Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

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

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

CLH-O-0000001412-86-197/F

Adopted

9 March 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON IMIPROTHRIN (ISO); [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: imiprothrin (ISO); reaction mass of: [2,4-dioxo-(2-propyn-1-yl)imidazolidin-3-yl]methyl(1R)-cis-chrysanthemate; [2,4-dioxo-(2-propyn-1-yl)imidazolidin-3-yl]methyl(1R)-trans-chrysanthemate
EC number: 428-790-6
CAS number: 72963-72-5
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	1

Comment received

I refer to the attached 4 (four) expert statements where each concludes that imiprothrin should not be classified for reproductive or developmental toxicity.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20160720 Position paper - imiprothrin - final.pdf

Dossier Submitter's Response

Thank you for your comments. Our reasoning for proposing classification for developmental effects has been explained in the CLH report alongside the data. Fusion of the nasal bone was considered to be a malformation. According to the ECETOC Guidance on Evaluation of Reproductive Toxicity Data, fusion of skull bones is considered to warrant a high level of concern. This finding, in combination with hypoplasia of the frontal bone, gave rise to a cause for concern for craniofacial development.

Maternal toxicity was covered in the CLH report. We acknowledged that Dam number 301 showed decreased bodyweight gain, food consumption and average foetal weight in comparison to the group average. However, we did not consider this to be unequivocal evidence that the observed effect was a secondary non-specific consequence of lower foetal bodyweight. Consequently, the findings were considered to be evidence of developmental toxicity.

With regards to the information about the monitoring study, please note that classification is based on hazard rather than risk under the CLP Regulation.

RAC will take your comments into consideration, together with the information in the CLH report, when concluding on the classification of imiprothrin.
RAC's response
RAC considers the skeletal variations and visceral finding as observed in the rat developmental toxicity study at maternally toxic doses to be indicative of delayed ossification or a manifestion of developmental delay. These effects do not constitute a high level of concern (they were additionally shown to be partially or completely resolved post-natally), and are considered insufficient to warrant classification. Similar to rats, RAC considers the increases in 27 pre-sacral vertebrae and in hypoplasia of frontal bone (both skeletal variations) in the rabbit developmental toxicity study at maternally toxic doses not to constitute a high level of concern; they are considered insufficient to warrant classification. As to the fusion of the nasal bone, this was only observed at a dose that was clearly above the MTD for the rabbit dams. RAC considers that effects at such a high dose level should be carefully taken into account as they might be secondary effects to maternal toxicity. On the total weight of evidence for the findings in rabbits, RAC does not consider classification for developmental toxicity warranted.

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	2
Comment received				
This is the 2nd of 4 expert statements supporting the non-classification of imiprothrin as H361d. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20160728 Expert AssessmentImiprothrin1 - Eric Wood + SCUK + EHSL comments V3 - sec.pdf				
Dossier Submitter's Response				
Thank you for your comments. Our reasoning for proposing classification for developmental effects has been explained in the CLH report alongside the data. Fusion of the nasal bone was considered to be a malformation. According to the ECETOC Guidance on Evaluation of Reproductive Toxicity Data, fusion of skull bones is considered to warrant a high level of concern. This finding, in combination with hypoplasia of the frontal bone, gave rise to a cause for concern for craniofacial development. We note that there is some uncertainity as to whether maternal toxicity contributed to the findings in the rabbit foetuses. The Dossier Submitter has taken maternal toxicity into account. Had the fusion of the nasal bone and hypoplasia occurred in the absence of maternal toxicity, it is considered that classification for reproductive toxicity in Category 1B could have been justified. Taking the maternal toxicity into consideration reduces the level of concern and classification in Category 2 is considered to be appropriate.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	3
Comment received				

The report (attached) provides robust data and arguments to challenge the CLH proposal relating to developmental toxicity - H361d, Repro Cat 2.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20170322 Imiprothrin Final Expert opinion - Tesh.pdf

Dossier Submitter's Response

Thank you for your comments. The proposed classification is primarily based on the findings in rabbits. Our reasoning for proposing classification for developmental effects has been explained in the CLH report alongside the data. Fusion of the nasal bone was considered to be a malformation. According to the ECETOC Guidance on Evaluation of Reproductive Toxicity Data, fusion of skull bones is considered to warrant a high level of concern. This finding, in combination with hypoplasia of the frontal bone, gave rise to a cause for concern for craniofacial development.

Whilst we note your arguments, the Dossier Submitter notes that there is some uncertainity as to whether maternal toxicity contributed to the findings in the rabbit foetuses. The Dossier Submitter has taken maternal toxicity into account. Had the fusion of the nasal bone and hypoplasia occurred in the absence of maternal toxicity, it is considered that classification for reproductive toxicity in Category 1B could have been justified. Taking the maternal toxicity into consideration reduces the level of concern and classification in Category 2 is considered to be appropriate.

RAC's response

See RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	4

Comment received

Imiprothrin should not carry the hazard classification H361d, repro cat 2. Four reports detailing expert opinions have been submitted from my company and the experts all agree that classification with H361d i not merited based on the changes observed in the rat and rabbit.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20170328 Imiprothrin CLH_REP_UK_SPS-013199-17.pdf

Dossier Submitter's Response

Thank you for your comments. The doses in mg/kg bw/day stated in the CLH report were taken from Doc IIIA and the NOAELs were taken from the Competent Authority Report. At this stage, we can no longer make changes to the CLH report. However, RAC will take your comment into consideration and use the appropriate values in their opinion.

In response to your comment on page 76 of the CLH report, we maintain that the findings in dams 301 and 310 were similar. The food consumption and pup weights of dam number 310 were similar to those of dam number 301 and both dams had reduced bodyweight gain, although we acknowledge that this was more marked in dam 301. Maternal toxicity was covered in the CLH report. We acknowledged the signs of maternal toxicity in dam number 301. However, we did not consider this to be unequivocal evidence that the observed effect was a secondary non-specific consequence of lower foetal bodyweight. Consequently, the findings were considered to be evidence of developmental toxicity.

To clarify the statement on page 78 of the CLH report, skeletal variations were observed from 200 mg/kg bw/day in rats (lumbar rib) and from 30 mg/kg bw/day in rabbits (27 pre-sacral vertebrae).
RAC's response
See RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	5
Comment received				
This is the 4th of 4 expert statements supporting the non-classification of imiprothrin as H361d. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Imiprothrin revised final report Nov2016.pdf				
Dossier Submitter's Response				
Thank you for your comments. The proposed classification is primarily based on the findings in rabbits. Our reasoning for proposing classification for developmental effects has been explained in the CLH report alongside the data. Fusion of the nasal bone was considered to be a malformation. According to the ECETOC Guidance on Evaluation of Reproductive Toxicity Data, fusion of skull bones is considered to warrant a high level of concern. This finding, in combination with hypoplasia of the frontal bone, gave rise to a cause for concern for craniofacial development. Whilst we note your arguments, the Dossier Submitter notes that there is no unequivocal evidence showing that the findings in rabbit foetuses were secondary to reduced foetal weight. In the absence of such unequivocal evidence, the findings were considered to be evidence of developmental toxicity and hence classification was proposed. We note that the author of the attached report considers that a more appropriate descriptor of hypoplasia of the frontal bone would be that of delayed ossification. We compiled the CLH dossier using the available information and terminology from the original study reports. The hypoplasia was considered to be a variation. However, the combination of the malformation (fusion of the nasal bone) and hypoplasia of the frontal bone gives rise to a cause for concern for craniofacial development, hence the proposal to classify imiprothrin in category 2 for adverse effects on development.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	6
Comment received				
This is the 3rd of 4 expert statements supporting the non-classification of imiprothrin as H361d.				
Dossier Submitter's Response				
From this comment, it is not clear which attachment is being referred to. We have				

considered all documents submitted during the Public Consultation and have provided responses to them in this RCOM document. Responses to comment numbers 1-20 should cover these points.
RAC's response
See RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2017	Germany		MemberState	7
Comment received				
The German CA supports the dossier submitters proposals but proposes that an additional classification as Carc. 2 and STOT SE 1 is considered. The German CA agrees with the proposed classification for environmental hazards as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) and the acute/chronic M-factor of 10. Additionally the German CA strongly urges the dossier submitter to propose harmonised ATE values for the two acute toxicity classes. Harmonised ATE values will greatly facilitate harmonised classification of mixtures and will improve legal certainty for suppliers and increase the safety of workers and consumers.				
Dossier Submitter's Response				
Thank you for your comments. Please see responses to comment numbers 9 and 24. ATE values have been proposed – please refer to page 28 of the CLH report.				
RAC's response				
The support for the ENV classification is noted. ATE values will be proposed for acute oral and inhalation toxicity. As to your comments on carcinogenicity and STOT SE, see RAC's responses to comments number 9 and 24, respectively.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	France		MemberState	8
Comment received				
18 month mouse study (lung)- Page 61 Lung tumours are reported in male rats. In female mice, it is difficult to exclude a lung carcinogen effect considering the high level of mortality at the high dose. Depending on the occurrence time of these mortalities, this can hide a potential carcinogenic effect occurring in late life. Therefore, couldyou please specify the period of exposure at which mortalities are observed? Moreover, could you please confirm that a statistic analysis was performed by combining the findings in dead and moribund animals (as it is mentioned for adenoma)? We consider it is more relevant to compare the incidence of lungs tumours with the laboratory historical control data provided by applicant than the historical control data provided by animal supplier considering that the laboratory historical control data are more representative of the condition of experimentation. Furthermore, in the in vitro mammalian chromosome aberration test a positive effect is observed with a metabolic activation. In the in vivo bone marrow micronucleus test available in the dossier, it is not clear that the bone marrow is reached. In this context, a mutagenic effect could not be excluded.				

In the table 22, it is mentioned that there is no indication of a substance with structural similarity for which there is a good evidence of carcinogenicity. However, a harmonised classification for carcinogen endpoint is available for another pyrethroid insecticide acting on the sodium channel: c. Do you consider the relevance to use data from this substance (or to other pyrethroid substances) as supportive information for carcinogenicity endpoint?

Overall, we question if a classification for carcinogenicity would be justified based on these above arguments.

Dossier Submitter's Response

Thank you for your comments.

Lung adenoma was observed in 0/50, 0/50, 0/50, 0/50 and 2/50 male rats at 0, 2, 9, 90 and 180 mg/kg bw/day, respectively. Lung adenocarcinoma was reported in 6/51, 5/51, 7/51 and 13/50 male mice at 0, 10, 354 and 702 mg/kg bw/day, respectively.

In female mice, the mortality rate increased significantly in the 3500 ppm group between weeks 49 and 73 and in the 7000 ppm group from week 50 until the end of treatment, according to the original study report. It is not possible to say whether the deaths masked a potential carcinogenic effect.

Table 18 in the CLH report presents the incidence of adenocarcinoma in all female mice. As can be seen from this table, no statistical significance was reported.

As you note, there was a positive result with metabolic activation in the *in vitro* mammalian chromosome aberration test. However, isolated positive results are not unusual and this could be a false positive. We consider the available *in vivo* test data to be adequately reassuring. Following oral dosing of radiolabelled imiprothrin isomers, absorbed radioactivity was widely distributed to a range of organs and tissues with the liver being the site of greatest localisation, as described on page 20 of the CLH report. Since the liver is exposed, it is reasonable to presume that the bone marrow was reached in the micronucleus assay following oral dosing.

The available data on imiprothrin were considered sufficient to conclude that no classification is warranted for carcinogenicity. Therefore reading across to data on other substances is not considered to be necessary.

As described in the CLH report, the concern for a carcinogenic potential of imiprothrin was lowered by the relatively high background incidence of lung 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 was considered that imiprothrin does not warrant classification for carcinogenicity.

RAC's response

RAC does not consider the tumour findings in rats to warrant classification, in view of only a slight, not statistically significant increase in benign tumours in one sex only. RAC also considers the slight, not statistically significant increase in benign liver tumours in one sex of mice only not to warrant classification. The increase in lung adenocarcinoma in male mice, however, does warrant classification (in category 2), a.o. because the increase is marked and dose-related, and it has not been convincingly shown that the elevated lung tumour incidences at the highest dose level are linked to a bad health status of the exposed males, in view of the relatively moderate reductions in body weight.

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2017	Germany		MemberState	9

Comment received

Classification for Carcinogenicity Category 2 should be considered in the light of significant treatment related increases in lung adenocarcinoma in male mice, supported by related findings in rats and indications for neoplastic change in livers of rats and mice:
In male mice of the top dose, the increase in number of adenocarcinoma was significantly different from concurrent controls and outside the laboratory historical control range (supplier data not relevant). The effect was clearly dose dependent, with p=0.0032 in the Cochrane Armitage linear trend test (data from Table 18 on page 58). For female mice in the same study, there was a treatment related increase in adenoma when examined by trend testing (p=0.0116) and for adenoma and adenocarcinoma combined (p=0.009). In the rat carcinogenicity study, doses of imiprothrin tested were lower than in the mice study. Nevertheless, a positive trend test for adenoma of the lung in male rats (p=0.0062, Cochrane Armitage test based on data in Table 16, page 56) indicates potential treatment related neoplasia also in rat lungs.
In addition to lung tumors, data presented in table 15, page 55, suggest a dose dependent increase (trend) in liver adenoma in male rats (p=0.033) but not in females (p=0.138). In mice, which were exposed to higher doses, there were clearly dose dependent increases in the incidences of hepatic "foci of cellular alterations" and liver adenoma in male animals (p=0.0089 and 0.0376, resp.; data from Table 17, page 57. A similar observation was made in livers of female mice for "foci of cellular alteration" (p=0.0019) and foci and adenoma combined (p=0.0008) while for adenoma alone there was no clear trend (p=0.1102) – all data from Table 17.
Overall, there was a significant and dose related increase in lung adenocarcinoma in male mice, supported by a dose-dependent increase in adenoma (and adenoma and carcinoma combined) in lungs of female mice as well as a dose related increase in lung adenoma in male rats despite lower doses in this species. In addition, there were indications for liver adenoma in both species. Taking further into account the chromosomal aberrations observed in vitro with metabolic activation, the structural alert identified by QSAR and the absence of a clearly negative in vivo assay for clastogenicity in a relevant target organ, classification in Carc Cat 2 appears warranted.

Dossier Submitter's Response

Thank you for your comments.

As described in the CLH report, 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.

As you note, there was a positive result with metabolic activation in the *in vitro* mammalian chromosome aberration test. However, isolated positive results are not unusual and this could be a false positive. We consider the available *in vivo* test data to be adequately reassuring. Following oral dosing of radiolabelled imiprothrin isomers, absorbed radioactivity was widely distributed to a range of organs and tissues with the liver being the site of greatest localisation, as described on page 20 of the CLH report. Since the liver is exposed, it is reasonable to presume that the bone marrow was reached in the micronucleus assay following oral exposure.

Imiprothrin has been tested in the convential bone marrow micronucleus test but we

recognise that this does not inform on the potential for highly reactive clastogenic species to be generated in tissues such as the liver or the lung.We acknowledge that your argument could point towards a plausible mechanism but since significant uncertainties remain, the argument is not considered sufficiently convincing to classify imiprothrin for carcinogenicity.
RAC's response
RAC does not consider the tumour findings in rats to warrant classification, in view of only a slight, not statistically significant increase in benign tumours in one sex only. RAC also considers the slight, not statistically significant increase in benign liver tumours in one sex of mice only not to warrant classification. The increase in lung adenocarcinoma in male mice, however, does warrant classification (in category 2), a.o. because the increase is marked and dose-related, and it has not been convincingly shown that the elevated lung tumour incidences at the highest dose level are linked to a bad health status of the exposed males, in view of the relatively moderate reductions in body weight.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2017	Germany		MemberState	10
Comment received				
The in vitro mammalian chromosome aberration test in CHO cells (page 51) was positive in the presence of S9 mix with a dose related increase in structural aberrations. Accordingly, the in vivo micronucleus test should have been performed in a metabolically active target organ. A negative bone marrow micronucleus test in mice (page 52) is not sufficient to address the concern raised by the in vitro assay. This is in particular the case, as the evidence from carcinogenicity studies point towards liver and lung as potential target organs. In addition, there was lack of evidence, that the test substance (or its relevant metabolite) has reached the bone marrow in sufficient amounts, as PCE:NCE ratio was not affected. Accordingly, when applying the criteria of the current OECD test guideline for study evaluation, the test result cannot be considered "clearly negative". The liver UDS test (page 52) is not suited to address the possibility of chromosomal changes in the liver, i.e. cannot compensate for the limitations of the micronucleus test. Further, QSAR analysis reveals the existence of a structural alert for in vivo clastogenicity within the imiprothrin structure (e.g. ToxTree v.2.6.13): SA34 H-acceptor-path3-H-acceptor, characterized by the presence of two hydrogen acceptors at a distance of 3 bonds/atoms. (Note: In an analysis by Benigni, Bossa & Worth (2010) Mutagenesis 25:335-341, 34% of 163 substances carrying this alert were true positives in in vivo MN assays) Overall, genotoxicity in somatic organs as indicated by the in vitro assay cannot be ruled out. However, the criteria for classification as Muta 2 are not met.				
Dossier Submitter's Response				
Thank you for your helpful comments, which will be taken into consideration by RAC. Whilst we appreciate the limitations of the available data, we agree that the criteria for classification as Muta. 2 are not met.				
RAC's response				
RAC notes that the available tests do not inform on the clastogenic potential in metabolically active organs like the liver or the lung. Whereas genotoxicity in somatic cells can therefore not be totally ruled out, RAC considers a conclusion for no classification justified given that the data available do not meet the criteria for classification.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	11
Comment received				
Imiprothrin should not carry the hazard classification H361d, repro cat 2. Four reports detailing expert opinions have been submitted from my company and the experts all agree that classification with H361d i not merited based on the changes observed in the rat and rabbit. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20170328 Imiprothrin CLH_REP_UK_SPS-013199-17.pdf				
Dossier Submitter's Response				
Please see response to comment number 4.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	12
Comment received				
I refer to the attached 4 (four) expert statements where each concludes that imiprothrin should not be classified for reproductive or developmental toxicity. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20160720 Position paper - imiprothrin - final.pdf				
Dossier Submitter's Response				
Please see response to comment number 1.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	13
Comment received				
This is the 4th of 4 expert statements supporting the non-classification of imiprothrin as H361d. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Imiprothrin revised final report Nov2016.pdf				
Dossier Submitter's Response				
Please see response to comment number 5.				
RAC's response				
See RAC's response to comment number 1.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON IMIPROTHRIN (ISO); [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	14
Comment received				
This is the 3rd of 4 expert statements supporting the non-classification of imiprothrin as H361d.				
Dossier Submitter's Response				
Please see response to comment number 6.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	15
Comment received				
This is the 2nd of 4 expert statements supporting the non-classification of imiprothrin as H361d. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20160728 Expert AssessmentImiprothrin1 - Eric Wood + SCUK + EHSL comments V3 - sec.pdf				
Dossier Submitter's Response				
Please see response to comment 2.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2017	Germany		MemberState	16
Comment received				
The proposal of the DS for classification in Reproductive Toxicity Category 2 (H361d), based on skeletal malformations in the rabbit but not the rat study is supported.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
RAC considers the increases in 27 pre-sacral vertebrae and in hypoplasia of frontal bone (both skeletal variations) in the rabbit developmental toxicity study at maternally toxic doses not to constitute a high level of concern; they are considered insufficient to warrant classification. As to the fusion of the nasal bone, this was only observed at a dose that was clearly above the MTD for the rabbit dams. RAC considers that effects at such a high dose level normally should not be taken into account for classification. On the total weight of evidence for the findings in rabbits, RAC does not consider classification for developmental toxicity warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.04.2017	United States		Individual	17
Comment received				
Imiprothrin should not be classified as Repro Tox 2, H361d based on findings observed at the high dose of 300 mg/kg/day in the rabbit dev tox study because this dose was above the maximum tolerated dose and resulted in extensive maternal toxicity. Toxicity was observed in the form of maternal deaths (2 of 17 does), extensive abortions (5 of 17 does, extreme body weight losses (versus body weight gains in the controls) and severely reduced food consumption (24% of control values at the end of dosing). These findings obviate consideration of fetal effects observed at this dose.				
Dossier Submitter's Response				
Thank you for your comments. Our reasoning for proposing classification for developmental effects has been explained in the CLH report alongside the data. Fusion of the nasal bone was considered to be a malformation. This finding, in combination with hypoplasia of the frontal bone, gave rise to a cause for concern for craniofacial development. Maternal toxicity was covered in the CLH report. Had the fusion of the nasal bone and hypoplasia occurred in the absence of maternal toxicity, it was considered that classification for reproductive toxicity in Category 1B could have been justified. Taking the maternal toxicity into consideration reduces the level of concern and classification in Category 2 was considered appropriate.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
27.04.2017	United Kingdom		Individual	18
Comment received				
The hazard classification of Repro Category 2 has been proposed by the UK eCA for imiprothrin based on the finding of fused nasal bones observed in a small number of foetuses in the rabbit embryofoetal developmental toxicity study at the high dose level of 300 mg/kg bwt /day. The fusion was described as partial, affecting only the anterior part of the nasal bones and it was considered by the Japanese scientists who conducted the study to be a minor finding. No evidence of fusion or abnormality of any of the other cranial bones was observed. At this dose level severe maternal toxicity was recorded, evidenced by maternal death, abortion, and, in surviving females, an almost total lack of appetite, and marked loss of body weight. In view of the severely compromised condition of the dams, this dose level should be considered as inappropriate/unsuitable for assessment of developmental effects and findings at this level should not be used for classification purposes. At the lower dose level of 100 mg/kg bwt/day, which gave rise to a lesser degree of maternal toxicity, viz. slight reductions in food intake and body weight gain, there were no instances of foetuses with fused nasal bones. The short-term Acceptable Exposure Level (AEL) for imiprothrin quoted in Document IIA of the Competent Authority Report UK (May 2016) is 0.3 mg/kg bwt/day, whilst the long-term AEL is 0.1 mg/kg bwt /day. With reference to these figures, and on a body weight basis, the dose of 100 mg/kg bwt /day, at which no fusion of nasal bones was recorded, represents x300 the short-term AEL and x1000 the long-term AEL. It is considered, therefore, that on the basis of the results				

obtained at 100 mg/kg/bwt/day, imiprothrin should not receive any classification for reproductive toxicity.
Dossier Submitter's Response
Thank you for your comments. Our reasoning for proposing classification for developmental effects has been explained in the CLH report alongside the data. Fusion of the nasal bone was considered to be a malformation. This finding, in combination with hypoplasia of the frontal bone, gave rise to a cause for concern for craniofacial development. Maternal toxicity was covered in the CLH report. Had the fusion of the nasal bone and hypoplasia occurred in the absence of maternal toxicity, it was considered that classification for reproductive toxicity in Category 1B could have been justified. Taking the maternal toxicity into consideration reduces the level of concern and classification in Category 2 was considered appropriate.
RAC's response
See RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
04.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	19
Comment received				
The report (attached) challenges the CLH proposal relating to developmental toxicity - H361d. The report clearly demonstrates that imiprothrin should not be assigned the hazard classification H361d, Repro Cat 2. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20170322 Imiprothrin Final Expert opinion - Tesh.pdf				
Dossier Submitter's Response				
Please refer to response to comment number 3.				
RAC's response				
See RAC's response to comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	United Kingdom	Sumitomo Chemical (UK) PLC	Company-Importer	20
Comment received				
In view of the information found in the attached document, imiprothrin should not be classified with the hazard statement H361d (Suspected of damaging the unborn child) and associated pictogram GHS08. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20170428 Statement on Imiprothrin CLH - JR + KG.pdf				
Dossier Submitter's Response				
Thank you for your comments. Our reasoning for proposing classification for developmental effects has been explained in the CLH report alongside the data. Fusion of the nasal bone was considered to be a malformation. This finding, in combination with hypoplasia of the frontal bone, gave rise to a cause for concern for craniofacial development. Maternal toxicity was covered in the CLH report. Had the fusion of the nasal bone and				

hypoplasia occurred in the absence of maternal toxicity, it was considered that classification for reproductive toxicity in Category 1B could have been justified. Taking the maternal toxicity into consideration reduces the level of concern and classification in Category 2 was considered appropriate.
RAC's response
See RAC's response to comment number 1.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	France		MemberState	21
Comment received				
LD50 in males (mouse) is reported at 724 mg/kg bw in the summary table (page 22) or 725mg/kg (page 24) whereas deaths were reported at ≥760mg/kg in males (page 24). Please clarify the number of deaths at 760 mg/kg.				
Dossier Submitter's Response				
Thank you for your comments. The LD50 value in male mice was 724mg/kg bw/day. No male deaths were reported at 600 mg/kg bw/day. 3/5 males died at 760 mg/kg bw/day.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2017	Germany		MemberState	22
Comment received				
The proposal of the DS for classification in Acute Toxicity Category 4 for oral and inhalation routes is supported. However, in particular the presentation of the data on inhalation toxicity in separate chapters 4.2.1.2 and 4.2.1.4 was confusing.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	France		MemberState	23
Comment received				
Page 30 4.3.2 Comparison with criteria "In the range with classification with STOT RE 2 (…)". It seems to be STOT SE. Could you please clarify.				
Dossier Submitter's Response				
Thank you for your comment. This was a typographical error and should read, "…in the range for classification with STOT SE 2…"				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2017	Germany		MemberState	24
Comment received				
Pages 29 ff: Classification in STOT SE1 should be considered. Clinical signs of (acute) neurotoxicity appear following inhalation at clearly sublethal doses and below the Guidance Value of 1000 mg/m3 x 4h. Please refer to the additional document entitled "Imiprothrin - CAR for CIRCA - Doc II-A - May 20164889653254961313523.DOC" Chapter 3.5.3 from page 36 and for more detail document "Imiprothrin - Toxicology - Doc IIIA Sections A6.1-A6.12 - June 20102918278959916688883.doc" Section A6.3.3 from page 106 to 114. "A 28-day study has been conducted in rats to investigate the repeated dose toxicity of imiprothrin following inhalation exposure. Treatment-related toxicity was reported in animals of the high dose group only (186 mg/m3). There were no mortalities; however, clinical signs of toxicity characteristic of neurotoxicity were observed. These include decreased spontaneous activity, tiptoe gait, hypersensitivity and tremor. Irregular respiration, nasal discharge, salivation and urinary incontinence were also seen."				
Dossier Submitter's Response				
Thank you for your comment. The findings from the 28 day study do not appear to describe clearly the effects observed after a single exposure. Considering all of the data, and the nature of the general acute hazard, the UK CA felt that Acute Tox 4 was adequate.				
RAC's response				
Neurotoxicity is consistently observed across all acute oral and inhalation studies, at both lethal and non-lethal doses. The lowest non-lethal doses at which the neurotoxic effects are observed fall within the guidance values for STOT SE 2 ($300 < C \leq 2000$ mg/kg bw) for the oral route and for STOT SE 1 (≤ 1 mg/L) for the inhalation route. RAC however notes that details on the severity and incidence of each finding in the acute toxicity studies is missing, that most findings were transient in nature, and that their relevance to fulfil the severity criteria for STOT SE 1/2 is not totally clear. Nevertheless, given the consistent picture, and further supported by the fact that imiprothrin belongs to the group of pyrethroids, which is known to induce neurotoxic effects, RAC considers it important to flag the neurotoxic properties of imiprothrin. Overall, RAC therefore proposes to classify imiprothrin with STOT SE 2; H371 for its effects on the nervous system by the oral and inhalation route.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	France		MemberState	25
Comment received				
We support the classification proposal H400 with acute M factor 10 and H410 with chronic M factor 10. We also agree to use the surrogate approach to determine the chronic classification due to the lack of reliable chronic data.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON IMIPROTHRIN (ISO); [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-CIS-CHRYSANTHEMATE; [2,4-DIOXO-(2-PROPYN-1-YL)IMIDAZOLIDIN-3-YL]METHYL(1R)-TRANS-CHRYSANTHEMATE

PUBLIC ATTACHMENTS
1. 20170428 Statement on Imiprothrin CLH - JR + KG.pdf [Please refer to comment No. 20]
2. 20170328 Imiprothrin CLH_REP_UK_SPS-013199-17.pdf [Please refer to comment No. 4, 11]

CONFIDENTIAL ATTACHMENTS
1. 20170322 Imiprothrin Final Expert opinion - Tesh.pdf [Please refer to comment No. 3, 19]
2. Imiprothrin revised final report Nov2016.pdf [Please refer to comment No. 5, 13]
3. 20160728 Expert AssessmentImiprothrin1 - Eric Wood + SCUK + EHSL comments V3 - sec.pdf [Please refer to comment No. 2, 15]
4. 20160720 Position paper - imiprothrin - final.pdf [Please refer to comment No. 1, 12]