate.

Data from standard studies with imiprothrin showed no skin irritating potential and only slight, transient eye irritation which does not meet the EU criteria for classification. No evidence of irritating effects in the respiratory tract was seen in acute inhalation study with imiprothrin. Although nasal discharge was reported following 28-day inhalation exposure and in the acute study with the manufacturing use product (S-41311 MUP), it is predicted that imiprothrin is unlikely to cause respiratory tract irritation. Pralle® 0.5 % base liquid was not irritating to the eyes, but caused mild irritating effect on the skin of rabbit which was completely cleared within 7 days. Although there is no specific information on the respiratory tract irritation potential of Pralle® 0.5 % aerosol no indication of such an effect was reported in the acute inhalation study. Overall, Pralle® 0.5 % aerosol does not meet the EU classification criteria for skin, eye or respiratory tract irritation and hence, no further consideration is given to the irritation end-point in the risk characterisation and no local effects assessment has been performed.

In standard skin sensitisation tests (Magnusson & Kligman), neither imiprothrin nor S-41311 MUP demonstrated skin sensitising potential and do not require EU classification. No skin sensitisation reactions were seen in a standard study with Pralle® 0.5 % base liquid. There are no indications that imiprothrin is a respiratory sensitiser. Based on the known properties of the co-formulants, it is also predicted that respiratory sensitisation would not occur following exposure to Pralle® 0.5 % aerosol. Therefore, these endpoints will not be considered further in the risk characterisation and no local effects assessment is required.

Repeated dose toxicity

The effects of repeated oral exposure to imiprothrin have been investigated in a range of species and exposure periods (rat: 90 day/2 year dietary; mouse: 90 day/18 month dietary; dog: 90 day/1 year capsule). In addition subacute studies via the dermal (21 day) and inhalation (28 day) routes of exposure have been performed in the rat.

The study NOAELs and LOAELs are summarised in the following table:

Route	**Duration**	**Species**	**LOAEL (mg/kg/d)**	**NOAEL (mg/kg/d)**
Oral, diet	90 day	Rat	179	5.9
Oral, diet	90 day	Mouse	371	130
Oral, capsule	90 day	Dog	100	10
Oral, capsule	1 year	Dog	50	5
Oral, diet	18 month	Mouse	354	10
Oral, diet	2 year	Rat	90	9
Dermal	21 day	Rat	Systemic: 1000	Systemic: 300
			LOAEC (mg/m^3)	**NOAEC (mg/m^3)**
Inhalation	28 day	Rat	186 (systemic 36 mg/kg bw/d)	22 (systemic 4.2 mg/kg bw/d)

Following oral administration hepatotoxicity and haematotoxicity were reported across all 3 species, the mouse being less sensitive than the rat or dog; in addition, the salivary gland was also a target organ for toxicity in the rat and dog. The effects on the liver increased in severity with dose and were associated with increased ALT activity and decreased AST activity,

increased levels of cholesterol and phospholipids and decrease levels of triglycerides. Histopathological changes ranged from mild hepatocyte hypertrophy in the subacute studies to more marked changes in the longer term studies including pitted and altered hepatic foci, centrilobular/portal fibrous tissue and fibrous bridging, dilation of sinusoids, loss of hepatocytes, inflammatory cell infiltration and pigmented centrilobular hepatocytes.

Haematological changes (decreases in red blood cell count, haemoglobin and haematocrit levels and increased reticulocyte count) were manifest predominantly at higher dose levels in subchronic studies and associated with extramedullary haematopoiesis in the spleen indicating effects are reversible. Indeed, in studies of longer duration, effects on haematological parameters are not as significant.

The salivary gland was a target organ for toxicity in dogs and rats. Histopathological examination revealing increased incidences of swelling of acinar cells and proliferation of the serous gland of the submandibular gland.

The dose spacing in the 90 day dog study and the 1 year dog study involve 10 fold gaps between the NOAELs (5 and 10 mg/kg bw/d) and LOAELs (50 and 100 mg/kg bw/day). Taking account of the consistency of the findings and limited severity of effects at the LOAEL, the UKCA considers that an overall NOAEL for the dog studies can be determined at 10 mg/kg bw/day the NOAEL from the 90 day study.

A similarly large dose spacing is present in the rat chronic study (NOAEL 9 mg/kg bw/day; LOAEL 90 mg/kg bw/day). The findings at the LOAEL at 104 weeks were primarily of the salivary gland, similar to findings in the dogs. The NOAEL at 52 weeks in the rat study is 9.9 mg/kg bw/day. The NOAEL from the 18 month mouse study is also 10 mg/kg bw/day. The UK CA considers that an overall NOAEL for rats, mice and dogs of 10 mg/kg bw/day can be derived, this reflects the observed toxicity and the dose spacing and will be adequately protective.

A NOAEL for subchronic and chronic exposure of 10 mg/kg/d is established.

Following inhalation exposure of rats 4 h/d for 28 days, clinical signs characteristic of neurotoxicity (including decreased spontaneous activity, tiptoe gait, hypersensitivity and tremor) were reported. Effects on the liver were also observed associated with increased cholesterol and decreased triglyceride levels. The salivary gland was also a target for toxicity with an increased incidence of basophilic staining of the acinar cells. Slight indications of haematotoxicity were also noted. A NOAEC of 22 mg/m^3 (equivalent to a systemic dose of 3.6 mg/kg/d) was established. The NOAEC for the 28 day inhalation study is 22 mg/ m^3 with a LOAEC of 186 mg/m^3 these convert to systemic doses of approximately 4.2 and 36 mg/kg bw/d, spanning the NOAELs from the most sensitive oral studies. This indicates there is no significant quantitative difference in toxicity between oral and inhalation exposures to imiprothrin.

Following dermal exposure of rats to imiprothrin in corn oil 6 h/d for 21 days, the only indication of systemic toxicity was an increase in the absolute weight of the salivary gland at the top dose level. Although this finding was not associated with any histopathological changes, it was considered biologically significant given the similar effects observed in the oral studies. A systemic NOAEL of 300 mg/kg/d was established from this study. There was evidence of slight skin irritation (acanthosis and hyperkeratosis) therefore a local NOAEC of 150 mg/ml was also established. The product Pralle® 0.5 % aerosol is not classified for irritancy or sensitisation, therefore a local effects consideration has not been performed.

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 relevant for classification. Therefore the observations are not considered to be sufficient to warrant classification of imiprothrin as STOT RE.

Mutagenicity

In vitro, negative results were reported in a bacterial gene mutation test and a mammalian cell gene mutation assay. However, a positive response was observed with external metabolic activation (+S9) in a chromosome aberration assay. *In vivo*, negative results were reported in a mouse bone marrow micronucleus test and a rat liver UDS test. Overall, it is considered that imiprothrin does not express mutagenic activity *in vivo* and that the data on imiprothrin does not meet the EU classification criteria for mutagenicity. Similarly, classification for mutagenicity is not deemed necessary for Pralle® 0.5 % aerosol as none of the other co-formulants are classified as mutagens.

Carcinogenicity

In lifetime dietary studies, imiprothrin slightly increased the incidences of lung and liver tumours at the highest dose levels in male rats and mice.

Slightly increased incidences of benign lung and liver tumours were seen in male rats in the top dose group. Given the low numbers of tumours observed in the treated animals, the presence of both benign and malignant liver tumours in control males, and the absence generally of any clear dose-response, it seems unlikely that the liver tumours in rats were treatment-related.

Lung adenocarcinoma was observed in female rats in the low dose group only. In male rats, there was an increase in lung adenoma at the top dose only (4 %) against a 0 % incidence in controls and all other treatment groups. This finding is not statistically significant (Fisher exact test, $p > 0.05$), relates to a benign tumour and shows no correlation between the sexes; it is not considered to indicate imiprothrin has carcinogenic potential in the rat.

Increased incidences of lung and liver tumours were seen in mice at the top dose level. Both liver adenoma and carcinoma were evident in control males but not females. In male mice, 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 male. 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. 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.

Increased incidence of lung adenoma was observed in females in the top dose group at the end of the treatment period. 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. The incidence of lung adenoma in females at the top dose was above the incidence for historical controls in this test laboratory but within the broader historical control data range from the animal supplier. 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 in control and in all dose groups in both sexes. Adenocarcinoma was also observed in control animals.

Full details of the carcinogenicity considerations are presented in Document II-A Section 3.7. 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.

Reproductive toxicity

Developmental toxicity effects were mainly seen with imiprothrin at non-maternally toxic dose levels in standard studies in pregnant rats and rabbits. In the rat study, statistically significant increased incidence of skeletal variations and visceral anomalies were reported at dose levels causing mortality (600 mg/kg bw/day) and reduced bodyweight gain to the dams (≥ 200 mg/kg/d). In rabbits, reduction in foetal bodyweight, higher incidence of skeletal variations and anomalies were reported at 100 mg/kg/d and above, dose levels at which mortality (300 mg/kg bw/day) and significantly reduced bodyweight gain were reported in the dams (≥ 100 mg/kg bw/day). An increased incidence of a malformation (fusion of the nasal bone) was seen at the top dose level of 300 mg/kg bw/day.

Although some of the developmental findings at the top dose levels might be related to the high level of maternal toxicity, the secondary nature of all the developmental effects has not been unequivocally demonstrated. A marked increase in the incidence of a skeletal malformation, fusion of the nasal bone, was seen in rabbits exposed at 300 mg/kg bw/day (14 % versus 1.4 % in both controls and historic controls). The incidence of lumbar rib in the rat was clearly dose-related (16 %, 20 %, 48 % and 68 % at 0, 50, 200 and 600 mg/kg/d, respectively) with the only observed maternal toxicity observed at 200 mg/kg bw/day being transient reductions in body weight gain on gestation days 8 – 12. The dose-dependent increase in 27 pre-sacral vertebrae in rabbits (1.4 %, 8 %, 10.0 % and 17.2 % at 0, 30, 100 and 300 mg/kg bw/d) cannot be discounted on the basis of maternal toxicity since at ≤ 100 mg/kg bw/d there were no maternal deaths and only limited maternal toxicity observed. The significance of this observation is difficult to interpret because of the maternal toxicity observed at the top dose and the fact that the incidence at the low dose (8 %) fell within the updated historical control data range (0 - 8.6 %). However, the observation is considered to add to the weight of evidence, indicating that classification of imiprothrin as a reproductive toxicant might be appropriate. The finding of hypoplasia of the frontal bone was in 2 foetuses at 100 mg/kg/d in rabbits adds to the weight of evidence to support classification because this effect was only seen in treated groups. Furthermore 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 and the effects occurred in more than one litter, at least at the top dose. Moreover, fusion of skull bones is considered to be of a high level of concern. The foetal and litter incidences of the abnormalities give rise to a cause for concern for craniofacial development. On the basis of the available data, it cannot *be unequivocally demonstrated that the developmental effects are secondary to maternal toxicity* and therefore these effects are considered to be evidence of developmental toxicity. Using a weight of evidence approach, imiprothrin is considered to be toxic to reproduction (development) and warrants classification as a reproductive toxicant under CLP. Had the hypoplasia and fusion of the nasal bone occurred in the absence of maternal toxicity, it is considered that a classification for reproductive toxicity in category 1B would have been warranted. Full details of the developmental toxicity consideration are presented in Document II-A Section 3.8.

Taking the minimal maternal toxicity into consideration, a category 2 classification for reproductive toxicity is considered to be appropriate for imiprothrin.

Maternal toxicity and developmental effects were seen in the rat and rabbit developmental studies. NOAELs could be determined for each species. In the rat both the maternal and developmental NOAELs are 50 mg/kg bw/day. In the rabbit the maternal and developmental NOAELs are 30 mg/kg bw/day.

Imiprothrin showed no adverse effects on reproduction and fertility in a two-generation study in the rat at dietary concentrations of up to 6000 ppm (equivalent to approximately 288 mg/kg/d). The NOAEL for parental toxicity was 200 ppm (11 mg/kg/d) based on increased liver weight (although no pathology is reported this is considered biologically significant given the changes observed in the repeat dose studies) and evidence of blood cell changes (increased incidence of haemosiderin deposits in the spleen) at 2000 ppm (96 mg/kg/d).

Overall, classification for fertility is not appropriate. Similarly, no classification for Pralle® 0.5 % aerosol is appropriate given that the other co-formulants are not classified as having an adverse effect on fertility.

Neurotoxicity

The potential neurotoxicity of imiprothrin was investigated in an acute and a 90 day repeat dose study in rats. No neuropathological changes were detected in the acute and the sub-chronic neurotoxicity studies, and there were clear NOAELs identified for the clinical evidence of neurotoxicity. A NOAEL of 74 mg/kg/d was identified for general toxicity based on decreased bodyweight at the next higher dose of 219 mg/kg/d, in the sub-chronic study. Signs of neurotoxicity primarily tremors, decreased motor and locomotor activity were observed in the single dose gavage study at 1000 mg/kg, with minimal effects (including tremor in one female) at 300 mg/kg bw; no neurotoxic effects were seen at 100 mg/kg.

Immunotoxicity

No specific investigations but there were no effects reported on immune related parameters in the routine toxicity studies.

Pralle® 0.5 % aerosol

Pralle® 0.5 % aerosol is not acutely toxic by the oral (LD_{50} > 5000 mg/kg), inhalation (LC_{50} > 0.3 mg/l; the maximum achievable concentration) and dermal (LD_{50} > 2000 mg/kg) routes. Overall, no classification of Pralle® 0.5 % aerosol for acute toxicity is appropriate. It was concluded that Pralle® 0.5 % aerosol is non-irritating to the skin and eyes and no classification is required. Pralle® 0.5 % aerosol has no skin or respiratory sensitisation potential and no classification is proposed.

Pralle® 0.5 % aerosol has not been investigated for repeat dose toxicity, carcinogenicity or mutagenicity. However, given that neither imiprothrin nor the co-formulants are classified for these end-points, it is concluded that Pralle® 0.5 % aerosol would not trigger such classification.

Although there is a proposal to classify imiprothrin for developmental toxicity, classification for developmental toxicity is not appropriate for Pralle® 0.5 % aerosol as imiprothrin is present at < 1 % w/w and none of the co-formulants in the product are identified as developmental toxicants.

2.2.1.1.2. *Critical endpoints and derivation of AELs and AEC*

The relevant information for the risk characterisation for exposure to imiprothrin comes largely from oral studies. Limited data are available to assess systemic toxicity via the inhalation route (28 day study in rats; 4 h/day) and dermal routes (21 day study in rats). In both these studies, the findings were similar to those seen via the oral route (e.g. liver and salivary gland effects). The toxicokinetic information and toxicity profile over different routes indicates that there appears to be significant first-pass metabolism. Although there appears to be an increased sensitivity to imiprothrin when exposure is via inhalation, when the dose spacing is taken into account, the evidence is not conclusive. The NOAEC for the 28 day inhalation study is 22 mg/ m^3 with a LOAEC of 186 mg/m^3 these convert to systemic doses of approximately 4.2 and 36 mg/kg bw/d, spanning the NOAELs from the most sensitive oral studies. Overall, use of oral studies for the derivation of systemic AELs for imiprothrin is considered appropriate for inhalation and dermal exposure.

Following discussions at WGI 2017_Tox_6-2 it was agreed that a short-term inhalation AEC should be derived.

The relevant toxicity studies with imiprothrin are summarised in the table below:

Route	Duration	Species	LOAEL (mg/kg/d)	NOAEL (mg/kg/d)	Effects at LOAEL
Oral, diet	90 day	Rat	179	5.9	↓ triglycerides and food consumption. ↑liver wt., reticulocytes, cholesterol and salivary gland acinar cell swelling.
Oral, diet	90 day	Mouse	371	130	↑liver wt. ↓Hb and Hct
Oral, capsule	90 day	Dog	100	10	↑liver wt. ↑ salivary glands wt. and salivation.
Oral, capsule	1 year	Dog	50	5	↓ body wt. gain, uterus wt. and AST activity.
Oral, diet	18 month	Mouse	354	10	↑liver wt.; hypertrophy and foci. ↑loss hair ↓ body wt.
Oral, diet	2 year	Rat	90	9	↑liver wt. ↑ salivary gland wt. and acinar gland hypertrophy
Oral diet	Reproduction	Rat	96	12	↑haemosiderin and liver wt.
			288	96	↑ minor skeletal anomalies
			>288	288	No fertility effects
Oral	Developmental	Rat	200	50	↓ body wt. gain
			200	50	↑skeletal abnormalities
Oral	Developmental	Rabbit	100	30	↓ body wt. gain
			100	30	↑skeletal abnormalities
Oral	Developmental	Rabbit	30	-	No effects
			30	-	No effects
Oral gavage	Acute neurotoxicity	Rat	300	100	Tremors in 1 female
Oral diet	90 day Neurotoxicity	Rat	219	74	↓ body wt.
Dermal	21 day	Rat	Systemic: 1000 Local: 500 mg/l	Systemic: 300 Local: 150 mg/l	↑salivary gland wt. ↑ acanthosis and hyperkeratosis
			LOAEC (mg/m³)	**NOAEC (mg/m³)**	
Inhalation	28 day	Rat	186 (systemic 36 mg/kg bw/d)	22 (systemic 4.2 mg/kg bw/d)	↑relative organ wts including liver and salivary gland. ↑ toxicity and cholesterol. ↓food consumption and triglycerides

Short-term inhalation systemic AEC

The WGI 2017_Tox_6.2 agreed that an additional short-term inhalation systemic AEC should be derived from the available 28 day rat inhalation study as short-term systemic effects (clinical signs of toxicity indicative of neurotoxicity) observed following inhalation exposure appear to be more sensitive than short-term systemic effects observed following oral exposure. It was noted that such effects were noted in the 28 day inhalation study at the LOAEC of 186 mg/m^3, which is equivalent to a dose of 36 mg/kg bw/d (NOAEC = 22 mg/m^3 = 4.2 mg/kg bw/d). This LOAEL is very close to the NOAEL of 30 mg/kg bw/d (from the oral developmental toxicity study in rabbits) used to derive the short-term systemic AEL.

It was agreed at WGI 2017 that the AEC could be considered as applicable to all durations of exposure during a single day even though it was based on a study using a 4 hour exposure. This conclusion was based on the fact that the key neurotoxic effects seen at the LOAEC in the 28 day inhalation study were agreed at WG as likely to be related to the peak concentration of imiprothrin rather than a combination of the concentration and duration (AUC). There were no adverse pathological findings and the clinical signs were seen only during exposure, regressing before the first observation period after the cessation of exposure (at 1 hour). Additional reassurance is provided by the >8 fold margin between the NOAEC and the LOAEC, at which there were limited effects.

Proposal for the derivation of the short-term inhalation systemic AEC

It is proposed to use the NOAEC of 22 mg/m^3 identified from the 28 day study in which rats were exposed whole-body to imiprothrin aerosol for 4 hours/day.
By applying a default interspecies AF of 2.5 (the allometric scaling factor of 4 is already accounted for by the differences in ventilation rates between rats and humans) and a default intraspecies AF of 10, a 4 h-AEC of 0.9 mg/m^3 is derived.

$$\mathbf{AEC_{inhalation\ systemic\ short\text{-}term\ 4h}} = \mathbf{0.9\ mg/m^3}$$

No time extrapolation should be performed. This 4 h-AEC should be used in the risk assessment as such (without further time adjustment) and compared with daily inhalation exposures shorter or longer than 4 hours.

Short-term AEL

In the developmental toxicity study in the rabbit, a significant decrease in bodyweight gain of dams and increases in the incidences of skeletal anomalies (27 pre-sacral vertebrae and hypoplasia of the frontal bone) were observed at 100 mg/kg/d and based on this effect, a NOAEL of 30 mg/kg/d was determined for maternal and developmental toxicity. These effects are considered relevant to acute exposures. Based on these findings no additional assessment factors are considered appropriate for acute exposure scenarios. The NOAEL for malformations (fused nasal bones) is 100 mg/kg bw/day. Thus, an overall assessment factor of 100 is proposed, resulting in an Acceptable Exposure Level (AEL) of 0.3 mg/kg/d for acute exposure scenarios.

$$\mathbf{AEL_{systemic,\ acute}} = \mathbf{0.3\ mg/kg\ bw/day}$$

Medium-term AEL

Ninety day studies are available in the rat, dog and mouse. The lowest NOAEL derived from these studies was 5.9 mg/kg/d in the rat study with the LOAEL being 179 mg/kg/d. The NOAEL derived from the dog study was 10 mg/kg/d with a LOAEL of 100 mg/kg/d. Given the large dose spacing in the rat study, the NOAEL from the dog study is considered the most appropriate for use in medium-term oral exposure scenarios. In this study, liver enlargement accompanied by changes in enzyme activity, salivary gland effects and mild anaemia were reported at 1000 mg/kg/d but none of these effects were evident in recovery animals six weeks post-exposure. At the mid-dose of 100 mg/kg/d, signs of toxicity (transient salivation

and increased incidence of loose and watery faeces) and increase in weights of the salivary gland (8 -18 %) and the liver (relative, 10 - 13 %) were described. No effects were reported at 10 mg/kg/d, identified as the NOAEL. It is worth noting that in equivalent studies in the rat at dose level of 179 mg/kg/d the only effects observed were decreased in food consumption, increased reticulocyte number and increased swelling of the salivary gland cells (graded as minimal in severity). Based on these data no additional assessment factors are considered appropriate for medium-term oral exposure scenarios. Thus, an overall assessment factor of 100 is proposed, resulting in an Acceptable Exposure Level (AEL) of 0.1 mg/kg/d for medium-term exposure scenarios.

$AEL_{systemic,\ medium\ term}$ = 0.1 mg/kg bw/day

Long-term AEL

Following oral administration hepatotoxicity and haematotoxicity were reported across all 3 species, the mouse being less sensitive than the rat or dog; in addition, the salivary gland was also a target organ for toxicity in the rat and dog. The effects on the liver increased in severity with dose and were associated with increased ALT activity and decreased AST activity, increased levels of cholesterol and phospholipids and decrease levels of triglycerides. Histopathological changes ranged from mild hepatocyte hypertrophy in the subacute studies to more marked changes in the longer term studies including pitted and altered hepatic foci, centrilobular/portal fibrous tissue and fibrous bridging, dilation of sinusoids, loss of hepatocytes, inflammatory cell infiltration and pigmented centrilobular hepatocytes. Haematological changes (decreases in red blood cell count, haemoglobin and haematocrit levels and increased reticulocyte count) were manifest predominantly at higher dose levels in subchronic studies and associated with extramedullary haematopoiesis in the spleen indicating effects are reversible. Indeed, in studies of longer duration, effects on haematological parameters are not as significant. The salivary gland was a target organ for toxicity in dogs and rats. Histopathological examination revealing increased incidences of swelling of acinar cells and proliferation of the serous gland of the submandibular gland.

Although increases in tumours were seen at high dose levels, clear thresholds were identified at 90 mg/kg bw/d in rats and 354 mg/kg bw/day in mice.

The dose spacing in the 90 day dog study and the 1 year dog study involve 10 fold gaps between the NOAELs (5 and 10 mg/kg bw/d) and LOAELs (50 and 100 mg/kg bw/day). Taking account of the consistency of the findings and limited severity of effects at the LOAEL, the UKCA considers that an overall NOAEL for the dog studies can be determined at 10 mg/kg bw/day the NOAEL from the 90 day study.

A similarly large dose spacing is present in the rat chronic study (NOAEL 9 mg/kg bw/day; LOAEL 90 mg/kg bw/day). The findings at the LOAEL at 104 weeks were primarily of the salivary gland, similar to findings in the dogs. The NOAEL at 52 weeks in the rat study is 9.9 mg/kg bw/day. The NOAEL from the 18 month mouse study is also 10 mg/kg bw/day. The UK CA considers that an overall NOAEL for rats, mice and dogs of 10 mg/kg bw/day can be derived; this reflects the observed toxicity and the dose spacing and will be adequately protective.

Based on these data no additional assessment factors are considered appropriate for long term oral exposure scenarios. Thus, an overall assessment factor of 100 is proposed, equivalent to an Acceptable Exposure Level (AEL) of 0.1 mg/kg/d for long-term exposure scenarios.

$AEL_{systemic,\ long\ term}$ = 0.1 mg/kg bw/day

Dietary exposure reference doses

Although Pralle® 0.5 % aerosol is not intended for use on or near food or food preparation surfaces, dietary reference values for imiprothrin have been derived for completeness.

Acute dietary exposure (ARfD)

The ARfD can be derived on the same basis as the acute systemic AEL, by applying a 100 fold factor to the NOAEL of 30 mg/kg bw/d from the rabbit developmental study.

ARfD = 0.3 mg/kg bw

Lifetime dietary exposure (ADI)

The ADI can be derived on the same basis as the long-term systemic AEL, by applying a 100 fold factor to the overall NOAEL of 10 mg/kg bw/d from the 1 year dog study.

ADI = 0.1 mg/kg bw

2.2.1.2. Exposure assessment

2.2.1.2.1. *Primary exposure*

Professional users

There are no professional uses of Pralle® 0.5 % aerosol.

Non-professional users

Pralle® 0.5 % aerosol is a ready for use product and is intended to be used as a surface spray for spot, crack and crevice treatments indoors to control crawling insects. It is to be marketed solely for non-professional use. The directions state that it should be used with short bursts of 1 – 2 seconds with a total spray time of around 15 – 20 seconds and total exposure time of no more than 15 minutes. It is intended that only adults will carry out treatments and therefore children are not considered in the exposure scenario. During normal use, exposure may occur via the inhalation and dermal routes. Oral exposure as a result of deposition around the mouth and from hand-to-mouth contact may also occur, however, it is expected that the person carrying out the treatment will wash exposed skin immediately after treatment thereby minimising exposure by this route. The TNsG indicates that products of this type may be used an average of 9 times per year (TNsG, part 2, page 245), and the manufacturer recommends a minimum reapplication interval of 4 weeks. Based on the assumed pattern of use and considering that available ADME data indicate that imiprothrin is rapidly eliminated from the system (within 24 hours following oral administration), primary exposure will be assessed as a series of short-term exposures compared against the acute AEL or 4 h inhalation AEC.

The comparison of the estimated exposure and the toxicity is represented by a comparison with the appropriate AEL/AEC. In the AEL concept the exposure estimates should be compared with the determined systemic AEL= NOAEL (mg/kg/d)/ Assessment Factor (AF) if the ratio of Exposure/AEL ≤ 1 or the percentage is < 100, then the risk to the user under the conditions specified above is acceptable. The final assessment is based on total systemic exposure compared against the applicable systemic AEL.

There are no envisaged long-term primary exposure scenarios for imiprothrin as a result of the use of Pralle® 0.5 % aerosol.

Local effects

Pralle® 0.5 % aerosol is not classified for corrosion, irritancy or sensitisation therefore no local effects assessment is required.

2.2.1.2.2. *Secondary exposure*

Secondary exposure of adults, children, toddlers/infants (as bystanders) to imiprothrin as a result of the use of Pralle® 0.5 % aerosol may occur by inhalation and skin contact. Secondary exposure of toddlers may also occur by ingestion (hand-to-mouth). Exposure by inhalation may occur from breathing aerosolised material during and immediately after treatment. It is considered that exposure to aerosolised material will only occur within a short period after

treatment and is therefore expected to be of **medium-term duration**. The time during which aerosol droplets remain airborne and hence available for inhalation is determined by their falling time. The particle size of the Pralle® 0.5 % aerosol has been categorized as coarse based on the volume median diameter of around 40 µm measured for a similar aerosol product (Document II-B, Section 3). The TNsG indicate that the falling time for droplets with a diameter of 10 µm from a height of 3 metres is 17 minutes and for particles with a diameter of 100 µm is 11 minutes (TNsG, part 2, page 248). It will therefore be assumed that aerosolised material has declined to a negligible level within 1 hour of spraying. This is in accordance with data from [redacted] (1995) which showed that following a representative application of an imiprothrin-based product with a similar formulation to Pralle® 0.5 % aerosol, airborne imiprothrin was at a level below the limit of detection within 1 hour.

Occupants of treated premises could be exposed to volatilised a.s. residues from the applied product. Adults, children, toddlers and infants could inhale the vapours when in enclosed unventilated spaces. Although there are up to 9 applications per year there is a decline of active substance content and this is considered to be a **medium-term exposure scenario**.

Skin exposure may occur as a result of contact with treated surfaces and other surfaces onto which aerosolised material has deposited. Since the reapplication time recommended by the company is 4 weeks, it will be assumed that the active substance is available for 4 weeks following treatment both at the treated site and on nearby surfaces. Exposure for this scenario is expected to be of **medium-term duration**.

For toddlers there is also the potential for oral exposure as a result of hand-to-mouth contact. Since residues deposited on surfaces may persist over several days/weeks, exposure for this scenario is expected to be of **medium-term duration**.

Local effects

Pralle® 0.5 % aerosol is not classified for corrosion, irritancy or sensitisation therefore no local effects assessment is required.

2.2.1.2.3. *Combined exposure*

Imiprothrin is the only active substance in Pralle® 0.5 %. There are no substances of concern in Pralle® 0.5 %. There is no indication on the product label that Pralle® 0.5 % should be used with other products. Therefore no specific consideration of combined exposure to multiple compounds is required.

The UKCA considers that combined exposures could occur for the person (adult) using the aerosol spray (primary exposure) and being resident in the premises subsequently (secondary exposure). This is considered to be a short-term scenario for combined exposures.

2.2.1.3. Risk characterisation

2.2.1.3.1. *Primary exposure*

Professional users

The product Pralle® 0.5 % aerosol is intended for non-professional use. No professional use scenarios have been modelled.

Imiprothrin is produced outside the EU, therefore; no human health exposure scenarios have been assessed for the manufacture of the active substance.

Formulation of Pralle® 0.5 % aerosol takes place in the EU. The UK CA has taken into consideration the Framework Directive (89/391/EC) and its daughter directive (98/24/EC) which laid out the protection of the health and safety of workers from the risks related to chemical agents at work. As such, it is assumed that activities during the formulation of Pralle®

0.5 % aerosol are carried out in accordance with the requirements for worker protection.

Non-Professional users

Systemic dermal, inhalation and total systemic dose received as a result of carrying out treatments with Pralle® 0.5 % aerosol are summarised in Table 2.3 below, together with the risk characterisation for primary exposure by adult non-professional users. This does not take into account possible exposure arising from skin contact with residues at the treated site during application. This has been assessed as a secondary exposure.

Table 2.3 Summary of primary exposure assessments for non-professional uses of IMIPROTHRIN (0.5 % aerosol)

Exposure Scenario	Estimated Internal Exposure				
	estimated oral uptake (mg a.s./kg bw/day)	estimated inhalation uptake (mg a.s./kg bw/day)	estimated dermal uptake (mg a.s./kg bw/ day)	estimated total uptake (mg a.s./kg bw/day)	Total exposure as % of acute AEL of 0.3 mg/kg bw/d
Tier 1: Indicative data, assuming entire can used for 1 treatment	0	**1.760 x 10^{-2}**	***9.017 x 10^{-4}**	**1.85 x 10^{-2}**	**6.2**
Tier 2: Indicative data, assuming a total discharge time of 20 seconds	0	**2.642 x 10^{-3}**	***9.017 x 10^{-4}**	**3.5 x 10^{-3}**	**1.2**
Tier 3: Exposure based on data from [redacted] (1995)	0	**2.029 x 10^{-3}**	**3.72 x 10^{-4}**	**2.401 x 10^{-3}**	**0.8**

The risks to the non-professional user from inhalation and dermal exposure following application of Pralle® 0.5 % aerosol are acceptable as demonstrated by the relatively small percentage of the AEL obtained with even the worst case estimates. The greatest exposure at Tier 1 (0.0185 mg/kg bw/day) is 6.2 % of the applicable acute AEL (0.3 mg/kg bw/day), indicating that the risks posed to adult non-professionals from the use of Pralle® 0.5 % aerosol following the procedures specified by the applicant are acceptable.

Short-term inhalation exposures have been compared with the short-term (4 h) AEC of 0.9 mg/m^3.

Table 2.4 Summary of primary inhalation exposure assessments for non-professional uses of IMIPROTHRIN (0.5 % aerosol)

Exposure Scenario	Estimated Inhalation Exposure	
	estimated air concentration (mg/m^3)	Total exposure as % of short-term (4 h) AEC of 0.9 mg/m^3
Tier 1: Indicative data, assuming entire can used for 1 treatment. Initial concentration, no decline.[$]	0.248	**27 %**

Tier 2: Indicative data, assuming a total discharge time of 20 seconds. Initial concentration, no decline.$		0.248	**27 %**
Tier 3: Exposure based on data from [redacted] (1995). 20 minute TWA.*		0.0535	**5.9 %**

$ - Tables 8.1 and 8.2 of Document II-B corrected for 0.5 % active substance content
* Table 8.4 of Document II-B

Inhalation exposures are acceptable at Tier 1 (27 % of the AEC).

2.2.1.3.2. *Secondary exposure*

Table 2.5 Summary of secondary exposure assessments

Exposure Scenario	Estimated Internal Exposures				
	estimated oral uptake (mg a.s./kg bw/day)	estimated inhalation uptake (mg a.s./kg bw/day)	estimated dermal uptake (mg a.s./kg bw/day)	estimated total uptake (mg a.s./kg bw/day)	Total exposure as % of medium term AEL of 0.1 mg/kg bw/d
Adult					
Tier 1	0	0.0833	0.0128	0.0961	**96**
Tier 2	0	0.0161	0.0019	0.0180	**18**
Tier 3	0	6.56×10^{-4}	0.0014	0.002056	**2**
Child					
Tier 1	0	0.1569	0.0126	0.1695	**170**
Tier 2	0	0.0303	0.0024	0.0327	**33**
Tier 3	0	1.24×10^{-3}	0.0018	0.00304	**3**
Toddler (excluding crawling)					
Tier 1	0.0216	0.2498	0.0162	0.2876	**288**
Tier 2	0.0042	0.0483	0.0031	0.0556	**56**
Tier 3	0.00296	1.97×10^{-3}	0.00222	0.00715	**7**
Toddler (including crawling)					
Tier 1	0.0216	0.2498	0.67	0.9414	**941**
Tier 2	0.0042	0.0483	0.1304	0.1829	**183**
Tier 3	0.00296	1.97×10^{-3}	0.0278	0.0327	**33**
Infant					
Tier 1	0	0.2109	0	0.2109	**211**
Tier 2	0	0.0408	0	0.0408	**41**
Tier 3	0	1.66×10^{-3}	0	0.00166	**2**

The UK CA considers the risks to infants, children, toddlers and adults following secondary exposure to imiprothrin through the use of Pralle® 0.5 % aerosol to be acceptable.

With the exception of a toddler crawling over the treated surface, total systemic exposures below the medium term AEL were identified for all other scenarios at Tier 2. Further assurance that exposure by the dermal route would be low is demonstrated from measured data mimicking the possible “real life” situation (i.e. Tier 3) that were only small percentages of the AELs (less than 7 %). Although potential risks were identified in Tiers 1 and 2 due to high dermal exposure of a toddler crawling over the treated surface, the Tier 3 total exposure was 33 % of the medium-term AEL. The data for Tier 3 is based on surface residue data from the study by [redacted] (1995) which does not take account of the decline in surface residues over

time due to domestic activities such as cleaning or removal as a result of previous contact, exposure will again be substantially overestimated. In addition, given that the product is a spot, crack and crevice treatment and thus adults, children, toddlers and infants are not expected to routinely gain access to the exposed areas, an acute endpoint could be more appropriate to assess such exposures against. The Tier 2 exposure for a crawling toddler is below the acute AEL of 0.3 mg/kg bw/day.

2.2.1.3.3. *Combined exposure*

Imiprothrin is the only active substance in Pralle® 0.5 %. There are no substances of concern in Pralle® 0.5 %. There is no indication on the product label that Pralle® 0.5 % should be used with other products. Therefore no specific consideration of combined exposure to multiple compounds is required.

The UKCA considers that combined exposures could occur for the person (adult) using the aerosol spray (primary exposure) and being resident in the premises subsequently (secondary exposure). This is considered to be a short-term scenario for combined exposures. The scenario is summarised in Table 2.6 below.

Table 2.6 Summary of systemic exposures for combined scenario

User	Total systemic exposure during primary exposure (mg/kg bw/d)	Total systemic exposure during secondary exposure (mg/kg bw/d)	Combined exposure (mg/kg bw/d)	Combined exposure as % of acute AEL of 0.3 mg/kg bw/d
Non-professional application and resident in premises	Tier 1: Indicative data, assuming entire can used for 1 treatment **0.0185**	Tier 1: Inhalation and skin contact. No decline of atmospheric levels **0.0961**	**0.11434**	**38.2**

The combined exposure at Tier 1 is 0.11434 mg/kg bw/d. This is 38 % of the acute AEL of 0.3 mg/kg bw/d.

Combined systemic exposures from the application of Pralle® 0.5 % aerosol, by non-professional users and resident in the treated building, present acceptable risks using a conservative Tier 1 model.

A dietary risk assessment was not undertaken.

2.2.1.3.4. *Conclusion*

Overall, the UK CA considers that the application of imiprothrin via Pralle® 0.5 % aerosol is unlikely to present an unacceptable risk to infants, toddlers, older children and adults and accepts that the precautionary phrases on the product label proposed by the applicant are adequate to mitigate any residual risk from most uses. As Pralle® 0.5 % can be used in domestic and commercial kitchens an additional phrase needs to be included to warn against potential contamination of food. No risk assessment was performed for companion animals therefore a phrase regarding their exclusion is appropriate. Due to the potential for some sensitive individuals to suffer paresthesia, and to be consistent with good handling, skin contact should be avoided.

- DO NOT BREATHE SPRAY MIST

- USE ONLY IN WELL-VENTILATED AREAS
- KEEP OUT OF REACH OF CHILDREN
- KEEP PETS, ESPECIALLY CATS, AWAY FROM TREATED AREAS
- KEEP OFF SKIN, WASH HANDS AFTER USE
- DO NOT CONTAMINATE FOOD STUFFS, EATING UTENSILS OR FOOD CONTACT SURFACES

2.2.2. Environmental Risk Assessment

2.2.2.1. Fate and distribution in the environment

The exact composition of the representative product (Pralle® 0.5 % aerosol) is given in the confidential chemistry section but the *trans* and *cis* (R-isomers make up the approximately 90 % imiprothrin present in Pralle® in an approximate ratio of *trans*: *cis* of 80:20).

Due to the proposed indoor use of the representative product, a number of justifications for non-submission of data were provided by the Applicant for some of the additional product type specific studies for PT 18. It should be noted that the eCA has assessed the validity of such arguments and consider that a number of these justifications are acceptable. Further details are included in the relevant parts of Document III-A. Where environmental information requirements to support the use of imiprothrin as an insecticide (under PT 18) are addressed by studies, all data provided in the tables have been taken from studies where a full STUDY SUMMARY (according to the BPR Practicalities Guidance Document) is available, i.e. they are considered as KEY STUDIES with reliability of 1 or 2 unless otherwise indicated.

Unless otherwise stated, all tests have been performed on imiprothrin. The majority of the studies have been carried out using the active substance (a.s.) imiprothrin as either the *trans* or *cis* isomer (both in the R-configuration). The studies have used either the *cis* or *trans* isomer, or a mixture of both. Table 2.7 illustrates the compounds used in the studies, and shows the position of [^{14}C] radiolabel used. Where minor differences in degradation rates were observed between isomeric forms as a conservative measure the longer DT_{50} was taken for risk assessment. Where studies on surrogate compounds have been accepted (in the case of aquatic photolysis, aerobic soil degradation and an additional aquatic degradation study to support metabolite formation) this has been clearly indicated.

Based on the extensive range of comments raised by OMS following the first commenting phase for imiprothrin (under PT 18) on CIRCA (during 2010) it became clear that a number of additional data requirements and/ or justifications would be required to address the concerns raised. The UK presented a position paper at TM-I-2011 and the main conclusions from this meeting are summarised below;

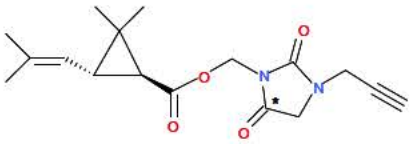
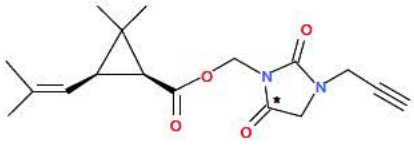
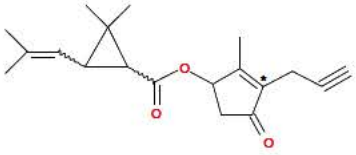
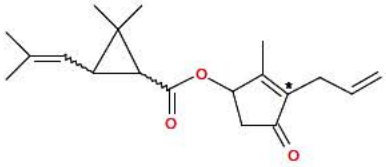
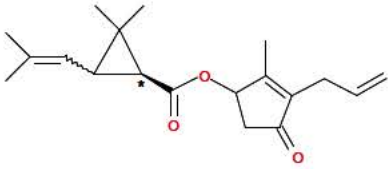
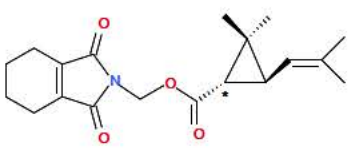
Water/ sediment study- the applicant agreed to provide a study with radiolabelling in the imiprothrin alcohol moiety along with an additional study on an analogue compound to support the fate of chrysanthemic acid. These were both provided to the UK in January 2016 so the original justification provided by the applicant to support the non-submission of a water/ sediment study has been removed from this document.

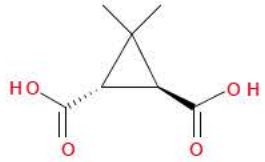
Aerobic soil study- it was agreed that the non-GLP soil study submitted by the applicant was not acceptable as a key study but can be used in a weight of evidence approach in conjunction with literature data. GLP studies to address the fate and behaviour of metabolites on both sides of the imiprothrin molecule were also requested.

Prior to WG-I-2017 further soil studies were submitted, however as only one soil type was tested the WG view was that a default of 1000 days should be used as a precautionary value in risk assessment for imiprothrin. All submitted studies have been presented although the DT_{50}

values (and maximum amounts formed) are used as indicative values only (or in PBT assessment).

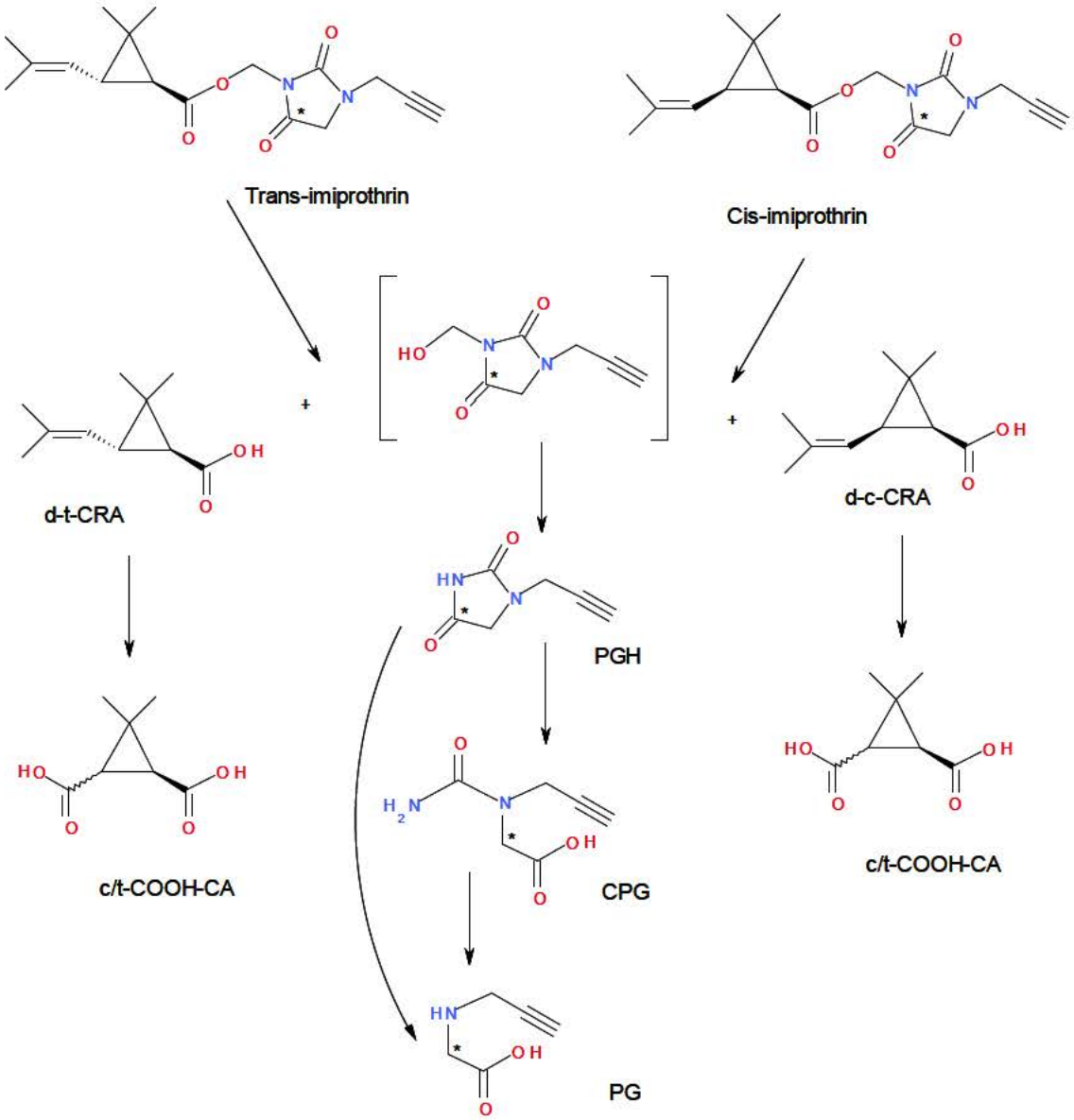
Table 2.7 Names and structures of compounds used in environmental studies

Name	Structure	Substrate in Study
(1*R*)-*trans*-[imidazolidinyl-5-^{14}C]imiprothrin, or [Alc-^{14}C] imiprothrin, or S-41311		Hydrolysis Aquatic degradation *#Aerobic soil degradation*
(1*R*)-*cis*-[imidazolidinyl-5-^{14}C]imiprothrin		Aquatic degradation *#Aerobic soil degradation*
Prallethrin or Etoc		Aquatic photolysis
Bioallethrin (Bioallethrin comprises [1R,trans: 1S]-isomer:[1R, trans;1R]-isomer: at a 1:1 ratio)		Aquatic photolysis
d-Allethrin [^{14}C] comprises cis and trans isomers (*RS*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl(1*R*)-*cis*-chrysanthemate ((1*R*)-*cis*-[cyclopropyl -1-^{14}C]Allethrin) and (*RS*)-3-allyl-2-methyl-4-oxocyclopent-2-enyl (1*R*)-*trans*-chrysanthemate ((1*R*)-*trans*-[cyclopropyl-1-^{14}C]Allethrin).		Aquatic degradation
(1RS)-trans Tetramethrin		Aerobic soil degradation

t-COOH-CA		Aerobic soil degradation

Where * represents ^{14}C radiolabelling; #Used as indicative values only

Figure 2.1 Degradation products of Imiprothrin



As shown in the preceding scheme the same metabolites PGH (1-Propargylimidazolidine-2,4-dione), CPG (*N*-Carbamoyl- *N*-propargyl glycine) and PG (*N*-Propargyl glycine) can be formed from both *trans* and *cis*-imiprothrin. The naming of metabolite chrysanthemic acid d-c/t-CRA (also abbreviated to KCA in the applicant dossier) was agreed at WG-I-2017, however the applicant abbreviation may still be found in Doc III-A.

Fate in the aquatic compartment (including sediment)

A hydrolysis study showed *trans*-imiprothrin to be relatively stable at pH 7 and 12 °C, with a calculated half-life of 166 d (at 12 °C). The calculated half-life of *trans*-imiprothrin was 2.11 d (at 12 °C) and, under basic conditions (pH 9) the formation of the metabolite *N*-carbamoyl-*N*-propargyl glycine (CPG) at levels approaching 90 % was identified. CPG itself is a hydrolysis product of another metabolite, 1-propargylimidazolidine-2,4-dione (PGH), which was only found at levels of < 5 % in the hydrolysis study. Although significant hydrolysis was demonstrated at pH 9, it is still unknown as to which point above pH 7 hydrolysis starts to become a significant pathway and depending on the local pH of surface waters hydrolysis could be a major degradation pathway for imiprothrin. However as CPG and PGH are both formed in the draft water/ sediment study the eCA considers the behaviour in these systems will be more representative of natural environmental conditions.

An aqueous photolysis study was conducted using structurally similar compounds (prallethrin and bioallethrin). The test compounds photodegraded rapidly with a maximum half-life of 2.44 d at 25 ºC (which is equivalent to 6.90 d at 12 °C). The eCA is in agreement with the applicant that imiprothrin is likely to have a half-life of a similar order. However photolysis can be considered to constitute a minor degradation pathway in the EU where water bodies may be of high turbidity, containing variable amounts of suspended matter and subject to a high seasonal variability in exposed light intensity. In addition no novel metabolites would be expected to be formed via aqueous photolysis based on read across from studies performed on the structural analogues of imiprothrin.

A ready biodegradation study, using activated sludge, concluded that imiprothrin was not readily biodegradable, but an aerobic water/ sediment study using two test systems showed rapid removal of imiprothrin with total system degradation half-lives ranging from 1.37 to 5.40 days (at 20 ºC). Significant amounts of CO_2 and bound residues were observed with a range of 39.6 – 52.3 % AR total system (CO_2) and 26.6 – 35.8 % AR total system (bound). This indicates that imiprothrin will be subject to significant levels of mineralisation in the aquatic environment.

A number of major degradates were identified in this study with total system DT_{50} values calculated for 12 ºC; PGH (DT_{50} 15.1 days, detected at a maximum of 52.6 % in the GR system), PG (DT_{50} 97.7 days, detected at a maximum of 16.7 % in the GR system), CPG (DT_{50} 82.7 days detected at a maximum of 49.2 % in the GL system on day 31). Due to the position of radiolabelling levels of d-c/t-CRA (or related degradate t-COOH-CA could not be identified or quantified in this study).

Taking the worst case DT_{50} obtained for the *cis* (minor) imiprothrin isomer as a conservative approach and converting to a more environmentally relevant temperature of 12 ºC gave a total system DT_{50} of 10.2 days for use in the risk assessment. The eCA notes that both water systems used in this study had a pH > 8, and it has previously been demonstrated that hydrolysis of imiprothrin is a significant process at pH 9. As it is unknown at what pH above pH 7 hydrolysis starts to become a major degradation pathway- it is impossible to state how much of the degradation observed in this study is due to aerobic degradation and, how much is due to hydrolysis.

A second water/ sediment study was submitted on an imiprothrin analogue, *d*-allethrin to support the fate of the common breakdown product chrysanthemic acid (d-t-CRA). [^{14}C] Cyclopropyl labelled *cis* and *trans* d-allethrin were investigated in two contrasting water/ sediment systems, Calwich Abbey and Swiss Lake. A worst case DT_{50} for chrysanthemic acid (d-t-CRA) of 39.6 days at 12°C was determined however the study cannot be used to set a maximum formation percentage from imiprothrin and a conservative default of 100 % will have to be assumed.

Fate in air

The fate of imiprothrin in air was investigated using the quantitative structure activity

relationship estimation method (AOPWIN v.1.70; 1995 and corrected in line with defaults taken from the draft ECHA guidance on Environmental risk assessment 2013) which considers the reaction with the daily air concentrations of hydroxyl (OH^-) radicals. A maximum estimated half-life of 3.552 hours was predicted but, as the active substance is not considered to be volatile as indicated by the reported vapour pressure of 1.86 x 10^{-6} Pa (at 25 ºC), the air compartment has not been considered further in the exposure assessment.

Fate in the terrestrial compartment

Following discussion at TMI-2011 it was agreed that the non-GLP soil study submitted by the applicant was not acceptable as a key study but can be used in a weight of evidence approach in conjunction with literature data. Hence the following DT_{50} values are presented as indicative only and an assumption of zero degradation in soil has been assumed for risk assessment. An aerobic soil degradation study in two soils was carried out and the rapid degradation of both *cis* and *trans*-imiprothrin were observed with half-lives of 1.13 to 16.1 days (first order kinetics at 12 ºC). Three major metabolites were identified and DT_{50} values (at 12 °C) were calculated as follows, PGH (DT_{50} 9.30 days, detected at a maximum of 48.7 %), PG (DT_{50} 169 days, detected at a maximum of 14.6 %), and CPG (DT_{50} 18.1 days, detected at a maximum of 8.9 %). Due to the position of radiolabelling levels of d-c/t-CRA (or related degradates could not be identified or quantified in this study).

Again significant amounts of CO_2 and bound residues were observed up to 68.0 % AR total system (CO_2) and 32.6 % AR total system (bound), indicating that imiprothrin will be subject to significant levels of mineralisation in the terrestrial environment.

However as Pralle® does not consist of equal quantities of (1R)- *trans* and *cis*-imiprothrin the eCA has proposed taking the more conservative DT_{50} for *cis*-imiprothrin of **16.1 days** (at 12°C) as an indicative value for the major isomers accounting for approximately 90 % of Pralle®.

The calculated K_{oc} value for imiprothrin (268 L kg^{-1}) using HPLC indicates that this substance is likely to be moderately mobile in soil / sewage sludge.

2.2.2.2. Effects assessment

Predicted No Effect Concentration in sewage treatment plants ($PNEC_{stp}$)

A respiration inhibition test (3 h), carried out in accordance with OECD Guideline for Testing of Chemicals No. 209 (1984), was submitted to assess the effects of imiprothrin on STP micro-organisms. A NOEC of 100 mg l^{-1} was reported with effects less than 10 %. The ECHA Guidance on the Biocidal Products Regulation: Volume IV Environment – Part B Risk Assessment (active substances) Version 1.0, April 2015 and hereafter referred to as ECHA (2015) states that, in the case of a respiration inhibition test, an assessment factor of 10 should be applied to a NOEC or EC_{10} to derive a $PNEC_{stp}$ thereby producing a $PNEC_{stp}$ of 10 mg/L. In addition, according to ECHA (2015), *'If no inhibition is observed at the highest test concentration, the NOEC is set equal to the water solubility which is subsequently used to derive the $PNEC_{stp}$'* (Infobox 7). The solubility of imiprothrin in water is 0.0935 g l^{-1} at 25 °C and pH 6.5 (paragraph A3.5, data set for the active substance) and therefore, in this case, the $PNEC_{stp}$ would be 9.35 mg l^{-1}.

Predicted No Effect Concentration in the freshwater compartment ($PNEC_{water}$)

The toxicity of imiprothrin to aquatic organisms is documented by acute studies only. A NOEC of 1.3 mg l^{-1} from an acute algal study was considered acceptable, but was not the most sensitive species. The most sensitive endpoint was from the acute fish toxicity study on rainbow trout (*Oncorhynchus mykiss*) which gave the lowest LC_{50} (96 h) of 0.038 mg l^{-1}. As there is at least one short-term $L(E)C_{50}$ available for each of the three trophic levels of the base set (fish, daphnia and algae), an AF of 1000 was applied to the most sensitive endpoint to give a $PNEC_{water}$ value of 3.8 x 10^{-5} mg l^{-1} [or 0.038 µg l^{-1}].

The toxophore (pyrethroid structure) in imiprothrin is not present in its major metabolites in water/sediment (namely d-c/t-CRA, t-COOH-CA, PGH, CPG and PG) and therefore these metabolites are not expected to be more toxic to aquatic organisms than imiprothrin.

For t-COOH-CA, aquatic toxicity data is available on the fathead minnow (*Pimephales promelas*), freshwater flea (*Daphnia magna*) and green algae (*Pseudokirchneriella subcapitata*).

In the absence of aquatic toxicity data for d-c/t-CRA, PGH, CPG and PG, their toxicity has been predicted using QSAR data. Although the UK CA considers there to be uncertainty in the predicted endpoints for metabolites PGH and CPG, the endpoints for d-c/t-CRA and PG are considered to be more reliable. Based on the QSAR data, d-c/t-CRA, PGH, CPG and PG are expected to be no more toxic to aquatic organisms than the parent compound, providing further evidence that the toxophore has been lost (for further details please refer to Document II-A, Appendix 1).

For t-COOH-CA, acute toxicity data is available for fish, aquatic invertebrates and algae. The lowest E/LC_{50} = 75 mg/L for green algae. Since acute toxicity data is available for three trophic levels, an assessment factor of 1000 is applied, to give a $PNEC_{water}$ (t-COOH-CA) = 0.075 mg/L.

Predicted No Effect Concentration in sediment ($PNEC_{sed}$)

It is stated in ECHA (2015), *'In general, substances with a K_{oc} < 500 – 1000 L/kg are not likely sorbed to sediment'.* Imiprothrin was demonstrated to have a K_{oc} of 268 L/kg, therefore a sediment effects assessment is not considered necessary.

Atmosphere

Not required for this use.

Terrestrial

Predicted No Effect Concentration in soil ($PNEC_{soil}$)

ECHA (2015) states, *'When no toxicity data are available for soil organisms or if experimental data are missing for the potentially most sensitive species group, the equilibrium partitioning method can be applied to aquatic data to identify a PNEC for soil organisms'.* As no data have been submitted, the equilibrium partitioning method (EPM) has been used to determine the $PNEC_{soil}$ for imiprothrin (based on the compound having a log K_{ow} of 2.9). The $PNEC_{soil,}$ is 1.84 x 10^{-4} mg kg^{-1} wet weight [or 0.184 μg kg^{-1} wet weight], calculated in accordance with equation 72 of ECHA (2015).

2.2.2.3. Exposure Assessment

The environmental exposure assessment, presented by the eCA, has been produced using all available information. This has been taken from submitted studies and the Organisation for Economic Co-operation and Development (OECD) 5th Draft Emission Scenario Document (ESD) on Insecticides, acaricides and products to control arthropods (PT 18) for household and professional use (OECD, 2008 Guidance on the Biocidal Products Regulation, Volume IV Environment, Part B Risk Assessment (active substances) (version 1 April 2015), and the Technical Agreements for Biocides (TAB) was also used in the drafting of this document. Where appropriate default values have been taken from these documents and where refinements are proposed these are clearly indicated.

The representative product is Pralle® 0.5 % aerosol, which is a public hygiene insecticide intended solely for non-professional use containing the active substance, imiprothrin, at a maximum concentration of 0.5 % w/w (label content states 0.48 - 0.50 %). It will be formulated as a ready-for-use oil-based aerosol spray packed into tinplate containers

containing 300 ml (208 g) of the preparation, equivalent to 1.04 g of imiprothrin. It will be sold as a surface spray for spot, and crack and crevice treatment for indoor use only and may be used for treatments in domestic or restaurant kitchens and other areas in buildings where small infestations and harbourages of crawling insects (e.g. cockroaches, bedbugs or cat fleas) may occur.
The directions for Pralle® 0.5 % aerosol state short bursts of 1 - 2 seconds with a total spray time of around 15 - 20 second should be used. The Applicant (manufacturer) recommends a re-application interval of approximately 4 weeks (effectively advising non-professional users to undertake treatments once a month). No product specific data on the environmental fate has been provided and none is required. The exposure and risk has only been presented for imiprothrin, should any substances of concern be identified in the final product formulation, the possible additive and/or synergistic effects would need to be considered via a mixed actives assessment at product authorisation.

Based on the OECD ESD for PT18 (5th draft 2008), the main relevant scenarios were identified as:

Scenario 1: Indoor domestic use (crawling insects) - Crack and crevice
Scenario 2: Indoor large building use (crawling insects) - Crack and crevice
Scenario 3: Indoor domestic use (flea and bed bug treatment) - Surface treatment

Discussion of the cleaning efficiency in the ESD (Section 3.3.7 and Table 3.3-8) indicates that an appropriate cleaning efficiency for an aerosol applied to crack and crevices in a domestic setting would be 3 % (F_{CE} of 0.03). However to address concerns raised by OMS during the first round of commenting the eCA proposes a two tier assessment using a cleaning efficiency of 10 % (F_{CE} of 0.10) at Tier 1 and 3 % (F_{CE} of 0.03) at Tier 2. This is included to clearly illustrate to OMS the risks in the individual scenarios when a different cleaning efficiency is assumed.

The use of this product to treat against cat fleas would be expected to take place on soft furnishings and carpeted areas (general surface are of 22 m^2- ESD) - however both of these would not be expected to be subject to regular wet cleaning. So to assess a potential flea treatment- the UK proposes to use an area of 5.9 m^2 to reflect the area wet cleaned in a domestic home (barrier) and use the default cleaning efficiency of 20 % (taken from the ESD)- this would also be protective of a bed bug treatment. Only a domestic dwelling has been assessed for this use as a bed bug or cat flea treatment would not be expected to take place in a large building by a non-professional user with this product.

PEC input assumptions for assessment of emissions from representative product (Pralle® 0.5 % aerosol)

Input/ Parameter (units)	Data/ Endpoint
Number of houses in catchment of STP (-) Domestic/ Large building	4000 / 300
Effluent discharge rate of STP (l d^{-1})	2 x 10^6
Number of applications (-) Crack and Crevice / Surface treatment	1 / 1
Cleaning efficiency (-) Crack and crevice Tier 1/ Crack and crevice Tier 2/ Surface	0.10/ 0.03 / 0.20
Treatment area Domestic/ Large building/ Domestic surface treatment(m)	2 / 9.3/ 5.9
Simultaneity Factor (%)- Monthly application	0.0138
*Fraction to water at STP (%)	96.8
*Fraction to sewage sludge at STP (%)	3.2
*Fraction to air at STP (%)	5.86E-08
*Fraction degraded (%)	0
Sludge rate : rate of sewage sludge production at STP (kg d^{-1})	710

* Derived by SimpleTreat 3.1;

Releases into the environment can take place from processes at any stage of the life-cycle of a substance. However, based on the Applicant's envisaged fields of use for Pralle® 0.5 % aerosol, the following have been considered to present the worst-case scenarios in terms of predicted environmental concentrations (PEC):

Indoor use

Emissions from treated hard surfaces (tiles, laminate, concrete etc) as a result of wet cleaning resulting in:

- Direct exposure to the sewage treatment plant (STP) compartment via drains with,
  i. indirect exposure to surface waters (including sediment) via STP effluent,
  ii. indirect exposure to soil compartment (including groundwater) via STP sludge application to land and
  iii. indirect exposure to biota via surface waters (bioconcentration in fish leading to secondary poisoning of fish-eating birds).

Further to the above assumptions, the indirect environmental exposure via domestic waste disposal to landfill (as a result of disposal of used packaging plus waste product and dry cleaning such as vacuuming of treated areas) has not been considered in this exposure assessment. This is because this route of exposure is less likely to be of concern when compared to the direct exposure via the STP compartment. In addition, the effect of its dilution with other wastes, biodegradation of the active substance (a.s.) and the significant containment measures at landfill sites according to European Union (EU) waste regulations (EU Directive 99/31/EC) further reduce any potential concerns.

Hence the potential environmental releases of imiprothrin resulting from the indoor use of Pralle® 0.5 % aerosol against small infestations of crawling insects will be largely associated with hard surface treatment.

An assessment of metabolites at STP has not been made as any formed will be present at lower concentrations than imiprothrin hence the resulting PEC / PNEC ratios will also be < 1, indicating acceptable risk at STP to micro-organisms from exposure to imiprothrin derived metabolites.

Values for major metabolites in the aquatic compartment were calculated taking into account the maximum amount formed in water from the water/ sediment study, adjusted for molecular weight. Due to the position of [^{14}C]-radiolabelled imiprothrin used in the study an assessment of the amount of d-c/t-CRA (or derived metabolite t-COOH-CA) could not be made so a conservative assumption of 100 % formation has been made. A water/ sediment study on an analogous pyrethroid (d-allethrin) has also been submitted and has been used to derive a total system water/ sediment and a sediment only DT_{50} for d-c/t-CRA.

As outlined in Section 3.3.3.2 of Document II-B, no predicted environmental concentrations of imiprothrin (or its metabolites) in air have been presented as these are expected to be negligible based on its low vapour pressure (1.86×10^{-6} Pa at 25 °C), and proposed non-professional uses.

The proposed use pattern of Pralle® 0.5 % aerosol does not allow for direct contamination of soil- however the application can come indirectly via the application of sludge from an STP. It was stated at TM-1-2011 that the submitted non-GLP soil study could not be used as a key study and it was agreed following WG-II-2017 that a second submitted soil study (in one soil type) could not be used to set a DT_{50} for risk assessment so the eCA proposes assuming a default DT_{50} of 1000 days for risk assessment. [This is clearly a worst case assumption as an indicative worst case soil DT_{50} value of 26.5 days (at 12 °C) was calculated from both studies].

An assessment of the levels of metabolites in soil has not been made for a number of reasons;

- Metabolites are present in lower amounts than parent, with a lower molecular weight.
- Reliable key study data for the metabolites is not available (either effects or concentration).
- Approximately 3 % imiprothrin is directed to sludge via STP (from SimpleTreat) - so the eCA is of the view that > 96 % of imiprothrin related material has already been covered under the aquatic risk assessment.

Hence at this time it is assumed that the risk assessment for metabolites in soil is covered by the risk assessment of parent imiprothrin.

A crude prediction of the levels of imiprothrin in groundwater using the equation from the ECHA guidance on ERA indicated that levels below the current quality standard set at 0.1 µg l^{-1} by the EU Drinking Water Directive (98/83/EC) for imiprothrin are expected for the proposed indoor crack and crevice uses of Pralle®.

A slight risk is predicted to groundwater for the indoor surface treatment (0.341 µg/ l) - however this can be expected to be low based on the large number of default worst assumptions applied in this calculation (namely, the lack of degradation in soil over 10 years plus lack of mobility).

An assessment of the risks posed by metabolites to the groundwater was not carried out.

Secondary Poisoning- terrestrial

As described the exposure of soil to imiprothrin could occur indirectly via the application of sewage sludge from indoor uses.

Secondary Poisoning- aquatic

The level of imiprothrin in fish has also been determined for the proposed indoor use where emissions are considered to enter surface water via STP.

2.2.2.4. Risk characterisation

2.2.2.4.1. *Risk to the aquatic compartment (including sediment)*

Risks to local STP

The following tables represent the risk characterisation (PEC: PNEC) values for imiprothrin at a local STP as a result of the proposed indoor uses of Pralle® 0.5 % aerosol;

Table 2.8 STP PEC: PNECs for imiprothrin resulting from the indoor crack and crevice use of Pralle® 0.5 % aerosol - Tier 1

Scenario	PEC (mg l^{-1})	PNEC (mg l^{-1})	PEC: PNEC
Indoor domestic	5.97E-04	9.35	6.38 E-05
Indoor large building	2.08E-04		2.23 E-05
Combined	8.05E-04		8.61 E-05

Table 2.9 STP PEC: PNECs for imiprothrin resulting from use the indoor crack and crevice use of Pralle® 0.5 % aerosol - Tier 2

Scenario	PEC (mg l^{-1})	PNEC (mg l^{-1})	PEC: PNEC
Indoor domestic	2.51E-04	9.35	2.69 E-05
Indoor large building	8.76E-05		9.37 E-06
Combined	3.39E-04		3.62 E-05

Table 2.10 STP PEC: PNECs for imiprothrin as an insecticide resulting from a surface treatment of Pralle® 0.5 % aerosol

Scenario	PEC (mg l^{-1})	PNEC (mg l^{-1})	PEC: PNEC
Indoor surface	3.22E-03	9.35	3.44 E-04

From the data presented none of the proposed uses of Pralle® 0.5 % aerosol pose an unacceptable level of risk to the local STP compartment when used at the recommended application rate.

An assessment of metabolites has not been made as any formed at STP will be present at lower concentrations than imiprothrin hence the resulting PEC / PNEC ratios will also be < 1 if toxicity equivalent to parent is assumed, indicating acceptable risk at STP to micro-organisms from exposure to imiprothrin and any derived metabolites.

Risks to surface water

The proposed use pattern of Pralle® 0.5 % aerosol does not allow for direct exposure to surface waters, but indirect contamination *via* the STP can be assumed. However, as described in Document II-B Section 3.3, the cleaning step from indoor use will lead to emissions to local STP and indirectly to surface water and sediment.

Table 2.11 Aquatic PEC: PNECs for imiprothrin resulting from the indoor crack and crevice use of Pralle® 0.5 % aerosol - Tier 1

Scenario	PEC (mg l^{-1})	PNEC (mg l^{-1})	PEC: PNEC
Indoor domestic	5.97E-05	3.80E-05	**1.57**
Indoor large building	2.08E-05		0.548
Combined	8.05E-05		**2.12**

Table 2.12 Aquatic PEC: PNECs for imiprothrin resulting from the indoor crack and crevice use of Pralle® 0.5 % aerosol - Tier 2

Scenario	PEC (mg l^{-1})	PNEC (mg l^{-1})	PEC: PNEC
Indoor domestic	2.51E-05	3.80E-05	0.661
Indoor large building	8.75E-06		0.230
Combined	3.39E-05		0.891

Table 2.13 Aquatic PEC: PNECs for imiprothrin as an insecticide resulting from a surface treatment of Pralle® 0.5 % aerosol

Scenario	PEC (mg l^{-1})	PNEC (mg l^{-1})	PEC: PNEC
Indoor surface	3.22E-04	3.80E-05	**8.47**

From the data presented a risk has been identified to the aquatic environment from the indoor domestic use of Pralle® (at Tier 1 assumed 10 % removal by wet cleaning), for crack and crevice treatment. This risk is reduced to acceptable levels when a more realistic assessment (Tier 2) using the ESD agreed cleaning efficiency of 0.03 is applied.

A risk to the aquatic compartment has also been identified when Pralle® is applied as a surface spray.

The risk posed by the formation of aquatic metabolites has been assessed as follows;

Table 2.14 Aquatic PEC: PNEC values for metabolites t-COOH-CA, PGH and d-c/t-CRA - crack and crevice Tier 1

	PGH			d-c/t-CRA		
Compound	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**
Indoor domestic	1.00E-05	3.80E-05	0.264	3.15E-05	3.80E-05	0.830
Indoor large building	3.50E-06		0.922	1.10E-05		0.289
Combined	1.35E-05		0.356	4.25E-05		**1.12**
	t-COOH-CA					
Indoor domestic	2.96E-05	7.50E-02	3.95E-04			
Indoor large building	1.03E-05		1.38E-04			
Combined	4.00E-05		5.33E-04			

Table 2.15 Aquatic PEC: PNEC values for metabolite CPG and PG- crack and crevice Tier 1

	CPG			PG		
Compound	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**
Indoor domestic	1.44E-05	3.80E-05	0.379	3.54E-06	3.80E-05	0.093
Indoor large building	5.02E-06		0.132	1.23E-06		0.032
Combined	1.94E-05		0.511	4.77E-06		0.125

Table 2.16 Aquatic PEC: PNEC values for metabolites t-COOH-CA, PGH and d-c/t-CRA - crack and crevice Tier 2

	PGH			d-c/t-CRA		
Compound	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**
Indoor domestic	4.23E-06	3.80E-05	0.111	1.33E-05	3.80E-05	0.349
Indoor large building	1.47E-06		0.039	4.63E-06		0.122
Combined	5.70E-06		0.150	1.79E-05		0.471
	t-COOH-CA					
Indoor domestic	1.25E-05	7.50E-02	1.66E-04			
Indoor large building	4.35E-06		5.80E-05			
Combined	1.47E-05		2.24E-04			

Table 2.17 Aquatic PEC: PNEC values for metabolites CPG and PG - crack and crevice Tier 2

	CPG			PG		
Compound	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**
Indoor domestic	6.06E-06	3.80E-05	0.159	1.49E-06	3.80E-05	0.039
Indoor large building	2.11E-06		0.056	5.19E-07		0.014
Combined	8.17E-06		0.215	2.01E-06		0.053

Table 2.18 Aquatic PEC: PNEC values for metabolites t-COOH-CA, PGH and d-c/t-CRA - surface treatment

	PGH			d-c/t-CRA		
Compound	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**
Surface treatment	5.42E-05	3.80E-05	**1.43**	1.70E-04	3.80E-05	**4.47**
	t-COOH-CA					
Surface treatment	1.60E-04	7.50E-02	2.13E-03			

Table 2.19 Aquatic PEC: PNEC values for metabolites CPG and PG - surface treatment

	CPG			PG		
Compound	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**	**PEC (mg l^{-1})**	**PNEC (mg l^{-1})**	**PEC: PNEC**
Surface treatment	7.76E-05	3.80E-05	**2.04**	1.91E-05	3.80E-05	0.502

Making a number of worst case assumptions concerning the formation of metabolites in the aquatic compartment (including sediment) – acceptable risks for crack and crevice treatment have been identified for all metabolites at Tier 1 with the exception of d-c/t-CRA for a combined (domestic and large building) assessment. Acceptable risks were identified for all metabolites at Tier 2, for crack and crevice treatment.

Unacceptable risks were found for all metabolites (except PG and t-COOH-CA) from the proposed surface treatment use of imiprothrin.

Risks to the sediment compartment

As previously mentioned, although direct emissions to surface water are not envisaged during the application of this product, the eCA has concluded that indirect releases into surface water could occur as a result of wet cleaning from indoor uses. However a calculation of levels in sediment has not been made as detailed in Document II-B. As effects data are not available for imiprothrin (or metabolites) in sediment the same equilibrium partitioning method would be used to calculate PECs and PNECs. This would give the same PEC: PNEC ratio as that of the aquatic compartment- hence the risk to sediment can be assumed to be the same as that identified for surface water.

2.2.2.4.2. *Risk to the terrestrial environment*

Risks to the soil compartment

Due to the proposed use pattern of the product, the eCA considers that direct exposure of the terrestrial compartment will not occur. However, the risk posed to the soil compartment has been investigated following exposure via disposal of sewage sludge to land using $Elocal_{water}$ values. To address member state concerns over the lack of soil degradation data provided a default DT_{50} of 1000 days has been assumed for risk assessment.

Table 2.20 Soil PEC: PNECs for imiprothrin resulting from the indoor crack and crevice use of Pralle® 0.5 % aerosol- Tier 1

Scenario	PEC (mg kg^{-1} wwt)	PNEC (mg kg^{-1} wwt)	PEC: PNEC
Indoor domestic	2.99E-04	1.84E-04	**1.63**
Indoor large building	1.04E-04		0.567
Combined	4.04E-04		**2.19**

Table 2.21 Soil PEC: PNECs for imiprothrin resulting from the indoor crack and crevice use of Pralle® 0.5 % aerosol- Tier 2

Scenario	PEC (mg kg^{-1} wwt)	PNEC (mg kg^{-1} wwt)	PEC: PNEC
Indoor domestic	**1.26E-04**	1.84E-04	0.684
Indoor large building	**4.39E-05**		0.239
Combined	**1.70E-04**		0.923

Table 2.22 Soil PEC: PNEC for imiprothrin as an insecticide resulting from a surface treatment of Pralle® 0.5 % aerosol

Scenario	PEC (mg kg^{-1} wwt)	PNEC (mg kg^{-1} wwt)	PEC: PNEC
Indoor surface	**1.61E-03**	1.84E-04	**8.77**

From the data presented a risk has been identified to the soil compartment from the indoor domestic use of Pralle® (at Tier 1 assumed 10 % removal by wet cleaning) for crack and crevice treatment. This risk is reduced to acceptable levels when a more realistic assessment (Tier 2) using the ESD agreed cleaning efficiency of 0.03 is applied.

A risk to soil has also been identified when Pralle® is applied as a surface spray.

As detailed in Document II-B a separate assessment of the risks to soil from imiprothrin related degradates has not been made and it is considered that any risks posed will be covered by the assessment of parent imiprothrin.

Risks to the atmosphere

As outlined in Section 3.3.3.2 of Document II-B, no predicted environmental concentrations of imiprothrin (or its metabolites) have been presented as these are expected to be negligible based on its low vapour pressure (1.86 x 10^{-6} Pa at 25 °C), and proposed non-professional uses.

Furthermore, upon reaching the atmosphere, imiprothrin is expected to degrade rapidly with a half-life based upon photo-transformation predicted to be less than 1 day. Therefore, imiprothrin is not considered to be a concern for the air compartment when used in Pralle® 0.5 % aerosol with the proposed use pattern.

Risks of secondary poisoning – terrestrial

This section considers potential risks to predatory birds and mammals arising from the consumption of earthworms contaminated with imiprothrin.
A concentration based approach of assessing the risk to earthworm-eating birds and mammals has carried out by comparing the $PEC_{oral\ predator}$ to the PNEC expressed in terms of food consumption (mg kg^{-1}) as follows;

Table 2.23 Oral Predator PEC: PNECs for imiprothrin as an insecticide resulting from indoor use of Pralle® 0.5 % aerosol

Scenario		$PEC_{oral\ predator}$ as $C_{earthworm}$ (mg kg^{-1})	PNEC (mg kg^{-1} wwt)	PEC: PNEC
Combined **Tier 1**	Birds	**8.17 E-04**	1.87	4.37 E-04
Combined **Tier 1**	Mammals	**8.17 E-04**	6.67	1.23 E-04
Combined **Tier 2**	Birds	**3.44 E-04**	1.87	1.84 E-04
Combined **Tier 2**	Mammals	**3.44 E-04**	6.67	5.15 E-05
Indoor surface	Birds	**3.27 E-03**	1.87	1.75 E-03
Indoor surface	Mammals	**3.27 E-03**	6.67	4.90 E-04

Acceptable risks to birds and mammals from the consumption of contaminated earthworms can be predicted from all proposed uses of Pralle® aerosol.

Risks of secondary poisoning- aquatic

This section considers the potential risks to predatory birds and mammals arising from the consumption of fish contaminated with imiprothrin.

A concentration based approach of assessing the risk to fish-eating birds and mammals has carried out by comparing the $PEC_{oral\ predator}$ to the PNEC expressed in terms of food consumption (mg kg^{-1}) as follows;

Table 2.24 Oral Predator PEC: PNECs for imiprothrin as an insecticide resulting from indoor use of Pralle® 0.5 % aerosol

Scenario		$PEC_{oral\ predator}$ (mg $kg_{wet\ fish}^{-1}$)	PNEC (mg kg^{-1} wwt)	PEC: PNEC
Combined **Tier 1**	Birds	1.16E-02	1.87	6.20E-03
Combined **Tier 1**	Mammals	1.16E-02	6.67	1.74E-03
Combined **Tier 2**	Birds	4.88E-03	1.87	2.61E-03
Combined **Tier 2**	Mammals	4.88E-03	6.67	7.31E-03
Indoor surface	Birds	4.63E-02	1.87	2.48E-02
Indoor surface	Mammals	4.63E-02	6.67	6.94E-03

Acceptable risks to birds and mammals from the consumption of contaminated fish can be predicted from all proposed uses of Pralle® aerosol.

Overall conclusion

An acceptable level of risk from imiprothrin is predicted for all environmental compartments from the proposed crack and crevice use of Pralle® (even when combined scenarios are considered), when the realistic cleaning efficiency of 3 % is used.

This evaluation has assumed that the four major metabolites formed in the aquatic compartment (including sediment) present the same level of toxicity to the environment as parent (imiprothrin), which is a conservative assumption based on the presented metabolite QSAR data. The fifth metabolite (t-COOH-CA) has a PNEC based on measured data submitted in support of another active (see Document IIA Section 4.3.1). This leads to acceptable levels of risk to the aquatic compartment being predicted for the proposed indoor crack and crevice use of this product (with the exception of an unacceptable risk for domestic and large building, for d-c/t-CRA, at Tier 1 where 100 % formation has been assumed).

When the proposed surface treatment with Pralle® is considered, an unacceptable risk is identified to the environment for imiprothrin (every compartment except STP) and the major metabolites PGH, CPG and d-c/t-CRA (the aquatic compartment including sediment). There are no mitigation measures that can be proposed to reduce the levels of risk to the environment to acceptable levels. Surface use is therefore considered to be unacceptable to the environment.

2.2.2.5. PBT and POP assessment

PBT assessment

According to the TGD In line with Annex III of Regulation (EC) No 1907/2006 (REACH), the Persistent, Bioaccumulative and Toxic (PBT) assessment is considered to be different from the local and regional assessment approaches, as it seeks to protect ecosystems where risks are more difficult to estimate. Under the Biocidal Products Regulation (BPR), any active substance that is found to be either a PBT or very Persistent very Bioaccumulative (vPvB) substance shall not be Approved unless a specific derogation applies. Any active substance which now has

been demonstrated to trigger any two of the P or B or T criteria must be considered as a "candidate for substitution".

Persistence

The measured DT_{50} values (normalised to 12°C) following discussion at WG-II-2017 and subsequent follow up consultation are summarised in the following table;

Table 2.25 PEC Degradation and dissipation rates in Aquatic and Terrestrial compartments (in days at 12 °C) for use in PBT assessment- following harmonisation discussions at WG-II-17

Compound	Water dissipation DT_{50}	Aquatic (total) degradation DT_{50}	Aerobic Soil DT_{50}	Persistence
Trans-imiprothrin	3.70	3.02	5.21	Not persistent
Cis-imiprothrin	7.24	10.2	26.5	Not persistent
PGH	Not calculated	15.1	13.7*	Not persistent
CPG	Not calculated	82.7	Not major metabolite	Not persistent
PG	Not calculated	97.7	Not major metabolite	Not persistent
d-t-CRA	Not calculated	35.8[#]	Not major metabolite	Not persistent
d-c-CRA	Not calculated	52.9[#]	Not major metabolite	Persistent
t-COOH-CA	Not calculated	101[#]	10.1[##]	Very Persistent

*Worst case value formed from *trans*-imiprothrin, [#]Worst case value based on data submitted to support cyphenothrin, [##]Worst case based on metabolite applied study

Based upon results from an OECD 301C ready biodegradation study where imiprothrin was found not to be readily biodegradable, the P criterion cannot automatically be discounted (as outlined in screening criteria taken from Chapter R11 – PBT Assessment of the ECHA (REACH) Guidance on information requirements and chemical safety assessment). Additionally imiprothrin was found to be hydrolytically stable under environmental pH and temperature conditions. Following discussion at WG-II-17 the two isomers will be considered separately against the criteria for Persistence.

Consideration of the Cis- Isomer

The route and rate of degradation of the *cis* isomer of imiprothrin in freshwater were investigated in two water-sediment systems according to OECD guideline 308, using (*1R*)-*cis*-[imidazolidinyl-5-^{14}C] imiprothrin. For the *cis* isomer $DissT_{50}$ of 4.06 and 7.24 days were calculated by the eCA for the Goose River and Golden Lake water phases respectively (values for 12 °C).

These values are lower than the trigger values of 40 days for persistence in freshwater.

Considering the total system, half-lives of 5.40 and 1.44 days (10.2 and 2.73 days at 12 °C) were calculated in Goose River and Golden Lake respectively.

In both water/sediment systems *cis*-imiprothrin showed transfer to the sediment compartment and based on the worst case total system degradation value of 10.2 days cis-imiprothrin can be considered not to fulfil the P criterion in either freshwater or sediment.

A soil simulation study recently provided to the UK (and carried out to OECD guidelines 307 and GLP) in one soil (Mutchler sandy clay) has been used to calculate a DT_{50} value for *cis*-imiprothrin of 9.35 days (26.5 days at 12 °C) following fitting of the degradation curves with SFO. It was the view of other member states that this single soil could not support a DT_{50} value for use in risk assessment- but the eCA view is that this indicative value can be used in PBT assessment.

[This is in agreement with a non-GLP study considered to be not reliable for use in risk assessment where degradation values in California soil and Mississippi soil were obtained for *cis*-imiprothrin of 2.19 and 5.70 days (6.20 and 16.1 days at 12 °C)].

This means that the Persistence criterion for soil is also not fulfilled.

Consideration of the Trans- Isomer

The route and rate of degradation for the *trans* isomer of imiprothrin in freshwater were investigated in two water-sediment systems according to OECD guideline 308, using (*1R*)-*trans*-[imidazolidinyl-5-^{14}C] imiprothrin. For the *trans*-isomer $DissT_{50}$ of 2.11 and 3.70 days were calculated by eCA for the Goose River and Golden Lake water phases respectively (values for 12 °C). These values are below the trigger value of 40 days for persistence in freshwater.

Considering the total system, half-lives of 1.59 and 1.37 days at 20°C (3.02 and 2.60 days at 12 °C) were recalculated for *trans*-imiprothrin in Goose River and Golden Lake respectively.

In both water/sediment systems *trans* -imiprothrin showed rapid transfer to the sediment compartment and based on the worst case total system degradation value of 3.02 days *trans*-imiprothrin can be considered not to fulfil the P criterion in either freshwater or sediment.

A soil simulation study recently provided to the UK (and carried out to OECD guidelines 307 and GLP) in one soil (Mutchler sandy clay) has been used to calculate DT_{50} values for the different imiprothrin isomers.

A value for 1.84 days for *trans*-imiprothrin (5.21 days at 12 °C) has been obtained following fitting of the degradation curve with SFO. (Again it was the OMS view that this value could not be used in risk assessment).

[This is in agreement with a non-GLP study considered to be not reliable for use in risk assessment where degradation values in California soil and Mississippi soil were obtained for *trans*-imiprothrin of 0.404 and 1.28 days (1.13 and 3.62 days at 12 °C)].

This means that the Persistence criterion for soil is also not fulfilled.

In summary it has to be concluded that neither isomer of imiprothrin should be considered to be Persistent (P) (or vP).

Metabolites

The imiprothrin major metabolites can be considered against the persistence criteria using the DT_{50} values generated from the submitted *in vitro* degradation studies (soil and water/ sediment) as well as *in silico* screening using EPISUITE v 4.11 (provided by the applicant).

When persistence screening results are generated using EPISUITE v 4.11, the following results are obtained;

Table 2.26 EPISUITE 4.11 modelling of Metabolites

Source	PGH	CPG	PG	d-c/t-CRA	t-COOH	**Imiprothrin**
Biowin2	0.7403	0.8076	0.9591	0.3869	0.5808	0.6993
Biowin3	2.8939 weeks	3.2187 weeks	3.3382 days-weeks	2.9799 weeks	3.3688 days-weeks	2.4237 weeks - months
Biowin6	0.3109	0.5029	0.7250	0.2788	0.6006	0.0533
Ready biodegradability	No	Yes	Yes	No	Yes	No
Screening criteria						
Predicted Solubility (mg l^{-1} using Fragments)	3041	1000000	135380	1017	34012	1.16 (93.5 measured)
Predicted Koc	2.95 - 10	0.36 – 10	0.04 – 3.27	59.5 – 122	2.24 – 33.3	162- 242

Where the values for BIOWIN2 and BIOWIN6 relate to the probability of fast degradation (with 1 most likely to have fast degradation) and the values for BIOWIN3 predict the timeframe required for biodegradation to occur.

P (or vP) fulfilled if

BIOWIN2 < 0.5 and BIOWIN3 < 2.25

OR

BIOWIN6 < 0.5 and BIOWIN3 < 2.25

PGH

The metabolite PGH was identified as a major metabolite in a water/ sediment simulation study conducted with cis and trans [^{14}C] radiolabelled imiprothrin as well in a soil simulation study. In the water/sediment study a DT_{50} was calculated based on the conservative approach of modelling kinetics from the peak onwards or in combination with parent imiprothrin to give DT_{50} values ranging from 3.99 to 7.94 days, (7.57 to 15.1 days at 12 °C).

In a recently submitted aerobic soil study a DT_{50} was calculated based on SFO modelling in combination with the parent to give values of 3.33 days (from *cis*-imiprothrin or 9.42 days at 12 °C), and 4.86 days (from *trans*-imiprothrin or 13.7 days at 12 °C).
Based on these degradation rates and QSAR modelling it can be concluded that the metabolite PGH should not be considered to be persistent (P) (or vP).

CPG

The metabolite CPG was identified as being a major metabolite in a water/ sediment study conducted with *cis* and *trans*-[^{14}C] radiolabelled imiprothrin- but was not identified as a major metabolite in the submitted GLP soil simulation study.
In the water/ sediment study a DT_{50} was calculated based on the conservative approach of modelling kinetics from the peak onwards using a SFO fit to give total system DT_{50} values ranging from 23.3 to 43.6 days, (44.2 to 82.7 days at 12 °C).
As rapid removal from the water layer was observed for this metabolite, this total DT_{50} should be considered to be the degradation of CPG from sediment, and hence compared against the trigger value for freshwater sediment of 120 days.
Hence as CPG was not identified as a major metabolite in soil and the worst case water/sediment total system DT_{50} value is 82.7 days- this metabolite should not be considered

as either persistent (P) (or vP). This is further supported by the QSAR modelling.

PG

The metabolite PG was identified as being a major metabolite in a water/sediment study conducted with *cis* and *trans*-[^{14}C] radiolabelled imiprothrin- but was not identified as a major metabolite in the submitted GLP soil simulation study.
In the water/ sediment study a DT_{50} was calculated based on the conservative approach of modelling kinetics from the peak onwards using a SFO fit to give total system DT_{50} values ranging from 42.7 to 51.5 days, (81.0 to 97.7 days at 12 °C).
As rapid removal from the water layer was observed for this metabolite, this total DT_{50} should be considered to be the degradation of PG from sediment, and hence compared against the trigger value for freshwater sediment of 120 days.
As PG was not identified as a major metabolite in soil and the worst case water/sediment total system DT_{50} value is 97.7 days- this metabolite should not be considered as either persistent (P) (or vP). This is further supported by the QSAR modelling.

Chrysanthemic acid (d-c/t-CRA)

Due to the position of radiolabelling used in the *cis* and *trans*-imiprothrin simulation studies levels of the potential metabolite d-c/t-CRA could not be measured in either of the imiprothrin dosed soil or aquatic (including sediment) degradation studies.

Calculation of ready biodegradability of d-c/t-CRA using BioWin v4.10 gives no indication of persistence with a probability for fast biodegradation of 0.3869 (does not biodegrade fast) for BioWin 2 and 2.9799 (weeks) for BioWin 3, as well as 0.2788 (not readily biodegradable) for BioWin 6.

(d-t-CRA) The applicant has submitted a water/sediment simulation study for a related active *d*-trans-Allethrin the eCA used a kinetic fit from the peak onwards to calculate a worst case total system DT_{50} value of 20.9 days (Swiss Lake 39.6 days at 12 °C). However following harmonisation discussions at WG-II-2017 it was decided to use an endpoint derived from a study submitted to support cyphenthrin- where the parent and metabolite had been fitted simultaneously- this gave a DT_{50} value of 35.8 days (at 12 °C).

The applicant has also submitted studies to support the degradation of d-t-CRA in soil from the structural analogues d-trans-Allethrin and (1RS)-trans-tetramethrin. d-t-CRA was not present at high enough levels in either study to be considered as a major metabolite and rapid degradation to a further metabolite t-COOH-CA was indicated.

Based on the water/sediment DT_{50}, not being triggered as a major metabolite in soil and the QSAR prediction for rapid biodegradability it should be considered that the P (or vP) criteria are not fulfilled for d-t-CRA.

(d-c-CRA) Following harmonisation discussions during WG-II-17 it was agreed that the water/ sediment study submitted in support of Cyphenothrin to the EL CA giving a total system DT_{50} of 52.9 days (at 12 °C) would be used in the PBT assessment.
The whole system DT_{50} value has been compared with freshwater trigger value, since d-c-CRA shows moderate to high water solubility and low soil adsorption, based on QSAR predictions (EPIsuite). This means d-c-CRA must be considered as a persistent metabolite.

t-COOH-CA

Due to the position of radiolabelling used in the *cis* and *trans*-imiprothrin simulation studies levels of the potential metabolite t-COOH-CA could not be measured in either of the imiprothrin dosed soil or aquatic (including sediment) degradation studies.

No studies have been submitted to address the persistency of this metabolite in the aquatic system, however following discussions at WG-II-17 it was agreed that a worst case total system value of 101 days at 12 °C could be used based on a water/ sediment study submitted

in support of cyphenothrin to the EL CA.

The conclusion drawn from this study was that as t-COOH-CA shows a very high water solubility and low soil adsorption the whole system total DT_{50} value is more reflective of the water compartment. So the DT_{50} value of 101 days should be compared to the freshwater trigger value of 40 or 60 days- meaning t-COOH-CA must be assumed to be very persistent.

From the applicant submitted studies to support the degradation of d-c/t-CRA (based on the structural analogues d-trans-allethrin and (1RS)-trans-tetramethrin) DT_{50} values were obtained in excess of 1 year at 12 °C. A separate study where t-COOH-CA was directly applied to three different soils was also submitted- this gave a worst case DT_{50} of 5.3 days (10.1 days at 12 °C). It was agreed at WG-II-17 that this study could be used to support the PBT assessment of this metabolite.

However based on the water/ sediment total system DT_{50} of 101 days this metabolite has to be considered as vP.

Bioaccumulation

Imiprothrin

A substance is considered to have the potential to fulfil the criterion of bioaccumulation when the log K_{ow} exceeds 4.5 (ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11: PBT/vPvB assessment, Version 2.0, November 2014 hereafter referred to as the ECHA Guidance, Chapter R.11). For imiprothrin, a log K_{ow} of 2.9 has been shown from available data. However imiprothrin is considered to be surface active (surface tension = 46.6 mN/m (21 °C)). The Guidance on the Biocidal Products Regulation (Volume IV: Environment, Part A: Information Requirements, Point 9.1.4) states: *'An estimation of the intrinsic potential for bioconcentration in aquatic organisms should be submitted on the basis of physical and chemical properties (e.g. partition coefficient n-octanol/water). For surface active substances (surface tension lower than 60 mN/m) and dissociating or inorganic substances such as metals, toxicokinetic studies (including metabolism), residue studies or monitoring data on aquatic organisms (e.g. residue data in aquatic organisms and environmental concentrations) should be submitted.'*

Mammalian studies have shown that there is rapid and almost complete absorption and elimination (> 90 %) of imiprothrin (Doc IIA - 3.1.1). It is extensively metabolised (ester hydrolysis, oxidation and hydroxylation) (Doc IIA - 3.1.3). There was thorough depletion from tissues (Doc IIA - 3.1.2). Overall, the data indicate no potential for accumulation.

A bioconcentration and metabolism study (Kang, S., 2014) has been submitted. The bioconcentration factor of imiprothrin is $BCF_{lipid\text{-}normalised\ total\ residue}$ = 144 L kg^{-1} (whole fish) or $BCF_{lipid\text{-}normalised\ imiprothrin}$ = 5.80 L kg^{-1} (whole fish) which is less than 2000. Therefore, the bioaccumulation criterion (B) is not fulfilled according to Annex XIII of Regulation (EC) No 1907/2006.

Metabolites

Limited information is available on aquatic bioaccumulation or surface tension/activity of the major metabolites. It was agreed at Environment WG-1-2017 that experimental data would not be needed for the metabolites but better argumentation should be provided by the UK CA in order to confirm that the metabolites are not surface active and therefore the BCF potential can be estimated by QSARs. The UK CA was limited in the argumentation it could provide and therefore the Applicant was asked to provide further information in order to address this requirement (for further details please refer to Document IIA, Appendix 2). It is not expected that the major metabolites fulfil the B criterion.

Toxic (T)

Imiprothrin

At the time of writing it is proposed that Imiprothrin be classified as toxic to reproduction (Category 2 with assigned hazard phrase H361d: Suspected of damaging the unborn child), this will be confirmed when the RAC opinion is adopted in 2017. If Imiprothrin is classified as H361d, the toxicity criterion (T) would be fulfilled according to Annex XIII of Regulation (EC) No 1907/2006 (REACH).

The most sensitive endpoint available for imiprothrin (fish LC_{50} (96 h) = 0.038 mg l^{-1}) is less than 0.1 mg/l and therefore meets the screening criteria for T (See Figure R.11-5 of ECHA Guidance, Chapter R.11). No chronic data for marine or freshwater organisms is available.

Metabolites

Toxicity of the major metabolites in water/sediment (namely d-c/t-CRA, t-COOH-CA, PGH, CPG and PG) has been predicted using QSAR data.

For PGH and CPG the QSAR data sets are small and therefore there is uncertainty in the predicted toxicity endpoints. Despite this, the T criterion cannot be excluded for PGH as the predicted algal endpoint is 0.01 mg/L. For CPG the predicted endpoints are at least two orders of magnitude above the screening criteria and hence it is considered that the T criterion is not fulfilled.

The toxicity endpoints for PG, d-c/t-CRA and t-COOH-CA are considered to be more reliable. PG, d-c/t-CRA and t-COOH-CA are not considered to fulfil the T criterion as the predicted toxicity endpoints for PG, d-c/t-CRA and t-COOH-CA are at least two orders of magnitude above the screening criterion.

For t-COOH-CA, aquatic toxicity data is also available which indicate low acute toxicity to fish, aquatic invertebrates and algae.

It is noted that the toxophore, present in imiprothrin, is not present in d-c/t-CRA, t-COOH-CA, PGH, CPG, or PG and therefore they are not expected to be more toxic to aquatic organisms than imiprothrin.

PBT Conclusion

Imiprothrin
Imiprothrin (*trans* and *cis* isomers) only fulfils one criterion (T), out of the three considered. Therefore, imiprothrin is considered not to be a PBT or vPvB substance or a candidate for substitution.

Metabolites
For persistence, d-c-CRA and t-COOH-CA are considered to be persistent and very persistent respectively. PGH, CPG, PG and d-t-CRA are not considered to be persistent.

It is not expected that the major metabolites fulfil the B criterion (for further details please refer to Document IIA, Appendix 2).

For toxicity, CPG, PG, d-c/t-CRA and t-COOH-CA are not considered to fulfil the T criterion. For PGH the T criterion cannot be excluded.

Therefore, the relevant metabolites are considered not to be PBT or vPvB substances or candidates for substitution.

Summary of PBT criteria for Imiprothrin, d-c/t-CRA, t-COOH-CA, PGH, CPG, and PG

Substance	Persistence criteria fulfilled?	Toxicity criteria fulfilled?	Bioaccumulation criteria fulfilled?
Trans-imiprothrin	No	Yes	No
Cis-imiprothrin	No	Yes	No
PGH	No	Potentially	No
CPG	No	No	No
PG	No	No	No
d-t-CRA	No	No	No
d-c-CRA	Yes P	No	No
t-COOH-CA	Yes vP	No	No

POP assessment

The criteria for a substance being a persistent organic pollutant (POP) are 'P', 'B' and having the potential for long range transport. In addition, high toxicity can breach the 'B' criterion, in which case a substance will be a persistent organic pollutant if it is 'P', demonstrates the potential for long range transport, and is either 'B' or 'T'.

Theoretically, imiprothrin will not pose a possible risk for long-range transport on the basis of an estimated atmospheric half-life of < 4 h (assuming a 12 h day and an OH radical concentration of 5.0 x 10^5 OH^-/ cm^3 when estimated using the AOPWIN v 1.92 QSAR modelling tool). This conclusion is further supported by the compound's very low vapour pressure (1.86 x 10^{-6} Pa at 25 °C), low predicted Henry's Law constant plus limited environmental exposure from current non-professional use patterns.

Given the above, imiprothrin does not meet the criteria for being a persistent organic pollutant.

2.2.3. Assessment of endocrine disruptor properties

Imiprothrin has been investigated in a wide range of toxicological tests. There were no significant effects on endocrine organs and/or reproduction in standard mammalian toxicity studies. A reduction in uterine weight in the 1 year dog study was at a dose level producing significant reductions in body weight gain and food consumption. The uterine weight changes are considered to be secondary to reduced body weight and nutritional status. It is therefore concluded that imiprothrin does not have endocrine-disrupting properties.

Imiprothrin is not currently classified for carcinogenicity or reproductive toxicity. The UK CA has submitted a CLH report to ECHA.

2.3. Overall conclusions

The outcome of the assessment for imiprothrin in product-type 18 is specified in the BPC opinion following discussions at the 21st meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

2.4. List of endpoints

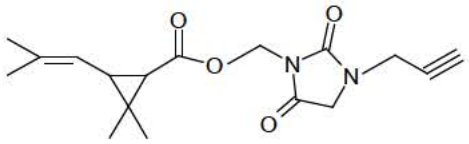
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

Appendix I: List of endpoints

Chapter 1:Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Name)	Imiprothrin, Pralle®
Product-type	Insecticide
Applicant	UK

Identity

Chemical name (IUPAC)	Reaction mass of: 2,5-dioxo-3-prop-2-ynylimidazolidin-1-ylmethyl (1*R*)-*cis*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; 2,5-dioxo-3-prop-2-ynylimidazolidin-1-ylmethyl (1*R*)-*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate (ca 20:80)
Chemical name (CA)	[2,5-dioxo-3-(2-propyn-1-yl)-1-imidazolidinyl]methyl (1R)-2,2-dimethyl-3-(2-methyl-1-propen-1-yl) cyclopropanecarboxylate
CAS No	72963-72-5
EC No	428-790-6
Other substance No.	NA
Minimum purity of the active substance as manufactured (g/kg or g/l)	Purity: 870 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Please see confidential annex
Molecular formula	$C_{17}H_{22}N_2O_4$
Molecular mass	318.37 g/mol
Structural formula	

Physical and chemical properties

Melting point (state purity)	Not required. The substance is a liquid at room temperature.
Boiling point (state purity)	Decomposes at 128 °C (92 % pure)
Thermal stability / Temperature of decomposition	As above
Appearance (state purity)	Clear viscous liquid, colour amber 10YR 7/10, slightly sweet odour (92 % pure)

Relative density (state purity)	1.122 (92 % pure*)
Surface tension (state temperature and concentration of the test solution)	46.6 mN/m at 21 °C
Vapour pressure (in Pa, state temperature)	25 °C = 1.86 x 10^{-6} Pa 35 °C = 1.15 x 10^{-5} Pa 45 °C = 9.64 x 10^{-5} Pa
Henry's law constant (Pa m^3 mol^{-1})	6.33 x 10^{-6} Pa m^3 mol^{-1} at 25 °C (calculated)
Solubility in water (g/l or mg/l, state temperature)	pH 6.5: 0.0935 g/l (25 °C) Imiprothrin has no ionisable groups and undergoes hydrolysis in basic conditions, so the effect of pH on water solubility is not required.
Solubility in organic solvents (in g/l or mg/l, state temperature)	The test material is soluble in all proportions in n-octanol, methanol, acetonitrile and acetone. In hexane the solubility was determined as 0.62 g/100 ml (25 ±1°C).
Stability in organic solvents used in biocidal products including relevant breakdown products	Imiprothrin is stable in the presence of isopropyl myristate for at least one year.
Partition coefficient (log P_{OW}) (state temperature)	2.9 (25 °C, pH 6.2 – 6.6, Purity 99.7 %*)
	As there are no ionisable moieties associated with imiprothrin, a change in pH will not affect the partition coefficient.
Dissociation constant	No measurable dissociation constant could be obtained. Imiprothrin does not dissociate.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	No spectral maximum was observed between 210 nm and 360 nm.
Flammability or flash point	Autoignition temperature 359 °C Flash point 141 °C (997 mbar)
Explosive properties	Imiprothrin does not possess explosive properties.
Oxidising properties	Imiprothrin does not possess oxidising properties.
Reactivity towards container material	Active will only be transported in the form of a manufacturing use product – no reactivity/incompatibility towards container material noted.

Classification and proposed labelling

with regard to physical hazards	None
with regard to human health hazards	**Proposed classification according to Regulation 1272/2008** Acute Tox 4 – Inhalation Acute Tox 4 – Oral Repro Tox 2

with regard to environmental hazards	**Proposed classification according to Regulation 1272/2008** Aquatic Acute Category 1 Aquatic Chronic Category 1

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	GC-FID & HPLC UV det (230 nm)
Impurities in technical active substance (principle of method)	As active

Analytical methods for residues

Soil (principle of method and LOQ)	Not relevant
Air (principle of method and LOQ)	Extraction from XAD-2 tubes. Quantitation by GC/FTD LOQ 2.667 µg/m^3. Data gap – additional supporting information and confirmatory method.
Water (principle of method and LOQ)	Groundwater, sediment – not required, waiver provided. Surface water, drinking water – data gap.
Body fluids and tissues (principle of method and LOQ)	Not relevant
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not required – waiver provided on the basis of the proposed use.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not required – waiver provided on the basis of the proposed use.

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Rapid and extensive (ca 90 % in urine at 24 hours) in the rat
Rate and extent of dermal absorption:	5 % from an ethanolic formulation [1 % (w/v) imiprothrin in ethanol] human skin *in vitro* 75 % default for the product Pralle® 0.5 %
Distribution:	Predicted to be widely distributed. No information prior to extensive excretion.
Potential for accumulation:	Low given rapid and extensive excretion
Rate and extent of excretion:	Rapid > 90 % in 24 hours
Toxicologically significant metabolite(s)	None identified

Acute toxicity

Mouse LD_{50} oral	724 mg/kg (m), 550 mg/kg (f) in corn oil
Rat LD_{50} dermal	>2000 mg/kg
Rat LC_{50} inhalation	1.4 – 2.2 mg/L

Skin irritation	Not irritating

Eye irritation	Not irritating

Skin sensitisation (test method used and result)	Negative (Magnusson and Kligman)

Repeated dose toxicity

1) Species/ target / critical effect	Dog / salivary gland / increased salivation and weight. Dog /liver / increased weight
Lowest relevant oral NOAEL / LOAEL (short term)	NOAEL -10 mg/kg bw/d LOAEL- 100 mg/kg bw/day (90 day)
Lowest relevant oral NOAEL / LOAEL (long term)	NOAEL-10 mg/kg bw/d LOAEL-50 mg/kg bw/day (90 day and 1 year dog studies combined), supported by rat (NOAEL 9 mg/kg bw/day) and mouse chronic studies (NOAEL 10 mg/kg bw/day)
2) Species/ target / critical effect	Rat/salivary gland / increased weight and swelling of acinar cells Rat / liver / increased weight and cholesterol, decreased TG
Lowest relevant NOAEL / LOAEL	NOAEL-5.9 mg/kg bw/day LOAEL-179 mg/kg bw/day (90 day) NOAEL- 9 mg/kg bw/day LOAEL- 90 mg/kg bw/day (2 year)
Lowest relevant dermal NOAEL / LOAEL	Systemic NOAEL- 300 mg/kg bw/d LOAEL - 1000 mg/kg bw/day (21 day rat)
Lowest relevant inhalation NOAEL / LOAEL	NOAEC- 22 mg/m^3 LOAEC- 186 mg/m^3 (rat 28 day; ca 4.2 and 36 mg/kg w/day)

Genotoxicity	Clastogenic *in vitro*. Not genotoxic *in vivo*.

Carcinogenicity

Species/type of tumour	Rat – lung adenoma and liver adenoma Mouse – lung adenoma /adenocarcinoma and liver adenoma Slightly increased incidences not triggering classification

Lowest dose with tumours	Rat – 188 mg/kg bw/day Mouse – 702 mg/kg bw/day

Reproductive toxicity

Species/ reproductive target / critical effect	Rat / No effects on reproduction
Lowest relevant reproductive NOAEL / LOAEL	LOAEL-288 mg/kg bw/day (highest dose tested)
Species/Developmental target / critical effect	Rat / skeletal abnormalities / increased pre-sacral vertebrae, thymic remnants and lumbar ribs. Rabbit/ skeletal abnormalities / increased 27th pre-sacral vertebrae, hypoplasia of frontal bone and nasal bone fusion Repro Cat 2 classification proposed as link with maternal toxicity not clearly demonstrated.
Lowest relevant developmental NOAEL / LOAEL	NOAEL-30 mg/kg bw/day LOAEL- 100 mg/kg bw/day (Rabbits)

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	Rat / reduced motor and locomotor activity in acute gavage study at 1000 mg/kg bw
Lowest relevant neurotoxicity NOAEL / LOAEL.	NOAEL-100 mg/kg bw/day LOAEL- 300 mg/kg bw/day.

Exposure via residue in food

The product is not to be used as a general broadcast surface spray treatment over kitchen surfaces and its use will be restricted to inaccessible areas in the kitchen, exposure via residue in food is therefore not expected.

Other toxicological studies

No data

Medical data

No data

Summary	Value	Study	Safety factor
ADI	0.1 mg/kg bw	90 d & 1 year dog	100
ARfD	0.3 mg/kg bw	Rabbit developmental	100
$AEL_{system\ c,\ acute}$	0.3 mg/kg bw/d	Rabbit developmental	100

$AEL_{system\ c,\ medium\ term}$	0.1 mg/kg bw/d	90 day dog	100
$AEL_{system\ c,\ long\ term}$	0.1 mg/kg bw/d	90 d & 1 year dog	100
$AEC_{inhalation,\ system\ c,\ short\text{-}term\ 4h}$ (no time adjustment needed)	0.9 mg/m^3	28 day rat	25

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	pH 5: stable pH 7: DT_{50} = 166 d at 12 °C pH 9: DT_{50} = 2.11 d at 12 °C Metabolites: *N*-Carbamoyl-*N*-propargylglycine (CPG) (max 89.6 % study end at pH 9) and chrysanthemic acid (d-c/t-CRA) - (assumed 100 % for risk assessment).
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Analogue study to support imiprothrin gave the following; DT_{50} (12 °C) 1.92 days (Prallethrin) DT_{50} (12 °C) 6.90 days (Bioallethrin)
Readily biodegradable (yes/no)	No – 58 % residual imiprothrin following 28 d modified MITI test comparable to OECD 301C
Biodegradation in seawater	Not applicable
Distribution in water / sediment systems (active substance)	Under aerobic conditions at 20 °C dissipation of [^{14}C]-*trans* and *cis* -imiprothrin were observed in both water / sediment systems. Dissipation T_{50} values ranged from 1.11 days to 3.82 days at 20 °C. Total system degradation values were calculated as *cis*-imiprothrin DT_{50} (2.73 – 10.2 days at 12 °C) and *trans*-imiprothrin DT_{50} (2.60 – 3.02 days at 12 °C). A worst case value of **10.2** days was selected for use in risk assessment.
Distribution in water / sediment systems (metabolites)	A number of major metabolites were formed both in the water and sediment phases of the study. The following DT_{50} values are corrected for 12°C. From [^{14}C]-*cis*-imiprothrin was formed PGH (DT_{50} 7.57 – **15.1** days max 21.6 % AR), CPG (DT_{50} **82.7** days, max 46.0 % AR) and PG (DT_{50} **97.7** days, max 13 %). From [^{14}C]-*trans*-imiprothrin was formed PGH (DT_{50} 12.6 days, max 52.6 % AR), CPG (DT_{50} 44.2 – 82.3 days, max 49.2 % AR) and PG (DT_{50} 81.0 days, max 16.7 % AR). Analogue study carried on *d*-allethrin gave a total system DT_{50} for d-t-CRA at 12 °C of 24.7 – 39.6 days.

	Post WG-II-2017 harmonisation endpoints agreed as d-t-CRA **35.8** days at 12 °C, d-c-CRA **52.9** days at 12 °C and t-COOH-CA **101** days at 12 °C.
Mineralization	CO_2 maximum levels 39.6 – 44.5 % AR (*cis*) and 39.9 – 52.3 % AR (*trans*)
Non-extractable residues	Bound residues 26.6 – 35.8 % AR (*cis*) and 26.2 – 35.7 % AR (*trans*)

Route and rate of degradation in soil - it was agreed at TM-I-2011 that the submitted soil studies could not be used to derive DT_{50} values for use in risk assessment. Values are presented as indicative and have been used in the PBT assessment.

Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (12 °C, aerobic): **16.1** d (cis-imiprothrin) 3.62 d (trans-imiprothrin) Range 6.2 – 16.1 days χ^2 10.3 – 5.48 (n=2) (cis) Range 1.13 – 3.62 days χ^2 11.5 – 9.36 (n=2) (trans)
	DT_{50lab} (12 °C, aerobic): 5.21 days (cis-imiprothrin) and **26.5** days (trans-imiprothrin).
Mineralization (aerobic)	51 – 68 % CO_2 after 60 d (n = 4)
Non-extractable residues	24.8 – 32.6 % after 60 d (n = 4)
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	A number of major metabolites were formed in soil The following DT_{50} values are corrected for 12°C: The following DT_{50} values are corrected for 12°C. From [^{14}C]-cis-imiprothrin was formed PGH (DT_{50} 10.0 – 11.5 days), CPG (DT_{50} not calculated) and PG (DT_{50} **169** days). From [^{14}C]-trans-imiprothrin was formed PGH (DT_{50} 5.40 - 12.1 days), CPG (DT_{50} **18.1** days) and PG (DT_{50} 58.6 - 88.0 days). PGH geomean DT_{50} 9.30days at 12 °C.
	Only one metabolite was identified in Mutchler soil, PGH at a maximum of 39.4 % derived from trans-imiprothrin. DT_{50lab} (12 °C, aerobic): 9.42 days (from cis-imiprothrin) and **13.7** days (from trans-imiprothrin).
	Analogue studies used to derive harmonised metabolite endpoints (WG-II-2017 and by e-consultation). t-COOH-CA range 10.1 days (at 12 °C from a t-COOH-CA dosed study used in PBT assessment) to > 1 year at 12 °C (analogue studies).

Field studies (state location, range or median with number of measurements)	DT_{50f}: Not applicable
Anaerobic degradation	Not applicable
Soil photolysis	Not applicable
Non-extractable residues	Not applicable
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Not applicable
Soil accumulation and plateau concentration	No testing is required if DT_{90} of the total residue is < 1 year.
Laboratory studies (range or median, with number of measurements, with regression coefficient)	Not applicable

Adsorption / desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Koc = 268 at 20 °C (mean log K_{oc} = 2.43 at 20 ºC) by HPLC

Fate and behaviour in air

Direct photolysis in air	Not applicable
Quantum yield of direct photolysis	Not applicable
Photo-oxidative degradation in air	3.552 h (calculated using AOPWIN v.1.91 as modified by criteria taken from TGD – 24 hour day, 5.0 x10^5 OH^- radicals per cm^3)
Volatilization	Not applicable

Monitoring data, if available

Soil (indicate location and type of study)	Not applicable
Surface water (indicate location and type of study)	Not applicable
Ground water (indicate location and type of study)	Not applicable
Air (indicate location and type of study)	Not applicable

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)
ACTIVE: OIT

Species	Time-scale	Endpoint	Toxicity[1]
Fish			

Oncorhynchus mykiss	96 hour	LC_{50}	0.038 mg l^{-1}
Lepomis macrochirus	96 hour	LC_{50}	0.070 mg l^{-1}
Invertebrates			
Daphnia magna	48 hour	EC_{50}	0.051 mg l^{-1}
Algae			
Selenastrum capricornutum	72 hour	NOE_rC	1.3 mg l^{-1}
Aquatic microorganisms			
Activated sludge	3 hour	EC_{50}	> 100 mg l^{-1}

[1] Based on mean measured (mm) or geometric mean measured (geo-mm) concentrations.

Effects on earthworms or other soil non-target organisms

Acute toxicity to *Eisenia fetida*	Not applicable
Terrestrial plants	Not applicable

Effects on soil micro-organisms

Nitrogen mineralization	Not applicable
Carbon mineralization	Not applicable

Effects on terrestrial vertebrates

Acute toxicity to mammals	Not applicable
Acute toxicity to birds	Not applicable
Dietary toxicity to birds	LC_{50} > 5620 ppm (Anas platyrhynchos)
Reproductive toxicity to birds	Not applicable

Effects on honeybees

Acute oral toxicity	Not applicable
Acute contact toxicity	Not applicable

Effects on other beneficial arthropods

Bioconcentration

Bioconcentration factor (BCF)	$BCF_{lipid\text{-}normalised\ total\ residue}$ = 144 L/kg (whole fish) $BCF_{lipid\text{-}normalised\ imiprothrin}$ = 5.80 L/kg (whole fish)
Depration time	DT_{50}: 0.173 days (0.07 µg a.s./L) and 0.303 days (0.7 µg a.s./L) from whole fish tissues.

Level of metabolites (%) in organisms accounting for > 10 % of residues	During the 28-day exposure period, ω*c*-CH_2OH-*d*-*t*-CRA, ω*c*-COOH-*d*-*t*-CRA, and *d*-*t*-CRA/*d*-*c*-CRA were characterized as major metabolites. In the low and high concentration exposures, ω*c*-CH_2OH-*d*-*t*-CRA ranged from 11.1 to 24.6% TRR, ω*c*-COOH-*d*-*t*-CRA ranging from 3.17 to 12.0% TRR, *d*-*t*-CRA/*d*-*c*-CRA ranging from 3.09 to 39.8% TRR, *c*/*t*- COOH-CA ranging from below detection limit to 10.9% TRR and caronic anhydride ranging from below detection limit to 3.25% TRR in the whole fish.

Appendix II: List of Intended Uses

Imiprothrin has been evaluated for its intended use as an insecticide for indoor use (PT 18); data were provided and accepted in support of this intended use.

The product is intended for use by non-professional users.

Data supporting imiprothrin for its use against the intended target organisms have demonstrated sufficient efficacy for active substance approval to be recommended.

To date, there are no known resistance issues when using imiprothrin against the target organisms.

Product Type	Insecticide PT 18
Object and/or situation	Used to maintain human hygiene.
Product name	Pralle®
Packaging	Tinplate aerosol can containing 300 ml (208 g) of the preparation (1 g imiprothrin).
Categories of User	Non professional
Organisms controlled	Primary target - cockroaches (dictyoptera) adults and nymphs including: *Blatella germanica* – German cockroach *Blatella orientalis* – Oriental cockroach *Periplaneta Americana* – American cockroach and other crawling household pests
Formulation type	Pre-pressurised handheld aerosol.
Concentration in formulation	0.5 % w/w
Application method/kind	Indoor surface, spot, crack and crevice treatment use only.
Application number min/max	Apply as required.
Application interval (min)	Apply as required.
Applied amount per treatment	The discharge rate is 1.3 g s^{-1} and treatment is recommended using 1 – 2 s bursts, with 15 – 20 s total spray per treated area. This is equivalent to 97.5 – 130 mg imiprothrin.
Storage	Store in a safe place out of reach of children. Protect from sunlight and do not expose to temperatures exceeding 50 °C.

Appendix III: List of studies

Active Substance Reference List (by Author)

Year	Title	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Section No in Doc II-A / Doc III-A / Non-key study
1992	Three-month subchronic toxicity study of S-41311 by dietary administration in rats	Yes	No	Yes	II-A 3.5 III-A 6.4.1/01
1992	Acute toxicity test. (Translated from Japanese, January 2008, approved February 2008).	No	No	Yes	II-A 4.2.1.1, Non-key study
1996a	S-41311 Algal Growth Inhibition.	Yes	No	Yes	II-A 4.2.1.3, III-A 7.4.1.3
1996b	S-41311 Inhibition effect on the respiration of activated sewage sludge.	Yes	No	Yes	II-A 4.2.1.4, III-A 7.4.1.4/01
1996	S-41311 Determination of Soil Adsorption Coefficient (K_{oc}) by HPLC	Yes	No	Yes	II-A 4.1.2.1, III-A 7.1.3
1997	S-41311 Physicochemical Properties	Yes	No	Yes	II-A 1.3 III-A 3.11. 3.12/01, 3.13, 3.15
1995a	An acute study of the potential effects of orally administered S-41311 on behaviour and neuromorphology in rats	Yes	No	Yes	II-A 3.9 III-A 6.9/01
1995b	A 13-week dietary study of the potential effects of S-41311 on behaviour and neuromorphology in rats	Yes	No	Yes	II-A 3.9 III A 6.9/02

Year	Title	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Section No in Doc II-A / Doc III-A / Non-key study
1993a	Acute Flow-Through Toxicity of S-41311 to Bluegill *(Lepomis macrochirus)*	Yes	No	Yes	II-A 4.2.1.1, III-A 7.4.1.1/01
1993b	Acute Flow-Through Toxicity of S-41311 to Rainbow Trout (*Onchorhynchus mykiss*)	Yes	No	Yes	II-A 4.2.1.1, III-A 7.4.1.1/02
1993c	Acute Flow-Through Toxicity of S-41311 to *Daphnia magna.*	Yes	No	Yes	II-A 4.2.1.2, III-A 7.4.1.2
1994	S-41311 - A dietary LC50 study with the mallard.	Yes	No	Yes	II-A 4.2.2, Non-key study
1990	Sunlight Photodegradation of [Alc-^{14}C]-d-trans-Allethrin in a Buffered Aqueous Solution at pH 5.	Yes	No	Yes	II-A 4.1.1.1.2, III-A 7.1.1.1.2/02
2002	Determination of melting/freezing temperature		No		II-A 1.3 III-A 3.1.1
1995	Preliminary test for the determination of dissociation constant of S-41311.	Yes	No	Yes	II-A 1.3 III-A 3.6
1995a	Storage stability of S-41311 manufacturing use product		No		II-A 1.3 III-A 3.10/02
1995b	Stability of S-41311 technical grade.	Yes	No	Yes	II-A 1.3 III-A 3.10/01
1995c	Corrosion characteristics of S-41311 Manufacturing Use Product.	No	No	Yes	II-A 1.3 III-A 3.17
1995d	Storage stability of S-41311 manufacturing use product at ambient temperature for one year.	Yes	No	Yes	II-A 1.3 III-A 3.17

Year	Title	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Section No in Doc II-A / Doc III-A / Non-key study
2001	Toxicity of S-41311 to activated sludge in a respiration inhibition test.	Yes	No	Yes	II-A 4.2.1.4, Non-key study
2006a	Imiprothrin: *in vitro* absorption from a 1 % imiprothrin formulation through human epidermis	Yes	No	Yes	II-A 3.1 III-A 6.2/03
2006b	Imiprothrin: *in vitro* absorption from a 1 % imiprothrin formulation through pig epidermis – preliminary study	Yes	No	Yes	II-A 3.1 Non-key study
1992a	*In vitro* chromosomal aberration test of S-41311 in Chinese hamster lung cells	Yes	No	Yes	II-A 3.6.1 III-A 6.6.2
1992b	*In vitro* gene mutation test of S-41311 in V79 Chinese hamster cells	Yes	No	Yes	II-A 3.6.1 III-A 6.6.3
1992c	Micronucleus test of S-41311 in mice	Yes	No	Yes	II-A 3.6.2 III-A 6.6.4
1992d	*In vivo* / *in vitro* unscheduled DNA synthesis (UDS) test of S-41311 in rat hepatocytes	Yes	No	Yes	II-A 3.6.2 III-A 6.6.5
1994	Reproductive effects of S-41311 administered orally via the diet to Crl:CD®BR VAF/Plus® rats for two generations	Yes	No	Yes	II-A 3.8.2 III-A 6.8.2
1996	Biological efficacy of imiprothrin oil-based aerosol formulation against cockroaches. (English report)	No	No	Yes	II-A 2.3 III-A 5.3/01
1991	A single-dose inhalation toxicity study of S-41311 in rats	Yes	No	Yes	II-A 3.2 III-A 6.1.3/01
1992	A 4-week inhalation study of S-41311 in rats.	Yes	No	Yes	II-A 3.5 III-A 6.3.3

Year	Title	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Section No in Doc II-A / Doc III-A / Non-key study
1992	Study on oral administration of S-41311 during the period of foetal organogenesis in rabbits	Yes	No	Yes	II-A 3.8.1 III-A 6.8.1/02
1992	Sunlight Photodegradation of [Alc-^{14}C]-d-trans-Etoc in a buffered Aqueous Solution at pH 5	Yes	No	Yes	II-A 4.1.1.1.2, III-A 7.1.1.1.2/01
1992	Reverse mutation test of S-41311 in bacteria	Yes	No	Yes	II-A 3.6.1 III-A 6.6.1
1995	Skin sensitization test of S-41311 MUP in guinea pigs (maximization test)	Yes	No	Yes	II-A 3.4.1 III-A 6.1.5/03
1994a	S41311 – Vapour pressure.	Yes	No	Yes	II-A 1.3 III-A 3.2
1994b	S41311 –Water solubility.	Yes	No	Yes	II-A 1.3 III-A 3.5
1994c	S41311 - Solubility	Yes	No	Yes	II-A 1.3 III-A 3.7
1994d	S41311 – Octanol/water partition coefficient.	Yes	No	Yes	II-A 1.3 III-A 3.9
1992	Bioaccumulation test of 1-(2-propynyl)-2,4-imidazolidinedione (abbreviation: PGH). (Translated from Japanese, January 2008, approved February 2008).		No	Yes	II-A 4.1.3.2, Non-key study
1992a	Single-dose oral toxicity study of S-41311 in rats	Yes	No	Yes	II-A 3.2 III-A 6.1.1/01
1992b	Single-dose oral toxicity study of S-41311 in mice	Yes	No	Yes	II-A 3.2 III-A 6.1.1/02
1992c	Single-dose oral toxicity study of S-41311 MUP in rats	Yes	No	Yes	II-A 3.2 III-A 6.1.1/03

Year	Title	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Section No in Doc II-A / Doc III-A / Non-key study
1992d	Single-dose oral toxicity study of S-41311 MUP in mice	Yes	No	Yes	II-A 3.2 III-A 6.1.1/04
1992e	Single dose dermal toxicity study of S-41311 in rats	Yes	No	Yes	II-A 3.2 III-A 6.1.2/01
1992f	Single dose dermal toxicity study of S-41311 MUP in rats	Yes	No	Yes	II-A 3.2 III-A 6.1.2/02
1995	21-day dermal toxicity study in rats with S-41311	Yes	No	Yes	II-A 3.5 III-A 6.3.2
1995	Combined chronic toxicity and oncogenicity study of S-41311 in rats	Yes	No	Yes	II-A 3.5, 3.7 III-A 6.5/01, 6.7/01
1994	Oncogenicity study of S-41311 in mice	Yes	No	Yes	II-A 3.5, 3.7 III-A 6.5/02, 6.7/02
1992a	Primary eye and skin irritation tests of S-41311 in rabbits	Yes	No	Yes	II-A 3.3.1, 3.3.2 III-A 6.1.4/01, 6.1.4/02
1992b	Primary eye and skin irritation tests of S-41311 MUP in rabbits	Yes	No	Yes	II-A 3.3.1, 3.3.2 III-A 6.1.4/03, 6.1.4/04
1992c	Skin sensitization test of S-41311 in guinea pigs (maximization method)	Yes	No	Yes	II-A 3.4.1 III-A 6.1.5/01
1992	Three-month oral toxicity study of S-41311 in dogs	Yes	No	Yes	II-A 3.5 III-A 6.4.1/03
1992	Reproduction study of S-41311 in rat with administration during the period of foetal organogenesis	Yes	No	Yes	II-A 3.8.1 III-A 6.8.1/01
2000	Henry's Law Constant for Imiprothrin (Pralle®).	Yes	No	Yes	II-A 1.3 III-A 3.2.1

Year	Title	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Section No in Doc II-A / Doc III-A / Non-key study
1993	Biotic degradation test of S-41311AI by activated sludge	Yes	No	Yes	II-A 4.1.1.2.1, III-A 7.1.1.2.1
1995a	Metabolism of *cis*-^{14}C-S-41311 in rats	Yes	No	Yes	II-A 3.1 III-A 6.2/01
1995b	Metabolism of *trans*-^{14}C-S-41311 in rats	Yes	No	Yes	II-A 3.1 III-A 6.2/02
1995	A Hydrolysis study of [ALC-^{14}C]-Imiprothrin	Yes	No	Yes	II-A 4.1.1.1.1, III-A 7.1.1.1.1
1994	Toxicity to dogs by repeated oral administration for 52 weeks	Yes	No	Yes	II-A 3.5 III-A 6.5/03
2003	Aerobic Soil Metabolism Study of S-41311 (Imiprothrin) (Preliminary study)	No	Yes	Yes	II-A 4.1.1.2.3, III-A 7.2.1
1993	Spectral studies of S-41311 technical grade.	Yes	No	Yes	II-A 1.3 III-A 3.4
1993a	S41311 Technical Grade Active Ingredient – Boiling Point.	Yes	No	Yes	II-A 1.3 III-A 3.1.2
1993b	S41311 Technical Grade Active Ingredient –Density.	Yes	No	Yes	II-A 1.3 III-A 3.1.3
1993c	S41311 Technical Grade active Ingredient –Color, Physical State, Odor	Yes	No	Yes	II-A 1.3 III-A 3.3.1, 3.3.2, 3.3.3
1993d	S41311 (Maunfacturing Use product) –Viscosity.	Yes	No	Yes	II-A 1.3 III-A 3.14
1993e	S41311 (Maunfacturing Use product) – Oxidation-Reduction.	Yes	No	Yes	II-A 1.3 III-A 3.16
1992	Preliminary thirteen-week subacute toxicity study of S-41311 in mice	Yes	No	Yes	II-A 3.5 III-A 6.4.1/02

Year	Title	GLP Study (Yes/No)	Published (Yes/No)	Data Protection Claimed (Yes/No)	Section No in Doc II-A / Doc III-A / Non-key study
1993	Acute inhalation toxicity study of S-41311 50% MUP in rats	Yes	No	Yes	II-A 3.2 III-A 6.1.3/02