Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethyl cyclopropanecarboxylate;

1R-trans-Z-momfluorothrin

EC Number: Not assigned
CAS Number: 1065124-65-3

CLH-O-0000001412-86-71/F

Adopted

11 September 2015

11 September 2015

CLH-O-0000001412-86-71/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemical name: **2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; 1R-trans-Z-momfluorothrin**

EC Number: **Not assigned**

CAS Number: **1065124-65-3**

The proposal was submitted by the **United Kingdom** and received by RAC on **17/12/2014.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

The United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **10/02/2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **27/03/2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteurs, appointed by RAC: **Marja Pronk, Pietro Paris**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonized classification and labelling was adopted on **11 September 2015** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	**No current Annex VI entry**										
Dossier submitters proposal		2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; 1R-trans-Z-momfluorothrin	-	1065124-65-3	Acute Tox. 4 STOT SE 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H371 (nervous system) H400 H410	GHS07 GHS08 GHS09 Wng	H302 H371 (nervous system) H410		M = 100 M = 100	
RAC opinion		2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; 1R-trans-Z-momfluorothrin	-	1065124-65-3	Acute Tox. 4 STOT SE 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H371 (nervous system) H400 H410	GHS07 GHS08 GHS09 Wng	H302 H371 (nervous system) H410		M = 100 M = 100	
Resulting Annex VI entry if agreed by COM		2,3,5,6-Tetrafluoro-4-(methoxymethyl)benzyl (Z)-(1R,3R)-3-(2-cyanoprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; 1R-trans-Z-momfluorothrin	-	1065124-65-3	Acute Tox. 4 STOT SE 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H371 (nervous system) H400 H410	GHS07 GHS08 GHS09 Wng	H302 H371 (nervous system) H410		M = 100 M = 100	

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC general comment

The active substance tested and reported in experimental toxicity studies is referred to as S-1563. The active substance S-1563 is stated to have a minimum purity of 95.2% w/w (based on the sum of all isomers). The major active isomer of S-1563 is the isomer 1*R*-*trans*-Z-momfluorothrin (sometimes abbreviated as RTZ) with a typical concentration of ≥ 86.0% w/w. Throughout this document, the substance will be referred to as momfluorothrin.

RAC evaluation of physical hazards

Summary of the Dossier submitter's proposal

The Dossier Submitter (DS) proposed no classification for physico-chemical properties based on negative results obtained in standard tests. The substance does not contain chemical groups which are indicative of explosive or oxidising properties.

Comments received during public consultation

No comments were received during public consultation (PC).

Assessment and comparison with the classification criteria

Since 1R-trans-Z-momfluorothrin does not have explosive or oxidising properties and is not (auto-)flammable, RAC supports **no classification** for physico-chemical properties, as proposed by the DS.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The DS proposed to classify 1R-trans-Z-momfluorothrin as Acute Tox. 4 by the oral route (H302). The acute toxicity of R-trans-Z-momfluorothrin was investigated in three GLP studies in rats.

The acute oral study was conducted according to OECD test guideline (TG) 420. Doses tested were 0, 50, 300 and 2000 mg/kg bw. At the highest dose, 7 of 10 rats died (2/5 males and 5/5 females). No deaths were observed at the lower doses. For female rats, an LD_{50} of 300-2000 mg/kg bw was derived, whereas for males the LD_{50} was > 2000 mg/kg bw. The DS proposed to classify the substance as Acute Tox. 4 (H302), based on the female LD_{50} value between 300 and 2000 mg/kg bw.

In an OECD TG 403 acute inhalation toxicity study, rats (5/sex/group) were nose-only exposed to 0, 583, 1110 or 2030 mg/m^3 1R-trans-Z-momfluorothrin for 4 hours. One female rat died at the highest achievable concentration of 2030 mg/m^3 (2.03 mg/L) where particles had an MMAD of 4.86 µm. No classification for acute inhalation is proposed by the DS, as the LC_{50} was > 2000 mg/m^3 (> 2 mg/L) for both males and females.

No mortalities were observed in an acute dermal toxicity study (OECD TG 402) at 2000 mg/kg bw 1R-trans-Z-momfluorothrin. Hence, the DS proposed no classification.

In conclusion, the DS proposed to classify 1R-trans-Z-momfluorothrin as Acute Tox. 4 – H302.

Comments received during public consultation

In their comments, two Member State Competent Authorities (MSCA) and an Industry representative agreed with the proposed classification as Acute Tox. 4. One of the MSCAs suggested to classify 1R-trans-Z-momfluorothrin also as Acute Tox. 4 by the inhalation route because at the maximum achievable concentration (2 mg/L) one female animal died. Since 50% mortality was not reached at 2 mg/L although it is > 1 and ≤ 5 mg/L, the DS responded that they do not consider this classification proposal appropriate.

Assessment and comparison with the classification criteria

Given that the oral LD_{50} value in female rats fits within the dose limits defining category 4 for acute oral toxicity (> 300 and ≤ 2000 mg/kg bw), RAC supports the conclusion of the DS that 1R-trans-Z-momfluorothrin warrants classification for acute oral toxicity as **Acute Tox 4 (H302)**.

RAC also supports the proposal not to classify 1R-trans-Z-momfluorothrin for acute dermal and inhalation toxicity. For the dermal route, the LD_{50} value in rats is above the threshold value for classification (2000 mg/kg bw). For the inhalation route, the available study does not allow classification, given that the LC_{50} value in both male and female rats is > 2.03 mg/L and higher concentrations could not be tested.

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

Summary of the Dossier submitter's proposal

According to the DS, data from acute oral, inhalation and neurotoxicity (oral) studies indicated that exposure to 1R-trans-Z-momfluorothrin gives rise to neurotoxicity after a single exposure.

In the acute oral toxicity study at the medium dose (300 mg/kg bw), tremors and urinary incontinence were observed in a limited number of animals, while at the highest at the highest dose causing mortality in 70% of the rats (2/5 males and 5/5 females) lethal dose (2000 mg/kg bw), these clinical signs were more frequently observed and alsoincluded salivation and clonic convulsions in both sexes, and tip toe gait in one female.

In the acute oral neurotoxicity study (10 rats/sex/group), there were no histopathological findings and no changes in functional tests. No clinical signs were observed at the low and mid dose of 30 and 80 mg/kg bw: At the high dose of 200 mg/kg bw, one female died, three females showed tremors and one had a Straub tail. The latter was also observed in one male at 200 mg/kg bw, with three males showing salivation.

In the acute inhalation toxicity study, neurotoxic effects were observed during exposure (only at the highest tested concentration of 2 mg/L, one female died and one to two females showed tremors and tremor of the tail) and post dosing. Clinical signs post-dosing included tremor, hypersensitivity, ataxic and tip toe gait, urinary incontinence and muscular rigidity mostly at 2 mg/L, and lasting up to 3 days. A clear dose response relationship was not observed for muscular rigidity (in 1/5 males at 2 mg/L and in 2/5 females at 0.5 mg/L) or for tremor (only in 1/5 females at 0.5 mg/L).

In the evaluation of the test results and in the weight of evidence analysis for the proposed classification, the DS considered the fact that 1R-trans-Z-momfluorothrin is a pyrethroid, a class

of chemicals known to induce neurotoxic effects. The DS further concluded that momfluorothin does not fulfil the criteria for STOT SE 3.

The DS proposed to classify 1R-trans-Z-momfluorothrin as STOT SE 2 – H371 (may cause damage to the nervous system), mainly based on the neurotoxic effects seen at 2 mg/L in the acute inhalation toxicity study, supported by the fact that the substance belongs to the group of pyrethroids, which is known to induce neurotoxic effects.

Comments received during public consultation

Two MSCAs and an industry representative supported the proposed classification in their comments.

Assessment and comparison with the classification criteria

In the available studies, 1R-trans-Z-momfluorothrin induces neurotoxicity following acute oral and inhalation exposure. The lowest doses at which the neurotoxic effects are observed (200 mg/kg bw and 0.5 mg/L for oral and inhalation administration, respectively) in principle fall within the guidance values for STOT SE 1 (≤ 300 mg/kg bw orally, ≤ 1 mg/L via inhalation). However, since there is no clear consistency in effects or dose-response at the next higher dose level (300 mg/kg bw and 1 mg/L, respectively), RAC agrees with the DS that STOT SE 2 (for effective dose levels ranging from 300-2000 mg/kg bw orally and from 1-5 mg/L via inhalation) is more appropriate.

The hazard class STOT SE 3 should cover 'transient' respiratory tract irritation and narcotic effects occurring after single exposure. Although classification in category 3 is primarily based on human data, if available, animal data can be included in the evaluation. Respiratory tract irritation and narcotic effects are generally assessed from standard acute inhalation studies, although it is possible that narcosis could be observed in studies using other routes (see section 3.8 of the CLP Guidance). The acute and sub-acute inhalation studies gave no indication that 1R-trans-Z-momfluorothrin causes an irritant effect in the respiratory tract. As such, RAC concludes that the available data do not indicate that classification for respiratory tract irritation (STOT SE 3) is required.

RAC also agrees with the DS not to specify the route of exposure for STOT SE 2. Indeed, both the oral and inhalation route resulted in clinical signs of neurotoxicity, although for the oral route this is already (partly) covered by the classification for acute toxicity. Hence, the proposal for **STOT SE 2 – H371 (nervous system)** is supported.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

The DS proposed no classification for skin corrosion/irritation. The skin irritation potential of 1R-trans-Z-momfluorothrin was assessed in a standard skin irritation GLP study (OECD TG 404) in three male New Zealand White rabbits. Neither erythema nor oedema was seen in any of the animals; the average individual scores over 24, 48 and 72 hours were equivalent to zero. The DS concluded that 1R-trans-Z-momfluorothrin does not warrant classification for skin corrosion/irritation.

Comments received during public consultation

No specific comments were received during PC, but 2 MSCAs agreed in general terms on the proposed classification for human health hazards.

Assessment and comparison with the classification criteria

In the available study, erythrema was reported in one animal at 1 and 24 hours, but this was not scored since there was no difference in reaction between the application site and the surrounding area. The two other animals did not show signs of erythema or oedema. For classification as a skin irritant in category 2, at least 2 out of 3 animals should demonstrate skin reactions, with a mean score of ≥ 2.3 for erythema and/or oedema. Since this is not the case, RAC supports the proposal for **no classification** for skin corrosion/irritation.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal

The DS proposed no classification for eye corrosion/irritation. The eye irritation potential of 1R-trans-Z-momfluorothrin was tested in a standard eye irritation GLP study (OECD TG 405) in male New Zealand White rabbits. In the three animals where the eyes were not washed after treatment, corneal lesions were not observed, whereas iridial congestion (grade 1) was seen in two animals at 1 hour post instillation, but not thereafter. Conjunctival redness and chemosis, both of grade 1, were observed in all three animals at 24 hours, but these effects had resolved by 48 hours post-application. As the average individual eye irritation scores for both conjunctival redness and chemosis were 0.3 over 24-72 hours, the DS concluded that 1R-trans-Z-momfluorothrin does not warrant classification for eye irritation.

Comments received during public consultation

No specific comments were received during PC, but 2 MSCAs agreed in general terms on the proposed classification for human health hazards.

Assessment and comparison with the classification criteria

Application of 1R-trans-Z-momfluorothrin to the eyes of rabbits resulted in a mild and transient effect on the iris and conjunctivae, whereas the cornea was not affected. Responses seen were completely reversed within 48 hours of application. In all animals the mean scores over 24-72 hours for iritis, conjuctival redness and chemosis were below the threshold values for classification (1, 2 and 2, respectively). RAC therefore agrees that **no classification** for eye corrosion/irritation is required.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

The potential of 1R-trans-Z-momfluorothrin to cause skin sensitisation was investigated in a GLP Magnusson and Kligman Guinea Pig Maximisation test conducted according to OECD TG 406. The induction phase consisted of intradermal injections of 5% (w/v) of the tested substance in corn oil; topical induction and challenge were performed with 50% 1R-trans-Z-momfluorothrin in acetone. No skin reactions were observed following the challenge.

Based on the absence of skin reactions, the DS proposed no classification for skin sensitisation.

Comments received during public consultation

No specific comments were received during PC, but 2 MSCAs agreed in general terms on the proposed classification for human health hazards.

Assessment and comparison with the classification criteria

RAC supports the conclusion from the DS for **no classification** since none of the animals showed signs of skin sensitisation upon treatment with 1R-trans-Z-momfluorothrin.

RAC evaluation of respiratory sensitisation

Summary of the Dossier submitter's proposal

The potential of 1R-trans-Z-momfluorothrin to cause respiratory sensitisation was not investigated directly. Since the substance does not require classification for skin sensitisation and the sub-acute inhalation study gave no indication of respiratory sensitisation, 1R-trans-Z-momfluorothrin is considered unlikely to be a respiratory sensitiser. Therefore the DS proposed no classification for this hazard class.

Comments received during public consultation

No specific comments were received during PC, but 2 MSCAs agreed in general terms on the proposed classification for human health hazards.

Assessment and comparison with the classification criteria

In the absence of data, RAC has not assessed this hazard class as in other RAC opinions.

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

Summary of the Dossier submitter's proposal

The DS proposed no classification for STOT RE for 1R-trans-Z-momfluorothrin based on the analysis of several standard repeated dose toxicity studies in rats, up to 52 weeks duration with oral exposure and with 28-day dermal or inhalation exposure, all GLP and OECD TG compliant. In addition, three oral studies in dogs (a range-finding study and two sub-chronic OECD TG compliant studies, of 13- and 52-weeks duration) as well as two GLP and OECD TG compliant long-term oral studies (a 104-week study in rats and a 78-week study in mice) were summarised and assessed by the DS.

No effects were seen in the 28-day dermal study in rats, with a NOAEL at the highest tested dose of 1000 mg 1R-trans-Z-momfluorothrin/kg bw/day. In the 28-day inhalation study in rats, the liver was the target organ. Although all concentrations tested (up to 320 mg/m^3) were below the guidance value for classification, the DS considered the liver effects induced by 1R-trans-Z-momfluorothrin (changes in liver weight and on some biochemistry parameters related to liver function, but not on liver histopathology) to be adaptive in nature and therefore not sufficient to justify classification.

Liver was also the target organ in the long-term oral study in mice, with 1R-trans-Z-momfluorothrin treatment resulting in increased liver weight accompanied by hepatocellular hypertrophy and, at the highest dose, enhanced single cell necrosis and brownish liver pigmentation. However, according to the DS, all effective dose levels in this study were above the guidance value for classification. The same was true for dogs, where liver toxicity

(indicated by (reversible) biochemical changes and increases in liver weight and hepatocellular hypertrophy) was only observed at doses above the respective guidance values for oral 13- and 52-week studies.

In rats, the main findings in an oral 13-week (+ 6-week recovery) and 52-week study were on body weight and the liver. At doses at or below the respective guidance values (100 and 25 mg/kg bw/day, respectively) the effects were relatively small, with up to 12.5% decrease in body weight gain (females only), increases in liver weight in males (11.3-13.3% in the 13- and 52-week study) and females (17.9% in the 52-week study), changes in clinical biochemistry indicative of functional liver changes and some brown pigmentation (lipofuscin) in the liver. At doses above the respective guidance values, these effects increased in incidence and/or severity with increasing dose, and were associated with histopathological changes characterised by hepatocellular hypertrophy, bile duct proliferation and ultrastructural modifications. Similar non-neoplastic liver findings were observed in the oral long-term study in rats, but only at doses above the guidance value for classification. In addition, from the 13-week study with a 6-week recovery period it appeared that most effects had reversed.

Other organs were also affected in the 13-, 52- and 104-week oral rat studies, but only at doses above the respective guidance values for classification. These included the kidney (deposition of a brown pigment similar to that in liver, without further evidence of kidney injury), mandibular glands (diffuse acinar hypertrophy) and, in the 52- and 104-week studies, the thyroid (follicular cell hypertrophy). The thyroid finding was considered secondary to the liver effects.

Overall, only the liver findings in rats occurred at dose levels relevant for classification. However, as the effects at these levels only related to increased weight, biochemical alterations and lipofuscin deposition without hepatocellular hypertrophy and bile duct proliferation of high severity/incidence, and were reversible, the DS concluded that these changes are considered to be adaptive and do not constitute a significant adverse toxicological effect warranting classification according to CLP criteria. Therefore, the DS proposed no classification for STOT RE for 1R-trans-Z-momfluorothrin.

Comments received during public consultation

No specific comments were received during PC, but 2 MSCAs agreed in general terms on the proposed classification for human health hazards.

Assessment and comparison with the classification criteria

The repeated dose toxicity of 1R-trans-Z-momfluorothrin has been investigated via the oral, dermal and inhalation routes, in three species (rat, mouse and dog). Special studies investigating possible immunotoxic (28-day study; Hosako, 2011) or neurotoxic (90-day study; Sommer, 2011a) effects of 1R-trans-Z-momfluorothrin following oral administration to rats were also provided in the CLH report.

Oral

In rats, the repeated dose toxicity was investigated in a 13-week (+ 6-week recovery), 52-week and 104-week study.

In the 13-week study, 1R-trans-Z-momfluorothrin was administered in the diet at doses of 0, 300, 1000, 3000 or 6000 ppm (23, 76, 223 or 485 mg/kg bw/day for males and 0, 25, 82, 236 or 501 mg/kg bw/day for females). The control and high dose groups subsequently received a control diet during a 6-week recovery period. At doses below the guidance value of 100 mg/kg bw/day, body weight gain was reduced by 12.5% in females, whereas in males the absolute and relative liver weights were increased by 11.3% and 12.1%, respectively. Upon microscopic examination a brownish pigment of minimal severity was observed in the livers of males (4/12) and females (10/12). Functional changes in the liver were demonstrated by changes in clinical biochemistry (increased levels of phospholipids and cholesterol in both sexes and increases in alpha2-globulin in males).

In the 13-week study, doses above the guidance value for classification as STOT RE 2 (≤ 100 mg/kg bw/day) showed a gradual increase in incidence and/or severity of the above-mentioned effects with increasing dose. In addition, from 3000 ppm liver enlargement was seen in male rats, and hepatocellular hypertrophy (mainly diffuse) and bile duct proliferation (both of minimal severity) in both sexes. Ultrastructural assessment of the liver samples from the 6000 ppm group revealed a moderate amplification and enlargement of the smooth endoplasmic reticulum (SER), an augmentation of rough endoplasmic reticulum (RER), and an intracellular accumulation of solid dark bodies (lysosomes). Other findings in both sexes included deposition of a brownish pigment in the kidneys and slight diffuse acinar hypertrophy in the mandibular glands. Upon recovery, the effects had considerably diminished or were no longer seen.

In the 52-week study, rats received 1R-trans-Z-momfluorothrin in their diet at 0, 200, 500, 1500 or 3000 ppm (0, 11, 27, 83 or 169 mg/kg bw/day (males), and 0, 12, 34, 103 or 199 mg/kg bw/day (females)). Results were comparable to the 13-week study: at doses around the (extrapolated) guidance value of 25 mg/kg bw/day for classification as STOT RE 2, the main effects were on the liver and body weight. Around the guidance value of 25 mg/kg bw/day, body weight was reduced by 12.1% in females and liver weights were increased in both males (absolute, 13.3%) and females (relative, 17.9%), and histopathologically a brownish pigmentation was seen in the liver (in 1/21 males and 2/21 females). In females, also a slight increase in phospholipid levels was observed, and an increased incidence of hepatocellular hypertrophy (mainly centrilobular, reported to be of minimal severity). At higher doses these effects increased in incidence and/or severity, and included also an increased incidence of bile duct proliferation (in females at 3000 ppm only). Further effects included deposition of a brown pigment in the kidney, and at 3000 ppm also increased incidences of diffuse acinar hypertrophy in the mandibular glands and thyroid follicular hypertrophy.

In the 104-week study (see also the section on Carcinogenicity), non-neoplastic liver findings started from 1500 ppm (73 mg/kg bw/day), i.e. at dose levels above the (extrapolated) guidance value of 12.5 mg/kg bw/day. At these dose levels also brown pigmentation in the kidney, diffuse acinar hypertrophy in the mandibular glands and thyroid follicular hypertrophy were seen, similar to the rat studies of shorter duration.

Liver was also the target organ in a long-term oral study in mice (see also the section on Carcinogenicity), with 1R-trans-Z-momfluorothrin treatment resulting in increased liver weight (from 600 ppm (72 mg/kg bw/day) in males and from 2500 ppm (427 mg/kg bw/day) in females), enhanced hepatocellular hypertrophy (from 2500 ppm) and, at the highest dose of 5500 ppm, enhanced single cell necrosis and brownish liver pigmentation. However, all effective dose levels in this study were above the (extrapolated) guidance value for classification (16.7 mg/kg bw/day for a 78-week study).

In dogs, the repeated dose toxicity was investigated in a 13-week (+ 6-week recovery) and 52-week study, following a 14-day range-finding study (all with administration of 1R-trans-Z-momfluorothrin via gelatin capsules).

In the 13-week study, with doses of 0, 50, 200 or 600 mg/kg bw/day, there were no treatment-related findings at the low dose. At doses above the guidance value for classification (100 mg/kg bw/day), some minor findings were observed at the mid dose whereas at the high dose there were clinical signs (vomiting, watery faeces and excess salivation) and findings indicative of an effect on the liver ((reversible) changes in biochemical parameters such as increases in cholesterol and triglycerides and decreases in glucose, alanine aminotransferase and alpha-1-globulin, increased liver weights and centrilobular hepatocellular hypertrophy).

In the 52-week study, with doses of 0, 25, 100 or 400 mg/kg bw/day, no adverse effects were observed at the level of the (extrapolated) guidance value for classification (25 mg/kg bw/day). Higher doses resulted in clinical signs (vomiting, watery faeces, salivation), changes in biochemical parameters and hepatocellular hypertrophy, but not in increased liver weight.

Inhalation

In a 28-day study, rats were exposed nose-only for 4 hours per day with 0, 62.2, 170 or 320 mg/m^3 1R-trans-Z-momfluorothrin. All doses tested are below the (extrapolated) guidance value for classification (900 mg/m^3 for a 28-day study with 4 hour exposure per day). The main findings in this study included clinical signs of neurotoxicity and effects on liver weight and on some biochemistry parameters. The clinical signs however only occurred in a limited number of animals (tremor, ataxic gait and muscular rigidity were observed in one male of the high dose group and tip toe gait in one female each of the mid and high dose groups) and were transient in nature (disappearance within one day, and occurrence only during the first three days of exposure). Increased liver weights were observed in both males and females of the mid and high dose group. In males this was accompanied by increases in aspartate aminotransferase and total cholesterol and a decrease in blood glucose level at the high dose, in females with increases in total cholesterol and phospholipids at both doses. In both sexes there were no correlating histopathological findings.

Dermal

In a 28-day dermal study, rats were treated with 0, 100, 300 or 1000 mg 1R-trans-Z-momfluorothrin/kg bw/day. No treatment related effects were seen at any dose.

Conclusion

From the inhalation study in rats and the oral studies in rats, mice and dogs it can be concluded that liver is the target organ of 1R-trans-Z-momfluorothrin toxicity. In mice and dogs, effects on the liver were only observed at dose levels above the guidance values for classification. In rats they also occurred at levels that would warrant classification. However, histopathological findings occurred in a few animals and were transient and of minimal severity. RAC agrees with the DS that this does not represent significant adverse toxicity. Besides, the liver effects were shown to be reversible to a large extent. Furthermore, 1R-trans-Z-momfluorothrin was shown not to be immunotoxic or neurotoxic upon repeated exposure. Therefore, RAC supports the **no classification** proposal for STOT RE for 1R-trans-Z-momfluorothrin.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

Three GLP compliant *in vitro* and two *in vivo* genotoxicity studies, all conducted according to their respective OECD TG, were included in the CLH report to evaluate the potential of 1R-trans-Z-momfluorothrin to cause mutagenicity. The bacterial reverse mutation assay (Ames test, OECD TG 471) and the mammalian gene mutation assay with Chinese hamster V79 cells (OECD TG 476) produced negative results in the presence and absence of metabolic activation. The *in vitro* chromosome aberration assay in Chinese hamster lung cells (OECD TG 473) was marginally positive for structural aberrations in the presence of metabolic activation at and above 100 μg/mL.

In the *in vivo* mammalian erythrocyte micronucleus test (OECD TG 474) no evidence of micronucleus formation was observed in rats following oral gavage exposure to 1R-trans-Z-momfluorothrin. The decline in PCEs in females at 48 hours indicated that 1R-trans-Z-momfluorothrin had reached the bone marrow. Furthermore, data from the toxicokinetic studies suggested detection at low levels in the bone marrow following oral dosing.

In the UDS assay (OECD TG 486), there was also no evidence of enhanced DNA repair in rat liver following oral gavage exposure to 1R-trans-Z-momfluorothrin.

Overall, the DS concluded that 1R-trans-Z-momfluorothrin has no *in vivo* mutagenic potential on somatic cells, and proposed no classification for mutagenicity.

Comments received during public consultation

No specific comments were received during PC, but 2 MSCAs agreed in general terms on the proposed classification for human health hazards.

Assessment and comparison with the classification criteria

1R-trans-Z-momfluorothrin tested negative in two *in vitro* assays (a bacterial mutation assay, and a mammalian gene mutation assay). It was mildly positive in another *in vitro* assay (a chromosome aberration assay), yet it was negative in an *in vivo* micronucleus test. In addition, it was also found negative in an *in vivo* UDS assay. RAC therefore supports the conclusion of the DS that **1R-trans-Z-momfluorothrin should not be classified for mutagenicity**.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

No classification for carcinogenicity was proposed by the DS. Two GLP compliant carcinogenicity studies (OECD TG 451) were summarised in the CLH report: a 104-week dietary study in rats and a 78-week dietary study in mice. In addition, several *in vitro* and *in vivo* studies investigating the mechanism of tumour formation in the rat were summarised (all non-GLP, non-guideline) and a Human Relevance Framework (HRF) analysis was performed, in order to establish the human relevance of the tumours induced by 1R-trans-Z-momfluorothrin (see also Annex I to CLH report).

1R-trans-Z-momfluorothrin at dose levels of 600, 2500 or 5500 ppm in the diet did not produce a carcinogenic response in the 78-week mouse study (which included a 52-week exposure satellite group). Treatment-related adverse effects were seen from 2500 ppm and included decreases in body weight and body weight gain, decreased food consumption, increased liver weight accompanied by hepatocellular hypertrophy (mainly centrilobular), and enhanced single cell necrosis and brown pigmentation in the liver (see Table below).

Table Main findings in 78-week mouse study

	Males				**Females**			
Nominal dietary concentration (ppm)	**0**	**600**	**2500**	**5500**	**0**	**600**	**2500**	**5500**
Mortality (Main groups)	6/52	3/52	4/52	6/52	12/52	11/52	5/52	8/52
(Satellite groups)	1/12	1/12	0/12	1/12	0/12	2/12	1/12	1/12
Body weight, Week 78 (g)	51.64	50.94	45.54**	41.89**	34.52	34.03	32.64	33.03
Food consumption, weeks 1-78 (g/mouse/day; mean of means)	5.24	5.03	5.01	4.45	5.07	4.88	4.99	4.53
Organ weights								
Satellite groups (52-week Interim sacrifice)								
Terminal bodyweight (g)	49.5	53.0	44.4	41.8*	33.5	33.3	31.7	31.8
Liver wt (g)	2.25	2.67	2.48	2.75*	1.54	1.67	1.85**	2.24**
(% bodywt)	4.54	5.02	5.59**	6.57**	4.61	5.06	5.83**	7.03**
Main groups (78-week terminal sacrifice)								
Terminal bodyweight (g)	50.3	49.2	44.2**	41.0**	34.8	33.4	32.4*	32.7
Liver wt (g)	2.33	2.61*	2.58*	2.97**	1.65	1.64	1.91**	2.35**
(% bodywt)	4.65	5.37**	5.85**	7.22**	4.77	4.90	5.89**	7.15**
Histopathological Findings Incidence								
Satellite groups (52-week Interim sacrifice)								
Liver (No. of animals examined)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

Hepatocellular hypertrophy	3	0	1	2	0	1	5*	9**
Main groups (78-week terminal sacrifice)								
Liver (No. of examined animals)	(52)	(52)	(52)	(52)	(52)	(50)	(52)	(52)
Hepatocellular hypertrophy	12	12	35**	32**	4	2	37**	47**
Increased single cell necrosis	0	0	0	4	0	0	1	2
Brownish pigment	0	0	0	13**	0	0	0	21**
Adenoma#	7	7	1	3	0	0	0	1
Carcinoma#	3	4	0	1	0	0	0	0

Values significantly different from control are : *p<0.05 and **p<0.01.
As reported in Annex I to CLH-report

In the rat carcinogenicity study, 1R-trans-Z-momfluorothrin was administered at dietary doses of 0, 200, 500, 1500 or 3000 ppm for 104 weeks. Treatment-related effects included decreased body weights (11% and 21% for males at 1500 and 3000 ppm, respectively, and 5%, 13% and 19% for females at 500, 1500 and 3000 ppm, respectively) and a corresponding decline in body weight gains, and increased relative liver weights (65.6% for males and 46.1% for females at 3000 ppm). Macroscopically, an increased incidence of liver nodules was seen in males at 3000 ppm (13/51) and of hepatic cysts in males (6/51) and females (13/51) at that dose level. Histopathologically, several non-neoplastic and neoplastic findings were reported for the liver, mainly at 3000 ppm in both sexes (see Table below).

The non-neoplastic liver findings included statistically significantly increased incidences of hypertrophy, brownish pigment, biliary cysts in both males and females and, in males only, cystic degeneration. The (pre-)neoplastic liver findings concerned increased incidences of eosinophylic foci, adenomas, carcinomas and combined adenomas and carcinomas in males and females at 3000 ppm. All increased incidences were statistically significant, with the exception of carcinomas in females. The incidences of tumours were also increased in males at 1500 ppm, but they were not statistically significant. Three high dose male rats died prematurely due to the presence of liver tumours. All non-neoplastic and (pre-)neoplastic liver effects reported in male and female rats were in excess of the mean value from historical control data but did not always exceed the maximum value reported (see Table below).

Other non-neoplastic effects considered to be of no concern included thyroid cell hypertrophy (considered secondary to the liver effects), brownish pigments in the kidney and diffuse acinar hypertrophy in the mandibular glands.

Table Non-neoplastic and neoplastic liver histopathological findings in the 104-week rat study (treatment-related findings are highlighted)

	Males						**Females**					
Nominal dietary conc. (ppm)	**0**	**200**	**500**	**1500**	**3000**	**HC#**	**0**	**200**	**500**	**1500**	**3000**	**HC#**
Liver (No. examined)	(51)	(51)	(51)	(51)	(51)	Mean (range)	(51)	(51)	(51)	(51)	(51)	Mean (range)
Hepatocellular hypertrophy	1 *2%*	1 *2%*	0	5 *9.8%*	14** *27.5%*	*2.57% (0-20)*	0	0	0	3 *5.9%*	10** *19.6%*	*2.93% (0-27)*
Brownish pigment					36 *70.6%*						18 *35.3%*	
Biliary cysts					8 *15.7%*	*1.22% (0-8)*					17 *33.3%*	*3.45% (0-14)*
Cystic degeneration				7 *13.7%*	7 *13.7%*	*1.03% (0-10.1)*						
Eosinophylic foci	0	2 *3.9%*	3 *5.9%*	3 *5.9%*	20** *39.2%*	*6.55% (0-44)*	2 *3.9%*	0	2 *3.9%*	5 *9.8%*	9* *17.6%*	*7.42% (0-56)*
Adenoma	1 *2%*	0	2 *3.9%*	4 *7.8%*	8** *15.7%*	*2.54% (0-8)*	0	0	1 *2%*	1 *2%*	4* *7.8%*	*2.8% (0-10.2)*

Carcinoma	0	0	0	4 *7.8%*	9** *17.6%*	*0.47%* *(0-2.8)*	0	0	0	0	1 *2%*	*0.32%* *(0-2)*
Combined adenoma & carcinoma	1 *2%*	0	2 *3.9%*	6 *11.8%*	17** *33.3%*	*3.01%* *(0-10)*	0	0	1 *2%*	1 *2%*	5* *9.8%*	*3.12%* *(0-12)*

NB: Level of statistical significance (*p<0.05 and **p<0.01) was only reported for hepatocellular hypertrophy, eosinophilic foci and tumours (in Annex I to CLH report).

Laboratory historical control (HC) data from twenty 104-week dietary studies conducted between 1981 and 2009, ass cited in CLH report and Annex I to CLH report (updated tumour data).

According to the DS, the available evidence suggests that the tumour formation is not a result of genotoxic activity. Hence, a non-genotoxic mode of action (MoA) is plausible. Non-genotoxic modes of actions include cytotoxicity, activation of constitutive androstane receptor (CAR) or peroxisome proliferator-activated receptor alpha (PPARα), porphyria or hormonal perturbation. None of the available data however gave indications of hormonal perturbation, porphyria or increased iron deposition. Since hepatocellular toxicity (e.g. fatty liver and necrosis) has not been observed in any of the rat studies, cytotoxicity is also not a contributing factor. The results of the mechanistic studies further suggest that 1R-trans-Z-momfluorothrin does not act via activation of the aryl hydrocarbon receptor (AhR), the pregnane X receptor (PXR) or PPARα. The latter is supported by the fact that electron microscopy did not provide evidence for peroxisome proliferation. The most plausible MoA is therefore that 1R-trans-Z-momfluorothrin acts via activation of CAR, resulting in altered gene expression specific to CAR activation and subsequently increased cell proliferation and formation of altered hepatic foci.

The postulated MoA involves the following sequence of key events:

1. Nuclear membrane receptor activation (CAR)
2. Altered gene expression specific to CAR activation (e.g. CYP2B)
3. Cell proliferation
4. Clonal expansion to generate altered liver cell foci
5. Increased liver adenoma/carcinoma

Associative events to these key events include CYP2B enzyme induction, liver hypertrophy (including weight), decreased apoptosis, altered epigenetic changes and inhibition of gap junction communication.

In rats, evidence for all key events and for 2 out of 5 associative events (i.e. CYP2B induction and hypertrophy, including increased liver weights) has been provided for 1R-trans-Z-momfluorothrin in the battery of *in vitro* and *in vivo* mechanistic studies and the short- and long-term toxicity studies. Dose-response and time concordance has also been shown. A study with human hepatocytes also demonstrated activation of human hepatic CAR following exposure to 1R-trans-Z-momfluorothrin, but in contrast to rat hepatocytes, no effect of 1R-trans-Z-momfluorothrin on replicative DNA synthesis was seen.

The DS noticed some datagaps and uncertainties. No evidence was provided for decreased apoptosis, inhibition of gap junction intercellular communication or altered epigenetic changes. However, it was considered more important that all key events had been demonstrated. Further, the species differences have not been fully addressed. Indeed, mechanistic studies in mice are consistent with CAR activation but in contrast to rats, 1R-trans-Z-momfluorothrin treatment did not result in increased tumour formation in mice. Yet, this appears to be consistent with findings for other pyrethroids, in particular metofluthrin, which is a close structural analogue to 1R-trans-Z-momfluorothrin.

Despite the above, the DS considers CAR activation the most plausible mechanism behind the liver tumour formation in the rat, based on all the available data. As to the relevance to humans of this MoA, the DS concluded that only certain elements of this MoA are predicted to occur in humans (see Table below). Notably, in human hepatocytes, induction of human CAR was not followed by DNA replication, which is a prerequisite for tumour formation. Hence, the findings with 1R-trans-Z-momfluorothrin were considered consistent with the conclusion expressed in the recent detailed review of Elcombe *et al.* (2014) that this MoA, for which phenobarbital (PB) is the

prototypical CAR activator, is qualitatively not plausible for humans. Consequently, the DS proposed no classification for carcinogenicity as the MoA of tumour formation has very limited or no relevance to humans.

Table Concordance table of Key and associative events for the CAR-mediated MoA, comparing evidence in rats and humans

Key and associative events	**Evidence in rats**	**Evidence in humans**
Activation of CAR	Suggested through the *in vitro* study with RNAi for CAR and induction of CYP2B enzymes	Probable at high doses based on the induction of CYP2B *in vitro*
Altered gene expression	Only changes in CYP2B reported	No experimental evidence in this submission but does occur in other published studies
Induction of CYP2B as a marker for CAR activation	Experimental evidence *in vivo* and *in vitro* with cultured rat hepatocytes	Experimental evidence based on the induction of CYP2B *in vitro*
Hypertrophy	Experimental evidence *in vivo*	Possible based on published evidence in humans treated with anticonvulsant drugs
Increased hepatocellular proliferation	Experimental evidence *in vivo* and *in vitro* with cultured rat hepatocytes	Not reported in cultured hepatocytes
Altered hepatic foci	Experimental evidence *in vivo*	No experimental evidence reported
Liver tumours	Yes	No experimental evidence reported

Comments received during public consultation

One MSCA agreed in general terms on the proposed classification for human health hazards. Another MSCA proposed to classify 1R-trans-Z-momfluorothrin as Carc. 2 because there are clear dose-related increases in hepatocellular adenoma and carcinoma in male and female rats and there is insufficient evidence to rule out the human relevance of the MoA. The MSCA stated that in the key experiment investigating the stimulation of replicative DNA synthesis *in vitro,* the conclusion on human non-relevance was not convincing as stimulation of replicative DNA synthesis was also not clearly demonstrated in rat hepatocytes (inhibitory effect from 100 µM onwards, effect of phenobarbital on increases on replicative DNA synthesis also not convincing). The results observed *in vivo* were accoding to the MSCA not supported by the results observed in this *in vitro* experiment. In response, the DS indicated that based on all available data, classification for carcinogenicity is not required.

Assessment and comparison with the classification criteria

There are no data on long-term exposure and carcinogencity of 1R-trans-Z-momfluorothrin in humans. In animal experiments (a 104-week study in Wistar rats and a 78-week study in CD-1 mice), administration of 1R-trans-Z-momfluorothrin via the diet resulted in increased incidences of liver tumours in rats at 1500 ppm (males) and 3000 ppm (both sexes). 1R-trans-Z-momfluorothrin was not carcinogenic in mice. The mechanism behind the carcinogenicity and the human relevance of the observed liver tumours were investigated/evaluated in several mechanistic studies and a HRF analysis.

In the long-term mouse study a satellite group (12/sex/dose) was exposed for 52 weeks and a main group (52/sex/dose) for 78 weeks. The animals received dietary doses of 0, 600, 2500 or 5500 ppm 1R-trans-Z-momfluorothrin (equal to 0, 72, 308 or 639 mg/kg bw/day for males and 0, 99, 427 or 853 mg/kg bw/day for females). No significant increases in mortality were observed in any dose group, nor any treatment-related tumours. In both the satellite and the main groups,

reduced body weight and body weight gain were observed in males at 2500 and 5500 ppm. Liver weight was increased in both groups, in both sexes, mainly at 2500 and 5500 ppm. In the main group this was accompanied by enhanced hepatocellular hypertrophy (from 2500 ppm) and, at the highest dose of 5500 ppm, enhanced single cell necrosis and brownish liver pigmentation. In the satellite group also an increase in hepatocellular hypertrophy was seen, but only in females. Based on these results, 1R-trans-Z-momfluorothrin is considered not to be oncogenic in mice.

In the long-term rat study, animals (51/sex/group) were dosed orally with 0, 200, 500, 1500 or 3000 ppm 1R-trans-Z-momfluorothrin in the diet for 104 weeks (equal to 0, 9.5, 23, 73 or 154 mg/kg bw/day for males and 0, 11, 28, 88 or 182 mg/kg bw/day for females). Survival rate was somewhat lower in females than in males, but was > 50% in all groups. Treatment with 3000 ppm resulted in the premature death of 3 male rats, which was due to the presence of liver tumours. In the 3000 ppm group, liver nodules (13/51 males) and hepatic cysts (6/51 males and 13/51 females) were observed at necropsy. Furthermore, increased incidences of eosinophilic cell foci (20/51 males and 9/51 females), adenoma (8/51 males, 4/51 females), carcinoma (9/51 males, 1/51 females) and combined adenoma and carcinoma (17/51 males, 5/51 females) were observed at this dose. In males at 1500 ppm the incidences of adenoma (4/51), carcinoma (4/51) and combined adenoma and carcinoma (6/51) were also increased, but this was not statistically significant.

Non-neoplastic findings in this study included decreased body weight and body weight gain at 1500 and 3000 ppm, increased relative liver weight at 1500 (22.5% for males and 20.3% for females) and 3000 ppm (65.6% for males and 46.1% for females) and hypertrophy, biliary cysts, cystic degradation and brown pigment in the liver (see Table 2). Brown pigment was also observed in the kidneys at 1500 (31/51 females) and 3000 ppm (25/51 males and 40/51 females). Additionally, diffuse acinar hypertrophy in the mandibular glands was observed in 34/51 males and 24/51 females at 3000 ppm, and thyroid follicular cell hypertrophy in 6/50 males at 3000 ppm (not statistically significant).

Based on the above, 1R-trans-Z-momfluorothrin is considered carcinogenic in rats, with the effect being more marked in male rats than in female rats. For male rats, the incidences of adenomas, carcinomas, and combined adenomas and carcinomas were all at or above the maximum incidence of the historical controls. For female rats, the incidences of adenoma and combined adenoma and carcinoma were within the historical control range, whereas the incidence of carcinoma was equivalent to the maximum incidence of the historical controls.

Mechanistic studies

Several *in vitro* and *in vivo* studies have been conducted to address the MoA responsible for the liver tumour formation. These studies are briefly summarised below (for more details see section 4.10.3 of Background Document and Annex I to Background Document). In several studies, the prototypical CAR activator phenobarbital (PB) was included as a positive control.

In vitro studies with rat hepatocytes
Primary rat hepatocytes (male, Wistar) transfected with CAR siRNA (short interfering RNA specific to CAR, used to block transcription of CAR mRNA and to decrease the amount of functional CAR) or control siRNA (negative control) were exposed to 100 µM 1R-trans-Z-momfluorothrin or to 50 or 500 µM PB. Treatment with CAR siRNA significantly reduced the levels of CAR mRNA in the presence of either 1R-trans-Z-momfluorothrin or PB (to 18-21% of negative controls), which in turn resulted in a significantly reduced induction of CYP2B1/2 mRNA levels by each compound (to 32% and 10-33% of controls, respectively). This indicates that CAR activation is involved in the induction of CYP2B1/2 mRNA by 1R-trans-Z-momfluorothrin.

In a second study, primary rat hepatocytes (male, Wistar) were treated with 1R-trans-Z-momfluorothrin (1–1000 µM) and PB (500 or 1000 µM) to study CYP2B1/2 induction (by mRNA analysis) and cell proliferation (measured as replicative DNA synthesis). For the latter experiment, also hepatocyte growth factor (HGF; 10 or 100 ng/mL) was tested as a positive control. PB induced CYP2B1/2 by 34- (500 µM) to 45-fold (1000 µM), whereas 1R-trans-Z-momfluorothrin induced CYP2B1/2 by 3-fold at 50 µM, but less at higher concentrations. An increase in DNA replication occurred with PB at both concentrations

(maximally 1.4-fold), and with 5 or 10 µM 1R-trans-Z-momfluorothrin (1.6- and 1.8-fold). Remarkably, at higher concentrations of 1R-trans-Z-momfluorothrin (≥ 100 µM), a decrease in DNA replication was observed. Such a decrease was not seen *in vivo* (see below). HGF showed a significant concentration-dependent increase in DNA synthesis (up to 4-fold).

In vitro studies with human hepatocytes

The same type of experiment as described above was performed for human hepatocytes. Primary hepatocytes from up to a total of 10 donors (5 males and 5 females, aged 10 months to 80 years) were treated with 1R-trans-Z-momfluorothrin (1–1000 µM) and PB (1000 µM) to study induction of CYP2B6 (the orthologue to rat CYP2B1/2). Cell proliferation was studied upon treatment with 1R-trans-Z-momfluorothrin (1–1000 µM), PB (500 or 1000 µM) and HGF (10 or 100 ng/mL).
PB treatment led to a 4.8-fold increase in CYP2B6 mRNA, which is much less than the induction of CYP2B1/2 in rat hepatocytes. With 1R-trans-Z-momfluorothrin, 1.7- and 1.8-fold increased levels of CYP2B6 mRNA were seen at 100 and 500 µM, respectively, whereas smaller increases were seen at 50 and 1000 µM. For 1R-trans-Z-momfluorothrin this induction rate is comparable to the one observed in rat hepatocytes. Replicative DNA synthesis was not increased upon treatment with either 1R-trans-Z-momfluorothrin or PB. In fact, decreased replicative DNA synthesis was observed at 100–1000 µM 1R-trans-Z-momfluorothrin, similar to that in rat hepatocytes. With 10 and 100 ng/mL HGF, there was an increase in DNA synthesis by 1.6- and 3.7-fold, showing that the human hepatocytes were capable of a proliferative response.

In vivo rat studies

As the 104-week rat study resulted in increased incidences of adenoma and carcinoma of the liver at 1500 and 3000 ppm, these doses and higher doses of 6000 and 10000 ppm were included in MoA studies with rats. Duration of oral exposure was for 7 or 14 days, and in one study recovery was studied (7-day treatment followed by 7 days of recovery). Investigations included liver weight, CYP2B and CYP4A activity, CYP mRNA levels indicative of AhR, PPARα, PXR and CAR activation, hypertrophy, cell proliferation and electron microscopy. For comparison, male rats were also dosed with 1000 ppm PB in the diet for 7 days.

Treatment-related increases were observed in liver weight, hypertrophy, cell proliferation and CYP2B activity in male and female rats, starting from 1500 ppm (but at 1500 ppm only relatively small effects). These increases were dose-related, and generally more marked after 14 days of treatment than after 7 days. For cell proliferation however the reverse was observed, with higher levels after 7 days of treatment in males (maximally 5.3-fold at 3000 ppm and 17.2-fold at 6000 ppm) and females (2.8-fold at 3000 ppm) as compared to 14 days of treatment (maximally 2.5-fold at 3000 ppm and 4.5-fold at 6000 ppm in males and 1.7-fold at 3000 ppm in females). The effects returned to control levels following a recovery phase of 7 days.
1R-trans-Z-momfluorothrin did not induce CYP1A2, CYP3A1 and CYP3A2 mRNA levels at 3000 ppm. CYP4A activity and CYP4A1 mRNA levels were slightly, but not statistically significantly, increased at 3000 ppm, but electron microscopy did not show evidence of peroxisome proliferation. CYP2B1/2 mRNA levels were markedly increased at 3000 ppm (17.8- and 16.4-fold after 7 and 14 days, respectively). Electron microscopy, however, revealed no increase in SER. PB at 1000 ppm similarly increased CYP2B activity (13-fold), liver weight, hypertrophy and cell proliferation (3.9-fold).

In some of the MoA studies, the effect of 1R-trans-Z-momfluorothrin on the thyroid was investigated, given the increase in thyroid follicular cell hypertrophy in the 52- and 104-week rat studies. When given to rats at 3000, 6000 or 10000 ppm for 7 or 14 days, 1R-trans-Z-momfluorothrin increased the incidence of follicular cell hypertrophy, but did not affect thyroid weight. Slight increases were also seen in hepatic UDP-glucuronosyltransferase (UGT) activity and TSH levels, whereas serum T4 (but not T3) levels were slightly but statistically significantly decreased. These effects suggest an effect on the hypothalamus-pituitary axis similar to PB, for which it is known that induction of hepatic UGT is mediated by CAR. It is therefore likely that the effects of 1R-trans-Z-momfluorothrin on the thyroid are secondary to the liver effects.

In vivo mouse studies

Similar studies as described above were conducted in mice (both sexes), with dietary treatment up to 5500 ppm 1R-trans-Z-momfluorothrin for 7 or 14 days, and including a recovery phase of 7 days. In these studies, mice showed dose-related CYP2B induction/CYP2B activity, increased liver weight, hepatocellular hypertrophy and cell proliferation, and upon electron microscopy an increase in SER was observed. There was also a slight increase in CYP4A induction and CYP4A activity, but electron microscopy did not show an accompanying increase in peroxisome proliferation. Following a recovery phase of 7 days the effects had returned to control levels.

Conclusion

From the mutagenicity data it can be concluded that 1R-trans-Z-momfluorothrin is not genotoxic. Hence, a non-genotoxic MoA is plausible. RAC agrees with the DS that of the known non-genotoxic MoAs behind liver tumour formation in rodents, hormonal perturbation/oestrogens/statins, porphyria, increased iron deposition, infections and increased apoptosis can be discounted for 1R-trans-Z-momfluorothrin, based on all data available. Although some signs of cytotoxicity were observed (e.g. brown pigmentation and cystic degeneration), there was no sustained proliferation and no diffuse, multifocal necrosis, so prolonged cytotoxicity can also be ruled out as the main cause of liver carcinogenicity.

The results of the mechanistic studies further suggest that 1R-trans-Z-momfluorothrin does not act via activation of AhR (no induction of CYP1A2 mRNA was seen), PXR (no evidence for CYP3A1 or CYP3A2 mRNA induction) or PPARα (no evidence for peroxisome proliferation upon electron microscopy). A MoA via immunosuppression is also not likely, as 1R-trans-Z-momfluorothrin is not immunotoxic.

RAC agrees with the DS that CAR activation is the most plausible mechanism behind the liver tumour formation in the rat, given the evidence presented for the key events and some of the associative events in this MoA, also with respect to dose-response relation and temporal association. The *in vitro* study with rat hepatocytes in which the CAR gene was knocked down showed that CAR activation is involved in the induction of CYP2B1/2 mRNA by 1R-trans-Z-momfluorothrin (key event 1). The *in vivo* MoA studies in rats consistently showed CYP2B induction, i.e. increased CYP2B1/2 mRNA expression (key event 2, also shown *in vitro* in rat hepatocytes) and increased CYP2B activity (associative event). MoA studies in mice showed the same picture. Electron microscopy further revealed increased SER (in the 7- and 14-day mouse MoA studies at 5500 ppm and in the 13-week rat study at 6000 ppm), which is characteristic of enzyme inducers.

Increased liver weights and increased incidences of hepatocellular hypertrophy (associative event) were observed in all toxicity (short- and long-term) and MoA studies in rats and mice. Evidence for increased cell proliferation (key event 3) was provided in the rat and mouse MoA studies and in an *in vitro* study with rat hepatocytes. Similar to what is known for PB, the stimulation of cell proliferation by 1R-trans-Z-momfluorothrin was transient and not sustained (i.e. effect smaller after 14 days than after 7 days). However, the overall cell proliferation will still be enhanced due to the increase in total number of hepatocytes.

These events ultimately resulted in increased incidences of eosinophilic foci (key event 4) and liver tumours (key event 5) in rats, but not in mice. This seems inconsistent, as generally mice appear more susceptible than rats to liver tumour formation by CAR activators. However, according to Elcombe *et al.* (2014) for some CYP2B enzyme inducers which appear to have a similar MoA for liver tumour formation to PB, such as pyrethrins and metofluthrin, liver tumours have been observed in the rat and not in the mouse. Metofluthrin is a close structural analogue to 1R-trans-Z-momfluorothrin.

RAC notes that evidence has not been presented for all associative events . However, RAC considers the CAR activation as the most plausible mechanism behind the liver tumour formation in the rat, in line with the DS. As to the relevance to humans of this MoA, the *in vitro* study with human hepatocytes has shown that CAR activation is also possible in humans: 1R-trans-Z-momfluorothrin induced expression of CYP2B6 mRNA. However,

1R-trans-Z-momfluorothrin did not induce replicative DNA synthesis in human hepatocytes, in contrast to rat hepatocytes where 1R-trans-Z-momfluorothrin slightly, but statistically significantly increased cell proliferation. PB, the positive control in the study with human hepatocytes, also induced CYP2B6 mRNA expression, but did not induce cell proliferation that was statistically significantly different compared to controls. In rat hepatocytes on the other hand, and in rats *in vivo*, PB induced replicative DNA synthesis, albeit moderately (maximally 1.4-fold and 3.9-fold, respectively).

RAC acknowledges the argumentation of the DS in discussing the concordance between rat and human evidence for the CAR MoA. RAC further acknowledges that similar to PB, the prerequisite for tumour formation, i.e. DNA replication, does not seem to occur with 1R-trans-Z-momfluorothrin in human hepatocytes following induction of human CAR, in contrast to rats. Due to this qualitative difference, the liver tumours as a result of CAR-activation by 1R-trans-Z-momfluorothrin are considered to be of little relevance to humans. This is in line with a recent review on the human relevance of CAR-mediated liver toxicity, for which PB is the example substance (Elcombe et al., 2014). Hence, RAC supports the conclusion of the DS that 1R-trans-Z-momfluorothrin **does not warrant a classification for carcinogenicity** following a comparison with CLP criteria and an in depth weight of evidence analysis (demonstration that the CAR-mediated MoA is present, that other MoA are excluded and that the relevance to humans is limited).

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The potential of 1R-trans-Z-momfluorothrin to affect reproduction was assessed using three GLP compliant studies, one in rats conducted according to OECD TG 416 (two-generation reproduction toxicity study), and two studies conducted according to OECD TG 414 (prenatal development toxicity study), one in rats and one in rabbits.

In the two-generation reproduction toxicity study (Pal-Kutas, 2012), rats received 0, 200, 500 or 1500 ppm 1R-trans-Z-momfluorothrin in the diet. No mortalities or clinical signs were observed and there were no effects on mating performance, the number of pregnant animals, and the number of implantations or post-implantation loss. Main effects in the parental generations at 1500 ppm included reduced food consumption and body weight (up to 10%) and increased liver weight (up to 30%) with correlating histopathological findings (hepatocellular hypertrophy) in both sexes. Body weight and liver weight were also slightly affected at 500 ppm in F1 and P generation males, respectively, and food consumption was reduced at 500 ppm in P generation females. In the offspring, pup weights up to weaning were decreased at 500 (<10%) and 1500 ppm (10-16%) in F1 and F2 as well as at 200 ppm in F2 (without a clear dose-response in F2). F1 pups showed a statistically significant delay in sexual maturation (26.3 *vs*. 25.0 days for preputial separation, 37.0 *vs.* 34.1 days for vaginal opening) at 1500 ppm, a dose at which the F1 males had 12% decreased body weight at maturation. The DS considered the effects on sexual maturation as secondary to general toxicity. In pups of both generations, reductions were seen in absolute thymus weight at 1500 ppm and in absolute and relative spleen weights at 1500 and 500 ppm, without any histopathological findings.

Developmental toxicity of 1R-trans-Z-momfluorothrin was tested in rats at oral (gavage) levels of 0, 10, 25 and 75 mg/kg bw/day from gestation days 6-19. No maternal deaths occurred during the treatment period. At 75 mg/kg bw/day, tremors were observed in 6 animals at a frequency of 1-2 animals per day during late gestation. The number of corpora lutea was decreased, and the gravid uterine weight, number of implantations and live foetuses were reduced. However, as the number of corpora lutea was established prior to dosing, the effect on this parameter is not treatment-related. As the decrease in the gravid uterine weight of dams and in the number of implantations and live foetuses are a consequence of the lower number of corpora lutea, these

effects are also considered not treatment-related. No effects on embryo-foetal development, foetal malformations or abnormalities were seen up to and including the highest tested dose.

Developmental toxicity of 1R-trans-Z-momfluorothrin was also tested in rabbits, at oral (gavage) levels of 0, 100, 300 and 1000 mg/kg bw/day from gestation days 6-27. No maternal deaths occurred during the treatment period. Significant reduction in food consumption was observed during the first 3 days of dosing in the 300 and 1000 mg/kg bw/day groups. In the 300 mg/kg bw/day group, this effect persisted until day 15 of gestation. No other effects were observed in the dams. There were also no effects on embryo-foetal development.

Overall, the DS concluded that 1R-trans-Z-momfluorothrin has no adverse effects on sexual function and fertility or on development and therefore proposed no classification for reproductive toxicity.

Comments received during public consultation

No specific comments were received during PC, but 2 MSCAs agreed in general terms on the proposed classification for human health hazards.

Assessment and comparison with the classification criteria

No effects on reproductive organs have been described for the repeated dose toxicity studies presented in the CLH dossier. In the rat two-generation study, levels up to and including the highest dose of 1500 ppm 1R-trans-Z-momfluorothrin (87.6-126 mg/kg bw/day) did not produce an adverse effect on reproductive performance/parameters. RAC therefore agrees with the DS that there is no need to classify 1R-trans-Z-momfluorothrin for effects on sexual function and fertility.

In the available developmental toxicity studies, 1R-trans-Z-momfluorothrin did not adversely affect development in rats and rabbits. In the rat two-generation study, a delay in sexual maturation was seen at 1500 ppm, but this is probably secondary to some general toxicity observed at this dose and the mid dose of 500 ppm, both in pups (reduction in body weight and in some organ weights) and in parental animals (reductions in body weight and food consumption, and effects on the liver). In conclusion, RAC agrees with the DS that these effects **do not warrant classification of 1R-trans-Z-momfluorothrin for developmental toxicity**.

ENVIRONMENTAL HAZARD ASSESSMENT

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

1R-trans-Z-momfluorothrin does not currently have a harmonised classification for environmental hazards. Based on the available data on aquatic toxicity and considering that the substance is not rapidly degradable, the dossier submitter (DS) proposed an environmental classification as Aquatic Acute 1 (M=100) and Aquatic Chronic 1 (M=100) according to the CLP Regulation.

Degradation

Hydrolysis
1R-trans-Z-momfluorothrin is considered stable under acidic conditions with limited hydrolysis at neutral pH. Under alkaline conditions, degradation is significant although it is likely to reflect a DT_{50} > 16 days.

The available hydrolysis study (following GLP and according to OECD TG 111) used 3 radio-labelled (^{14}C) 1R-trans-Z-momfluorothrin isomers. In a preliminary test, hydrolysis was assessed at pH 4, 7 and 9 at 50 °C for up to 5 days. The acid isomers used were stable at pH 4 and limited degradation occurred at pH 7 and 9. The definitive study was performed at pH 7 (up to 33 days for 40, 50 and 60°C) and pH 9 (up to 21 days for 25, 40 and 50°C). The calculated DT_{50} were: 660 to 1394 days at 20°C (pH 7) and 11.7 to 12.2 days at 20°C (pH 9). However, the DT_{50} converted to a more environmentally relevant temperature of 12°C were 18.3 to 20.3 days at pH 9.

Photolysis

An aqueous photolysis study was carried out, using a Xenon lamp, and 3 radio-labelled (^{14}C) 1R-trans-Z-momfluorothrin isomers, at pH 4 and 25 °C for 13 days, following GLP and OECD TG 316. Under light conditions, the isomerisation was not significantly different between the 3 labelled (^{14}C) 1R-trans-Z-momfluorothrin isomers. The photolytic DT_{50} of 1R-trans-Z-momfluorothrin was determined to be 13.4 days, equivalent to 25.9 OECD solar days and, including photoisomerisation, 7.5 days equivalent to 14.5 OECD solar days.

Biodegradation

Ready biodegradability was tested with one study following GLP and OECD TG 301B (CO_2 Evolution Test), using S-1563 (purity 95.6%, total momfluorothrin isomer content) as test material. The study was run a pH 7.53 to 7.68 and between 21 and 24°C. Validation criteria for the reference and toxicity controls were met. Ultimate biodegradation reached a maximum of 3.91%, demonstrating that the substance is not readily biodegradable.

A degradation study in a water-sediment system is available which followed OECD TG 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) and was GLP-compliant. Two aerobic systems were used. The study used 3 radio-labelled (^{14}C) 1R-trans-Z-momfluorothrin isomers. Initial nominal dose rates were 7.7 to 8.4 µg per sample with direct addition to the water phase. The study was run in the dark at 20 ± 2°C for between 100 and 146 days depending on the radio-label.

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

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

Bbioaccumulation

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

Method	**Results**	**Remark**	**Reference**
Partition coefficient n-octanol/water OECD TG 107, GLP	Log Kow: 2.99 at 25°C	RTZ isomer	Wright, 2011b
Partition coefficient n-octanol/water OECD TG 107, GLP	Log Kow: 2.88 at 25°C	RTE isomer	Wright, 2011c

Method	Results	Remark	Reference
Experimental aquatic BCF OECD TG 305, GLP	Steady state whole fish BCF: 600 to 612 L/kg Kinetic whole fish BCF: 753 to 784 L/kg (experimental 2.56% lipid). Lipid normalized to 5% kinetic whole fish BCF: 1471 to 1531 L/kg Depuration half-life DT_{50} whole fish: 9.76 to 11.7 days	Flow through, 35 days exposure, 28 days depuration Based on measured total radioactive [14C] residues (TRR)	Kang, 2012

Experimental $logK_{OW}$ values are 2.88 and 2.99 at 25°C for the RTE and RTZ isomers, respectivley.

These values are below the $logK_{OW}$ trigger value of 4 intended to identify substances with a potential to bioaccumulate according to CLP.

An experimental aquatic BCF is available following GLP and OECD TG 305. The study used 2 radio labels (^{14}C) momfluorothrin isomers in a combined ratio of 1:9. A flow-through system was used with Bluegill Sunfish (*Lepomis macrochirus*) and two exposure concentrations: 0.1 and 0.3 µg/L. The exposure period ran for 35 days followed by a 28 day depuration period. Test conditions reflected the OECD TG with a water pH between 7.1-8.4.

1R-trans-Z/E-momfluorothrin was only detected in fish tissue on day 1 of the exposure phase in edible, non-edible and whole body fish samples at both low and high concentrations. After this, it was considered metabolised and only [^{14}C] residues were observed. Steady state and kinetic BCFs based on the parent 1R-trans-Z/E-momfluorothrin could not be calculated and the provided BCFs were based on total radioactive residues, related to the major metabolites detected in fish (TFPA and MFOA-D).

In conclusion, momfluorothrin was observed to be extensively metabolised, resulting in a BCF less than 500. The provided BCFs, based on total radioactive residue, were greater than 500 L/kg but less than 2000 L/kg, reflecting metabolites. A clear depuration phase was observed.

Aquatic toxicity

Several acute and chronic aquatic toxicity studies conducted following GLP and standard test guidelines are available. The studies used technical 'S-1563' with an overall purity of 95.4 to 95.8% (based on total momfluorothrin isomer content) and ≥ 86% 1R-trans-Z-momfluorothrin isomer content.

No ecotoxicity data are described in the CLH report for the degradants. However the DS made reference to non-GLP acute toxicity studies with algal, *Daphnia* and fish (Miyamoto *et al*., 2013a, 2013b and 2013c) for the degradants MFOA-D, MFOA and t-COOH-CA, indicating they are significantly less toxic than the parent.

Valid ecotoxicological data are available for all three trophic levels. The lowest reliable ecotoxicity results in the CLH report were as follows (the key data are highlighted in bold).

Method	Test organism	Test system	Endpoint mg/l	Remarks	Reference
OECD 203, GLP	*Oncorhynchus mykiss*	96 h Flowthrough	**LC_{50} 0.0012**	mm	Fournier, 2011a
OECD 203, GLP	*Pimephales promelas*	96 h Flowthrough	LC_{50} 0.0097	mm	Fournier, 2011b
OECD 203, GLP	*Lepomis macrochirus*	96 h Flowthrough	LC_{50} 0.0029	mm	Fournier, 2011c
OECD 210, GLP	*Pimephales promelas*	28 d Flowthrough	NOEC ≥ 0.0031	mm Based on highest test concentration	York, 2012

				as no significant effects observed.	
OECD 202, GLP	*Daphnia magna*	48 h Flowthrough	EC_{50} 0.0078	mm	Fournier, 2011d
OECD 211, GLP	*Daphnia magna*	21 d Flowthrough	**NOEC 0.0005**	mm	Fournier, 2012
OECD 201, GLP	*Pseudokirchneriella subcapitata*	72 h Static	ErC_{50} >4.87 NOErC 0.33	twa	Softcheck, 2011a
OECD 221, GLP	*Lemna gibba*	7 d Static	ErC_{50} >2.5 NOErC ≥2.5	twa Based on the highest test concentration as no significant effects were observed.	Softcheck, 2011b
mm = mean measured twa = time weighted average					

From the available aquatic acute toxicity data, fish and invertebrates are the most sensitive trophic groups with $L(E)C_{50}$ values in the range 0.001 to 0.01 mg/L. In particular, the most sensitive species tested is fish *Oncorhynchus mykiss*. Fish were exposed to the test substance in a flowthrough test system for 96h. The LC_{50} of 0.0012 mg/L is based on mean measured concentrations, with 95% confidence intervals of 0.64 to 2.2 µg/L.

Based on chronic aquatic toxicity data, the lowest NOEC was for invertebrates in the range of 0.0001 to 0.001 mg/L. The most sensitive species tested is *Daphnia magna,* (21d flowthrough condition test) with a NOEC of 0.0005 mg/L, based on total body dry weight.

Comments received during public consultation

Three MSCAs and one industry representative contributed during public consultation stating a general agreement with the proposed environmental classification.
One MSCA suggested to recalculate the hydrolysis half-lives by application of the recommended EU outdoor temperature of 285 K (12°C); and to indicate the metabolites identified during the hydrolysis study and the aqueous photolysis of the parent as well as their quantified maximum percentages. The DS replied that since hydrolysis is pH dependant (increasing hydrolysis with increasing pH), the values presented in the CLH report (DT_{50} of 18.3 to 20.3 days at pH 9 and 12°C) were considered to represent the most rapid hydrolysis at a higher environmentally relevant pH range. The DS provided the % AR of the principal degrandants. However, other details about the degradants were not presented in the CLH report as the parent is considered to be more toxic than the degradation products and so the classification proposal focused on the parent substance alone.

The same MSCA provided some minor comments referring to the water/sediment study (mineralisation data, the temperature of all DT_{50} values, the maximum % recovery rates for major degradants). The DS replied that all relevant information was provided in the CLH report.

They aslo asked to provide a chapter on fate and behavior in atmosphere including results on indirect phototransformation in air. The DS replied that 1R-trans-Z-momfluorothrin is unlikely to partition to the atmosphere and environmental classification does not include consideration of the air compartment, with exception of substances hazardous to ozone layer.

A second MS pointed out to an editorial comment on the vapour pressure value and the DS agreed.The industrial representative proposed some editorial comments on the water-sediment simulation study, to which the DS agreed. They also suggested to consider an additional aquatic acute toxicity study of 2 degradants to fish, Daphnia and algae. The DS replied that since the studies indicate the degradants to be significantly less toxic than the parent and because 1R-trans-Z-momfluorothrin is considered not rapidly degradable, they were not used further and the CLH report focuses on the parent alone.

The industrial representative also proposed to consider appropriate the NOEC value of 0.50 µg/L. They argued that since the mean total body length at 0.50 µg/L (i.e. 4.44 mm) is within the variation range of control (4.14 mm) and solvent control (4.55 mm), the statistically significant difference observed at 0.50 µg/L for the length is not considered related to a toxicity effect. The DS replied the NOEC value for the parental body length parameter is 0.0031 mg/L. Conequently, should the statistical difference be valid for NOEC derivation, a resulting parental body length NOEC would, in any case, fall within the same range of the CLH criteria (0.0001 to 0.001 mg/L) as the dry weight NOEC and would have no impact on the classification proposal. On this basis the endpoint was not considered further for classification.
The industrial representative suggested to consider an additional toxicity test with sediment-dwellig midges. The DS clarified that the proposed test it isn't an aquatic exposure study and therefore not appropriate, to be included in the CLH report.

Assessment and comparison with the classification criteria

Degradation

According to all the provided information on degradation, RAC agrees with the DS proposal to consider 1R-trans-Z-momfluorothrin not readily biodegradable and not rapidly degradable.

Bioaccumulation

1R-trans-Z-momfluorothrin has log Kow values below 4. In a fish bioaccumulation study the provided BCFs were related to the metabolites, because the parental 1R-trans-Z-momfluorothrin was only detected in fish tissue on day 1 of the exposure phase and afther this it was considered extensively metabolised. Based on these results, a BCF less than 500 could be applied.

Aquatic toxicity

Acute aquatic hazard

Acute toxicity data are available for all three trophic levels. Fish and invertebrates are the most sensitive trophic groups with L(E)C_{50} values in the range 0.001 to 0.01 mg/L. The lowest reliable value is a 96 h LC_{50}=0.0012 mg/L (mean measured) for fish *Oncorhynchus mykiss.*

RAC concludes that 1R-trans-Z-momfluorothrin should therefore be classified as Aquatic Acute 1 (H400), with an M-factor of 100.

Chronic aquatic hazard

The long-term aquatic toxicity data are available for all three trophic levels. The lowest value is a 21 d NOEC=0.0005 mg/L (mean measured concentration) for *Daphnia magna.* This NOEC value is in the range of 0.0001 to 0.001 mg/L. Therefore, RAC concludes that 1R-trans-Z-momfluorothrin should be classified as Aquatic Chronic 1 (H410), with an M-factor of 100.

RAC notes that the species used for the single chronic fish test did not reflect the most sensitive fish species (*Oncorhynchus mykiss)* for the acute values, resulting in a chronic NOEC greater than the LC_{50} values for two fish species. On this basis, it is appropriate to consider the surrogate approach for chronic toxicity to fish. This also results in a classification of Aquatic Chronic 1 (H410), with an M-factor of 100, based on the lowest chronic aquatic toxicity value and the fact that 1R-trans-Z-momfluorothrin is not rapidly degradable.

In summary, RAC agrees with the DS proposal that 1R-trans-Z-momfluorothrin should be classified according to CLP as:

Aquatic Acute 1 (H400), M-factor of 100;
Aquatic Chronic 1 (H410), M-factor of 100.

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RACs' comments (excluding confidential information).