Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

imazamox (ISO); (RS)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid

EC Number: -

CAS Number: 114311-32-9

CLH-O-0000006726-66-01/F

Adopted

5 December 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON IMAZAMOX (ISO); (RS)-2-(4-ISOPROPYL-4-METHYL-5-OXO-2-IMIDAZOLIN-2-YL)-5-METHOXYMETHYLNICOTINIC ACID

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: Imazamox (ISO); (RS)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid
EC number: -
CAS number: 114311-32-9
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France	BASF	Company-Manufacturer	1
Comment received				
no comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Sweden		MemberState	2
Comment received				
The SE CA agrees with the proposed classification of Imazamox in Repr. 2 H361d based on the observed (rather slight) incidences of each of the fetal malformations/variants in rabbits in absence of maternal toxicity at 600 and 900 mg/kg bw/day.				
Dossier Submitter's Response				
Noted. Thank you for your support.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Belgium		MemberState	3
Comment received				
Fertility				

BE CA agrees with the no classification proposal based on the absence of adverse effects on sexual function and fertility in a two generation reproductive toxicity in rat. We however note that the percentage of mating males in the F1 generation controls (21/30, 70%) was below the historical control data's (70.8-100%, 88.2%). Developmental toxicity Adverse effects on developmental toxicity were assessed in two different studies. In the first OECD 414 study in Sprague-Dawley rats (25 females/group, doses 0 – 100 – 500 and 1000 mg/kg bw/day), maternal toxicity was reported at the highest dose with a decreased body weight and body weight gain. In the second study, and OECD 414 study in New Zealand rabbit (20 females/group, 0 – 300 – 600 and 900 mg/kg bw/day), effects in pups were observed from 600 mg/kg bw/day and included the reporting of malformations such as hemivertebrae and absent intermediate lobe of the lungs. At the same dose level, no clear maternal toxicity was reported as only slight reduced food consumption was noted in dams. At the highest dose of 900 mg/kg bw/day, dams showed 20% decreased body weight gain and 15% decreased food consumption. Other alterations were also reported at very low incidence. BECA considers that the main findings for classification are the dose-dependent increase in hemivertebrae and absent lobe of the lungs. Takin into consideration that the malformations were only observed in rabbit at low incidences, a Repr 2 H361d is supported.
Dossier Submitter's Response
Noted. Thank you for your support.
RAC's response
The support is noted, both for no classification for effects on fertility and for Repr Cat 2 for developmental toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2019	Germany		MemberState	4
Comment received				
We strongly support the proposal made by the dossier submitter to additionally classify the substance as Repr. 2; H361d.				
Dossier Submitter's Response				
Noted. Thank you for your support.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France	BASF	Company-Manufacturer	5
Comment received				
1) The CLH report states that the relevance of the provided HCD on fetal alterations in the rabbit developmental toxicity study, could be questionable, since the studies included in				

the HCD were performed by several routes of administration. In our opinion the crucial confounding factors influencing the spectrum of fetal morphological variability are genetic and age differences, followed by environmental conditions. Therefore, a historical database preferably considers animal strain, age and housing conditions (temperature, humidity, caging, lighting, feed, water etc.), making the database representative of the used animal population. The listed confounding factors have all been considered for the provided HCD, which makes them a valuable tool to understand the range of normal for the discussed fetal alterations. At second rate, an ideal historical database may also consider the amount and type of handling of the animals, characterizing the type and amount of environmental stress the animals were exposed to. Merging studies using different administration routes into one HCD file just merges different types of environmental stress, which is not ideal but shouldn´t be a big problem if accepted that genetic and age differences as drivers of fetal morphological background variability are dominant over environmental stress. (Ref.: E. Mylchreest and S. B. Harris, Historical Control Data in Reproductive and Developmental Toxicity Studies in: Teratogenicity Testing – Methods and Protocols p. 275 - 294, ed. P. Barrow, Humana Press 2013) (CLH report 10.10.4, Study 3, page 26/27)

2) BASF considers that the increased incidence of absent intermediate lung lobe was within the expected spontaneously occurring background range for this strain of rabbit at all dose levels. As described previously in the position paper provided by the study director of the developmental toxicity study, the laboratory 'examined the does for the incidence of this variation in adult rabbits' and the finding of absent intermediate lung lobe was found 'to be common variation present in adult rabbits, with no effect on the adult rabbits'. Due to the variable occurrence of this finding among the different studies it is considered more relevant to compare with the historical control range rather than the mean HCD in order to adequately reflect the normal range of variation. Thus, the finding of absent intermediate lung lobe is not considered treatment-related for imazamox but of spontaneous origin in this strain of rabbit. (CLH report 10.10.4, Study 3, page 27/28; and 10.10.6 page 33)

3) BASF would like to mention that the historical control data that were presented within the original report of the developmental toxicity study in rabbits covering the period 1990- June 1992 were not taken into account in the CLH report. The CLH Report states on page 29 that some vertebral findings exceeded the available HCD or were not reported in these HCD. However, these findings are reported in the respective HCD provided within the original study report (HCD covering the period 1990 – June 1992, see report page 240ff) and they should be given consideration. Thus, the finding of thoracic hemivertebrae (1 fetus at 600 mg/kg bw/d and 2 fetuses from 1 litter at 900 mg/kg bw/d) is considered to be fully covered by available HCD with a range number of 0-1 litter and 0-2 fetuses (please refer to HCD from 1990 to 1992 provided in the original study report on pages 249ff). Likewise, the findings of asymmetric thoracic centrum (2 fetuses from 2 litters at 900 mg/kg bw/d; HCD number litter/fetal range: 0-2/0-2), sacral arch not ossified (1 fetus at 900 mg/kg bw/d; HCD number litter/fetal range: 0-1/0-1), as well as unossified rib (1 fetus at 900 mg/kg bw/d; HCD number litter/fetal range: 0-1/0-1) are also considered to be fully covered by the same historical control dataset (1990-1992, please refer to original study report) and not treatment-related. (CLH report 10.10.4, Study 3, page 29)

4) BASF would like to highlight that the finding of cervical hemivertebrae does sporadically occur in the HCD set provided by the laboratory with a single incidence in control groups, i.e. in one study in the HCD presented in the original study report covering the period from 1990- June 1992, as well as in 2 studies in the pdf compiling

HCD studies from June 1997 to June 1999. two studies with single fetuses in control group with this effect. Thus, a single incidence of this malformation, as observed in the mid dose of the imazamox rabbit study, was sporadically seen in the historical control groups. (CLH report 10.10.4, Study 3, page 29)

Dossier Submitter's Response

1) Although the DS agrees with the applicant that genetic and age differences are the main confounding factors influencing background incidences of fetal anomalies, environmental conditions should not be excluded from the analysis of relevance of HCD. The DS considered the HCD of low relevance not only because of the different routes of administration (oral, intravenous, intramuscular, intradermal, intraperitoneal, dermal subcutaneous) used for the studies included in the HCD, but also because of the different vehicles, different administration periods … leading to different environmental stress/conditions which can influence the background incidences of foetal alterations. As the HCD have been provided by the laboratory performing the study with imazamox, it can be expected that the same housing conditions were used. It is also noted that the age of dams at C-section is very variable among studies (178 to 398 days considering the databases 1992-1995 and 1994-1996).
The DS considered therefore that the avaible HCD can give information on the rarity of an alteration and could be considered in a WoE assessment taking also into account e.g. the background incidences observed in the concurrent control group, the dose-relationship and the statistical significance of a finding.

2) Although incidences of agenesis of the intermediate lobe of the lung lied within HCD ranges, they clearly exceeded the mean value. Taking into account the low relevance of the HCD, the clear dose-relationship of this finding and the statistical significance reported at the highest dose level, the DS considered this finding as treatment-related. This was also the outcome of the peer-review of imazamox in the context of its renewal under Regulation (EC) No 1107/2009 (EFSA Journal 2016;14(03):4432) and the conclusion of the evaluation conducted by the Joint FAO/WHO Meeting on Pesticides Residues (JMPR) (IMAZAMOX 209-239 JMPR 2014).

3) The DS agreed that HCD covering the period 1990-June 1992 were available in the study report and could be considered acceptable in terms of covering period. Nevertheless, except the strain of the rabbits and the time period of the studies included in the HCD, no other data is available to conclude on their relevance (no description of the studies as available for the other files 1992-1995 and 1994-1996) and these HCD should therefore be considered of low relevance. As highlighted by the applicant in its comment, some findings were reported in the 1990-June 1992 HCD with higher incidence than in the HCD available in the CLH report:

Dose group (mg/kg bw/d)		**0**	**300**	**600**	**900**	**HCD 1990-1992 49 studies**	
						Total	*Range/study*
<u>Vertebrae</u> Thoracic, hemivertebra							
Litter incidence	N (%)	0	0	1 (7.1)	1 (5.3)	11 (1.39)	0-1 (0-7.1)
Fetal incidence	N (%)	0	0	1 (0.9) [f]	**2 (1.2) [i,k]**	12 (0.20)	0-2 (0-1.5)
						Total	*Range/study*
<u>Vertebrae</u> Thoracic, centrum, assymetric							
Litter incidence	N (%)	0	0	0	**2 (10.5)**	8 (1.01)	0-2 (0-11.8)
Fetal incidence	N (%)	0	0	0	**2 (1.2) [h,k]**	8 (0.14)	0-2 (0-1.7)

						Total	*Range/study*
Vertebrae							
Sacral, arch, not ossified							
Litter incidence	N (%)	0	0	0	**1 (5.3)**	1 (0.13)	0-1 (0-5.6)
Fetal incidence	N (%)	0	0	0	**1 (0.6)** [j]	1 (0.02)	0-1 (0-0.7)
						Total	*Range/study*
Ribs							
Not ossified							
Litter incidence	N (%)	0	0	0	**1 (5.3)**	2 (0.25)	0-1 (0-5.9)
Fetal incidence	N (%)	0	0	0	**1 (0.6)** [k]	2 (0.03)	0-1 (0-0.8)

For these findings, the incidences observed at the highest dose group with imazamox were the same as the upper range of the HCD but were far above the means of the HCD. These HCD of low relevance further confirmed the rarity of these findings.

4) The DS confirmed the occurrence of cervical hemivertebrae in 1 study out of 49 from 1990-June 1992: mean litter incidence = 0.13%, mean fetal incidence = 0.02%, litter range = 0-1 (0-5.3%), fetal range = 0-1 (0-0.6%). The DS noted that the HCD provided for the period 1997-1999 were not relevant considering the dates of the study with imazamox. Considering that cervical hemivertebrae are rare malformations and considering the dose-relationship and the lack of such effect in the concurrent control group, the DS considered that cervical hemivertebrae were treatment-related and toxicologically relevant form the intermediate dose level onwards. This was also the outcome of the peer-review of imazamox in the context of its renewal under Regulation (EC) No 1107/2009 (EFSA Journal 2016;14(03):4432) and the conclusion of the evaluation conducted by the Joint FAO/WHO Meeting on Pesticides Residues (JMPR) (IMAZAMOX 209-239 JMPR 2014).

Conclusion: Considering the comments provided by the applicant BASF, the DS considered that no change of the previous conclusions are needed. Classification of imazamox as Repr 2 H361d is warranted, based mainly on cervical hemivertebrae and absence of the intermediate lobe of the lungs observed in rabbits.

RAC's response

1) RAC agrees that genetic and age differences are major factors affecting the incidence of malformations. However, as pointed out by the DS, other factors may also affect the incidences, such as stress potentially caused by many different reasons and group size (big studies have a higher ability to pick up rare malformations). Furthermore, it is not clear to RAC if there are overlaps between the different sets of HCD provided, such that the same study may be used in several sets of HCD. Finally, RAC supports only using HCD which comes from studies conducted $\pm$5 years of the study (CLP guidance), and thus that one of the data sets should not be used because of not fulfilling this criterion.
2) Based on the information on missing lung lobes being observed in adult rabbits of this strain, RAC is less concerned with the findings of missing lung lobe in the foetuses. See also the RAC opinion.
3) Even if a malformation is occasionally observed in controls, the dose-responses observed, the increased incidences, and the overall spectrum of malformations observed in this case support a substance-related effect.
4) See the above response. RAC supports the response from the dossier submitter.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2019	Germany		MemberState	6
Comment received				
We agree with the proposal of classification for environmental hazards as Aquatic acute 1 (H400), Aquatic chronic 1 (H410) and the acute/chronic M-factor of 10.				
Dossier Submitter's Response				
Noted. Thank you for your agreement.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	United Kingdom		MemberState	7
Comment received				
Imazamox (EC: -; CAS: 114311-32-9) Toxicity to aquatic plants: Dorner, 2013b and 2013c: We note the lowest ErC10 endpoints are based on 'dry weight' rather than the primary observation endpoint 'frond number'. We wonder if frond number and dry weight endpoints are considered to have the same significance and both relevant for hazard classification. In this instance and considering the substance mode of action as an ALS inhibitor, we consider dry weight endpoints relevant for hazard classification. Dorner, 2013c: We note that 7day concentrations were less than 80% of nominal. Are mean measured (water phase) endpoints available? Backfish, 2013f: We note that analytical concentrations were less than 80% of nominal. Are mean measured endpoints available? Hoberg et al, 1995e: We note that only endpoints based on biomass/density are included. As Lemna appear to be the most sensitive data, is it possible to calculate growth rate endpoints from study data? Bioaccumulation: As a side, we note uncertainty is associated with the Kow values determined using a shake flask method because imazamox is surface active.				
Dossier Submitter's Response				
Dorner, 2013b and 2013c: All E_rC_{10} or E_rC_{50} endpoints are considered relevant for hazard classification. In our point of view, the lowest value has to be considered for the classification proposal. Dorner, 2013c: The mean measured concentrations of imazamox ranged from 94% to 100% of nominal concentrations at test initiation and from 74% to 80% of nominal at test termination. This means that the actual concentration at test termination are equal to or only slightly below 80% of nominal. Morevover, the reliability of this study for hazard classification is considered to be reduced due the presence of sediment in this toxicity study on *Lemna gibba* (non-rooted macrophyte). Thus, calculation of endpoints based on mean measured				

concentrations is not considered necessary as this study is not used to propose the environmental classification. Backfish, 2013f: The mean measured concentrations of imazamox ranged from 105% to 132% of nominal concentrations at test initiation and from 117% to 155% of nominal at test termination. Thus the results based on nominal concentrations are considered acceptable and calculation of endpoints based on measured concentrations are not necessary. Hoberg et al, 1995e: No endpoint values based on growth rate is proposed in the report of this study. Moreover, some deviations from the recommendations given in current guidelines were noted (i.e. test duration of 14 days instead of 7 days as recommended by the OECD guideline 221 (2006)). Thus this study is considered to be less reliable for the hazard classification and the estimation of endpoints based on growth rate from this study is not considered necessary as this study is not used to propose the environmental classification. Bioaccumulation: Considering that the BCF value of imazamox is estimated to be below 1 and since chronic toxicity data and degradation data in aquatic system are available, the Kow value of imazamox is of less importance for classification purpose.
RAC's response
Thank you for the clarifications. RAC notes that the toxicity data for effects on 'dry weight' and 'frond number' are very similar, and without consequence for the classification. The concern for an uncertain log Kow, potentially caused by imazamox being surface active, is noted in the opinion, but the low potential for bioaccumulation is also supported by the fish bioconcentration study (BCF<1).

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Belgium		MemberState	8
Comment received				
BE CA supports the proposed environmental classification with Aquatic Acute 1, H400 with Macute = 10 Aquatic Chronic 1, H410 with Mchronic = 10				
Dossier Submitter's Response				
Noted. Thank you for your agreement.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France	BASF	Company-Manufacturer	9
Comment received				
no comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				