Committee for Risk Assessment

RAC

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

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CLH-O-0000006726-66-01/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 harmonised classification and labelling (CLH) of:

Chemical 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**

The proposal was submitted by **France** and received by RAC on **7 February 2019**.

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

PROCESS FOR ADOPTION OF THE OPINION

France 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 **18 March 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **24 May 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bert-Ove Lund**

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 harmonised classification and labelling was adopted on 5 December 2019 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 and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	613-208-00-7	imazamox (ISO); (*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid	-	114311-32-9	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410			
Dossier submitters proposal	613-208-00-7	imazamox (ISO); (*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid	-	114311-32-9	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Repr. 2	**Retain** H400 H410 **Add** H361d	**Retain** GHS09 Wng **Add** GHS08	**Retain** H410 **Add** H361d		**Add** M=10 M=10	
RAC opinion	613-208-00-7	imazamox (ISO); (*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid	-	114311-32-9	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Repr. 2	**Retain** H400 H410 **Add** H361d	**Retain** GHS09 Wng **Add** GHS08	**Retain** H410 **Add** H361d		**Add** M=10 M=10	
Resulting entry in Annex VI if agreed by COM	613-208-00-7	imazamox (ISO); (*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid	-	114311-32-9	Repr. 2 Aquatic Acute 1 Aquatic Chronic 1	H361d H400 H410	GHS08 GHS09 Wng	H361d H410		M=10 M=10	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Imazamox is a herbicide acting by inhibiting an enzyme (acetohydroxyacid synthase) present in plants and bacteria, but not in animals or humans. Imazamox is highly water soluble, and rather resistant towards degradation in environmental media.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Adverse effects on sexual function and fertility

In the rat 2-generation study with imazamox, there were no treatment–related adverse effects on fertility or reproductive performance up to the highest tested dose of 1469 mg/kg bw/d. Moreover, in the whole toxicity database, the reproductive organs were not shown to be the target of imazamox up to the highest tested doses. Indeed, imazamox showed no short-term and long-term toxicity after oral exposure to rats, mice and dogs up to the limit top dose level tested in each study. Therefore, according to the Dossier Submitter (DS), based on the available data, no classification for adverse effects on sexual function and fertility is warranted for imazamox.

Developmental toxicity

No effects were observed in the rat studies, but several fetal alterations were observed in the rabbit foetuses in the developmental toxicity study. Skeletal malformations were observed and consisted mainly of dose-related increased incidence of cervical hemi-vertebrae, which is considered a very rare malformation not reported in the historical control data (HCD). One foetus presented cervical hemi-vertebrae in the intermediate dose group (600 mg/kg/day) and 3 foetuses from 2 different litters were affected at the highest dose level (900 mg/kg/day). In addition, two other skeletal malformations were reported: one fetus with thoracic hemi-vertebrae in the intermediate group and two foetuses in the high dose groups (in one litter in each group) as well as a reduced number of cervical vertebrae in one foetus in the high dose group. Other isolated skeletal alterations, considered rare in view of the incidences reported in the HCD, were observed at the high dose level.

A fetal gross external malformation, i.e. fused digits of the hind paw, was reported in one foetus in the high dose level. No occurrence of this finding was reported in the HCD.

Considering fetal soft tissue alterations, a dose-related increased incidence of absent intermediate lobe of the lungs was observed in foetuses from different litters in the intermediate and high dose level, the fetal incidence reaching a statistical significance at the highest tested dose.

In the rabbits of the intermediate dose group, a decreased food consumption was observed without consequences on body weight and body weight gains. At the highest tested dose, the maternal body weight gain was decreased by about 20%, without reaching statistical significance.

The fetal anomalies are not considered by the DS to be related to delayed development or secondary nonspecific consequences of maternal toxicity. Therefore, classification of imazamox for developmental toxicity is warranted (based on cervical hemivertebrae and other skeletal malformations/alterations, as well as absence of the intermediate lobe of the lungs), but the DS argued that due to the rather slight incidences and the absence of developmental toxicity in rats, classification in category 2 seems most appropriate (Repr 2; H361d).

Effects on or via lactation

In the 2-generation study performed with imazamox, no adverse effect was observed in the offspring. There was no indication of impaired nursing behaviour or any direct, adverse effect on the offspring due to transfer of the chemical via the milk or to the quality of the milk. Thus, the DS concluded that there were no effects to warrant classification of imazamox for effects on or via lactation.

Comments received during public consultation

Only one comment was received on adverse effects on sexual function and fertility, where a MSCA supported no classification.

Four comments were received in relation to developmental toxicity, with three MSCA supporting classification in category 2 based on the low incidences of the malformations in the rabbit study (conducted in 1993). One company-manufacturer argued that:

1. The HCD indeed cover studies using several routes of exposure, but that will not make the HCD less reliable, as stated by the DS, because it is genetic and age differences that are drivers of morphological variability (Mylchreest and 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).

2. The absence of an intermediate lung lobe was within the HCD and thus of spontaneous origin. In addition, findings of absence of intermediate lung lobe in adult, healthy rabbits in the laboratory conducting the study show that this is not a malformation.

3. There are HCD from 1990-1992 that are relevant and that show that thoracic hemi-vertebrae, asymmetric thoracic centrum, unossified sacral arch, and unossified rib are fully covered by the HCD, showing that those findings are not treatment-related.

4. Cervical hemi-vertebrae also occur in the HCD from 1990-1992 and 1997-1999, showing that the single incidence in the intermediate dose group could be a chance finding.

The dossier submitter responded that:

1. Although genetic and age differences are import determinants for morphological variations, the HCD covers not only different routes of exposure, but also different vehicles, administration periods, and age of animals. HCD should therefore be considered in a WoE assessment together with effects in the concurrent control group, dose-response, and statistical significance.

2. The agenesis of the intermediate lung lobe clearly exceeded the mean value, and the clear dose-response and statistical significance support a treatment-relation, which was also the conclusion of EFSA and FAO/WHO (IMAZAMOX 209-239 JMPR 2014).

3. HCD for the period 1990-1992 was indeed available, but as the only information about the data base was the rabbit strain and time period, the lack of further information make them

less relevant. Although of low relevance, the HCD indicates that thoracic hemi-vertebrae (12 foetuses), asymmetric thoracic centrum (8 foetuses), unossified sacral arch (1 foetuses), and unossified rib (2 foetuses) occasionally have been observed in the 49 studies conducted during that period, but the incidences seen with imazamox clearly exceed the means.

4. It is agreed that cervical hemi-vertebrae was observed in one out of 49 studies conducted 1990-1992, showing that it is a rare malformation. Considering the dose-response and the lack of such effects in the concurrent control, the effect is treatment-related and toxicologically relevant from the intermediate dose level (600 mg/kg/day), which was also the conclusion of EFSA and FAO/WHO. It was also noted that the HCD from the period 1997-1999 is not relevant, as the study was conducted in 1993.

No comments were received in relation to effects on or via lactation.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

A two-generation study in rats performed according to OECD TG416 and following GLP is available for the assessment (Anonymous, 1995). The rats were exposed via the diet to 0, 1000, 10000, and 20000 ppm imazamox, corresponding to 0, 50-143, 497-1487, and 984-3129 mg/kg/day, with the lower end representing the post-mating period and the upper end of the range the lactation period. As there were no effects on reproductive outcome or on pups, RAC concurs with the DS that **no classification is warranted for adverse effects on sexual function and fertility**.

Developmental toxicity

The dossier describes two full developmental toxicity studies in rats (Anonymous 1994) and rabbits (Anonymous, 1995), conducted according to OECD TG414 and GLP.

The rat study used dose levels of 100, 500, and 1000 mg/kg/day. A decreased body weight gain at the top dose was noted in the dams during the exposure period (-11% gestation days 6-16), but no treatment-related adverse finding were observed in the foetuses.

A dose-finding study in rabbits was conducted using doses of 500, 750, and 1000 mg/kg/day, showing a decreased maternal body weight gain of 60% during gestation days 7-29 at the top dose together with a non-significant decrease in litter size (4.3±2.8 vs 6.3±1.9 in controls). Based on the rather strong effect on the maternal body weight at 1000 mg/kg/day, and no effects at 750 mg/kg/day, the subsequent full study was conducted using a top dose of 900 mg/kg/day.

Groups of 20 pregnant New Zealand White rabbits were administered imazamox orally via stomach tube once daily on day 7 to 19 of gestation at 0, 300, 600, and 900 mg/kg/day in an aqueous suspension of 0.5% carboxymethylcellulose. Feed consumption was reduced by 16% and body weight gain non-statistically reduced by 20% at the top dose. There were no effects on litter averages for corpora lutea, implantations, litter sizes, live foetuses, early and late resorptions, fetal body weight and sex ratio. Further examinations of foetuses have shown alterations, and the most relevant will be described below, together with the HCD for those alterations. However, there are uncertainties as regards the HCD. HCD had first been submitted as three separate files covering partly overlapping time periods (June 1992-June1995; ≤60 studies, June 1994-June 1996; ≤37 studies, and June 1997-June 1999; unknown number of studies). RAC is of the opinion that only the two first sets of HCD are acceptable as the study was conducted in autumn 1993. During the preparation of the CLH dossier, a revised set of HCD covering 1992-1997 (60 studies) was submitted by industry. The DS found the HCD to be of low relevance, as they cover studies using different routes of exposure, vehicles, gestational periods,

group sizes, and age of animals. Industry has commented that these differences are not relevant as genetics and age are the most important determinants for morphological alterations. The view of RAC is that different ways of handling animals (e.g., intravenous injections) can be of importance if they elicit stress, and that group size is important with respect to finding rare malformations. Some other differences mentioned above are less likely to affect the pattern of serious malformations. However, the overlapping time periods may potentially result in some incidences being counted twice, which is of importance when discussing rare malformations. The provided HCD will be considered in conjunction with concurrent control incidences.

In the gross external examination of the foetuses, there was one finding each of a short tail and fused first and second digits in the left hindpaw at the top dose. As to short tail, there are no such cases in concurrent controls, low or mid dose groups, so it is clearly a rare malformation. As presented in Table 1, 14 cases of short tail has been seen in the 97 studies that constitutes the HCD, further supporting that it is rare, but also indicating that a spontaneous etiology cannot be ruled out. In contrast, there are no observations at all of fused digits in hindpaw among the 97 studies, increasing the concern for this malformation.

Table 1: *Fetal gross external alterations (table 10.10.4-12 of the CLH report)*

Dose group (mg/kg bw/d)	**0**	**300**	**600**	**900**	**HCD 1992-1995 60 studies**		**HCD 1994-1996 37 studies**	
Litter evaluated	**20**	**18**	**14**	**19**	**701**		**405**	
					Total	*Range/study*	*Total*	*Range/study*
Hindpaw, Digits, fused								
Litter incidence N (%)	0	0	0	1 (5.3)	-	-	-	-
Fetal incidence N (%)	0	0	0	1 (0.6)	-	-	-	-
					Total	*Range/study*	*Total*	*Range/study*
Tail, Short								
Litter incidence N (%)	0	0	0	1 (5.3)	6 (0.86)	0-1 (0-25.0)	5 (1.23)	0-1 (0-25.0)
Fetal incidence N (%)	0	0	0	1 (0.6)	9 (0.17)	0-4 (0-3.0)	5 (0.15)	0-1 (0-3.0)

Among the fetal soft tissue alterations, only the agenesis of intermediate lung lobe seems relevant. Although one case is occurring in the control group, and many cases in the HCD, the finding is supported by a dose-response (1, 0, 2, 6 cases, and 1, 0, 2, 4 litters affected at 0, 300, 600, and 900 mg/kg/day, respectively), and the incidence being much higher than the mean incidence in the 53 studies (Table 2). However, information in the public consultation from the manufacturer shows that adult rabbits often lack the intermediate lung lobe. This was also reported by Stadler *et al*. (1983). The finding therefore rather seems to be an alteration than a malformation, and thus contributes less to the classification issue. The second set of HCD covering 1992-1997 (60 studies), showed 140 cases in 60 studies, thus supporting the first set of HCD.

Table 2: *Fetal soft tissue alterations (extract from table 10.10.4-13 in the CLH report)*

Dose group (mg/kg bw/d)	**0**	**300**	**600**	**900**	**HCD 1992-1995 36 studies**		**HCD 1994-1996 17 studies**	
Litter evaluated N	20	18	14	19	593		297	
					Total	*Range/study*	*Total*	*Range/study*
Lung, Intermediate lobe, absent								
Litter incidence N (%)	1 (5.0)	0	2 (14.3)	4 (21.0)	53 (8.94)[b]	0-5 (0-29.4)[b]	30 (10.1)[b]	0-5 (0-29.4)[b]
Fetal incidence N (%)	1 (0.6)	0	2 (1.7)	**6 (3.8)****	76 (1.70)[b]	0-13 (0-6.9)[b]	41 (1.69)[b]	0-9 (0-6.9)[b]

** significantly different from the vehicle control group value ($p \leq 0.01$)

[b] One or more lobes, partial or complete agenesis (i.e. not only "absence of the intermediate lobe of the lung", which is the finding observed with imazamox)

Several skeletal alterations were observed in rabbit foetuses, with the most relevant concerning the vertebrae.
A simplified description of the finding is that the main effects on cervical and thoracic vertebrae consisted of one case of cervical and one case of thoracic hemi-vertebrae in the mid dose group (in total 2) and three cases of cervical and two of thoracic hemi-vertebrae in the top dose (in total 5). Thus, the occurrence of the malformation hemi-vertebrae is supported by dose-response, and clearly very rare as indicated by no findings of cervical hemi-vertebrae and 10 cases of thoracic hemi-vertebrae in 53 studies from the HCD. The substance-related findings on vertebrae are supported by finding rare fused cervical centra/arches, small arch in cervical vertebrae, asymmetric thoracic centrum, unossified sacral arch (see HCD in the table 3 below), and possibly short tail (table 1). Some of the supporting findings above may be alterations rather than malformations, but they support that the low incidences are indeed substance-related effects on the development of the vertebrae.

Table 3: *A selection of fetal skeletal alterations (extract from table 10.10.4-15 in the CLH report). Note that no effects were seen at the low dose (300 mg/kg/day), and that the table therefore does not include that dose level.*

Dose group (mg/kg bw/d)	**0**	**600**	**900**	**HCD 1992-1995 35 studies**		**HCD 1994-1996 18 studies**	
Litter evaluated	20	14	19	586		316	
Vertebrae Cervical, hemivertebrae				*Total*	*Range/study*	*Total*	*Range/study*
Litter incidence N(%)	0	**1 (7.1)**	**2 (10.5)**	-	-	-	-
Fetal incidence N(%)	0	**1 (0.9)**	**3 (1.9)[h,i,k]**	-	-	-	-
Vertebrae Cervical, centra/arches, fused				*Total* Arches fused	*Range/study* Arches fused	*Total* Arches fused	*Range/study* Arches fused
Litter incidence N (%)	0	1 (7.1)	2 (10.5)	1 (0.17)	0-1 (0-5.9)	1 (0.32)	0-1 (0-5.9)
Fetal incidence N (%)	0	1 (0.9)[g] (centra fused)	2 (1.2) (1 centra fused[h], 1 arches fused[i])	1 (0.02) Centra fused	0-1 (0-0.8) Centra fused	1 (0.04) Centra fused	0-1 (0-0.8) Centra fused
Litter incidence N (%)				1 (0.17)	0-1 (0-6.2)	-	-
Fetal incidence N (%)				1 (0.02)	0-1 (0-0.8)	-	
Vertebrae Cervical, arch, small				*Total*	*Range/study*	*Total*	*Range/study*
Litter incidence N (%)	0	0	**1 (5.3)**	-	-	-	-
Fetal incidence N (%)	0	0	**1 (0.6)[i]**	-	-	-	-
Vertebrae Cervical, 6 present				*Total*	*Range/study*	*Total*	*Range/study*
Litter incidence N (%)	0	0	**1 (5.3)**	-	-	-	-
Fetal incidence N (%)	0	0	**1 (0.6)[k]**	-	-	-	-
Vertebrae Thoracic, hemivertebrae				*Total*	*Range/study*	*Total*	*Range/study*
Litter incidence N (%)	0	1 (7.1)	1 (5.3)	7 (1.19)	0-1 (0-7.7)	3 (0.95)	0-1 (0-5.9)
Fetal incidence N (%)	0	1 (0.9)[f]	**2 (1.2)[i,k]**	7 (0.16)	0-1 (0-1.1)	3 (0.12)	0-1 (0-0.8)
Vertebrae Thoracic, centrum, asymmetric				*Total*	*Range/study*	*Total*	*Range/study*
Litter incidence N (%)	0	0	**2 (10.5)**	1 (0.17)	0-1 (0-6.2)	2 (0.63)	0-1 (0-6.2)
Fetal incidence N (%)	0	0	**2 (1.2)[h,k]**	1 (0.02)	0-1 (0-0.8)	2 (0.08)	0-1 (0-0.8)
Vertebrae Sacral, arch, not ossified				*Total*	*Range/study*	*Total*	*Range/study*
Litter incidence N (%)	0	0	**1 (5.3)**	-	-	-	-
Fetal incidence N (%)	0	0	**1 (0.6)[j]**	-	-	-	-

[f] Fetus 23543-1
[g] Fetus 23546-2 also had other skeletal malformations
[h] Fetus 23560-10 also had other skeletal malformations
[i] Fetus 23555-3 also had other skeletal malformations
[j] Fetus 23555-6 also had other skeletal malformations
[k] Fetus 23555-7 also had other skeletal malformations

In the view of RAC, the findings above provide some evidence of effects in one species (rabbit) on especially the development of vertebrae, with the cervical hemivertebrae as the finding of highest concern considering that it is a rare malformation. RAC acknowledges the comment in the public consultation that three cases have been seen in 10 years, assumingly covering more than hundred studies. The finding of four cases (one at 600 and three at 900 mg/kg/day) in this single rabbit study thus clearly exceeds any HCD, rules out a spontaneous etiology and supports classification. That most affected foetuses have multiple and/or rare skeletal malformations/alterations in different sections of the vertebral column, suggest a specific, substance-related effect, which increase the concern. The fused digits seen in one fetus also contributes to the concern, whereas RAC is less concerned with the agenesis of the intermediate lobe of the lung. Some maternal toxicity was present in the main study, but it was not excessive, i.e. mean feed consumption during the dosing period was reduced in the mid (600 mg/kg/day) and top doses (900 mg/kg/day) by 12 and 15%, respectively, and mean body weight gain was non-statistically reduced by 11 % and 19% at the mid and top doses during the same period.

The lack of similar findings in rats is not decreasing the concern. As no human data is available, Cat 1A is not relevant. Cat 1B could be considered, but in view of the rather low incidences of malformations, and that it is mainly the hemi-vertebrae (supported by the fused digit) that cause concern, RAC support that classification in Cat 2 is more relevant than Cat 1B.

Thus, RAC concludes that **classification in category 2 is warranted for developmental toxicity (Repr. 2; H361d)**.

Effects on or via lactation

As no effects were observed on the pups in the available two-generation study at dose levels well above the limit dose, RAC supports **no classification for effects on or via lactation**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Imazamox is presently classified with Aquatic Acute 1 and Aquatic Chronic 1 in Annex VI.

Imazamox is not considered readily biodegradable under the conditions of the available ready biodegradability tests. In addition, results from hydrolysis and water/sediment studies show very limited degradation. Thus, imazamox is considered not rapidly degradable. Imazamox is estimated to have a low bioaccumulation potential (log Kow < - 2.9 at 20°C and pH 7, and the estimated BCF is below 1).

Acute aquatic toxicity data is available for all three trophic levels (fish, crustacean, algae/aquatic plants) with an E_rC_{50} value of 0.021 mg/L (measured concentration) for *Lemna gibba* as the key toxicity value, leading to the proposed classification. Based on an EC_{50} in the range of 0.01-0.1 mg/L, classification with Aquatic Acute 1, H400, with an M factor of 10 is proposed by the DS.

Chronic aquatic toxicity data is also available for all three trophic levels, and *Lemna gibba* is the most sensitive species also with regard to chronic toxicity (E_rC_{10} 0.0044 mg/L).

As imazamox is considered not rapidly degradable and is estimated to have a low bioaccumulation potential for classification purposes, the criterion for classification as H410 "Very toxic to aquatic life with long lasting effects" is EC_{10}/NOEC $\leqslant$ 0.1 mg/L. According to the DS, Imazamox fulfils

this criterion and should be classified as Aquatic Chronic 1, H410, with a chronic M factor of 10 (considering 0.001 mg/L < NOEC ⩽ 0.01 mg/L for non-rapidly degradable substances).

Comments received during public consultation

Comments were received from three Member States, with two of them supporting the proposal and the third asking for some technical clarifications without expressing a view on the proposed classification. Clarifications are given in the RCOM document.

Assessment and comparison with the classification criteria

Two ready biodegradability tests (OECD TG 301B) have shown that imazamox is not readily biodegradable (25-37% $ThCO_2$ after 29 days, and < 10% $CO_2/ThCO_2$ after 28 days, respectively). No hydrolysis occurs at acid or neutral pH, but imazamox can be hydrolysed at high temperatures and pH 9. However, extrapolated DT_{50} values for hydrolysis at pH 9 and 25°C is 192 days, supporting limited potential for degradation even at high pH (see table below for studies related to rapid degradability).

Table 4: *Information on degradation*

Method	Results	Reference
Ready biodegradability OECD 301B	After 29 days, %ThCO2 is 25-37 % for imazamox.	Gorman, M.; 1994a
Ready biodegradability OECD 301B	After 28 days, %CO2/ThCO2 is <10% for imazamox.	Schwarz, H.; 2012a
Hydrolysis Commission Directive 92/69/EEC Method C.7	Imazamox is stable to hydrolysis at pH 4 and 7 at 50°C. At pH 9, DT50 are 11.9 days at 50°C, 4.17 days at 60°C and 1.7 days at 70°C. Extrapolated DT50 at 25°C is 192 days and imazamox is therefore considered stable to hydrolysis at pH9.	Holman, J.; 1997a

In two studies using water-sediment systems, a few percent were mineralised after 100 days, and DT_{50} for the whole systems were estimated to roughly 140 and 400 days, respectively. RAC thus supports that imazamox is not rapidly degradable, for classification purposes.

An estimated log K_{ow} of 0.3-(<-3.0) at pH of 4-9, a high water solubility, and a measured BCF below 1 (bluegill sunfish (*Lepomis macrochirus)),* GLP, flow-through at 0.48 mg/L radio-labelled imazamox for 28d) indicates a low potential for bioaccumulation. RAC notes the comment about imazamox being surface active, and that this may cause some uncertainty when assessing the log K_{ow}, but supports an overall low potential for bioaccumulation, for classification purposes.

A large number of toxicity tests are available, covering all three trophic levels and both acute and chronic exposure. The toxicity is low in fish and invertebrates, while algae are more sensitive (lowest LC_{50} and NOEC = 29.1 mg/L (E_rC_{50} (72h) and 5.1 mg/L (E_rC_{10} (72h), respectively). However, aquatic plants are the key species for the classification of this herbicide. Three studies on *Lemna gibba* are available, with two of them conducted according to OECD TG 201 and one according to US EPA guidelines (reporting E_bC50/NOE_bC values). They give consistent E_rC_{50} of 0.01-0.02 mg/L (7 or 14 days) and NOEC/E_rC_{10} of 0.004-0.005 mg/L (7 or 14 days). RAC supports choosing Dorner (2013b) as the key study, with an E_rC_{50} (7d) of 0.021 mg/L and an E_rC_{10} (7d) of 0.0044 mg/L (measured concentration in both cases). The values based on growth rate and biomass differ slightly, without affecting the classification.

***Table 5**: A large number of aquatic acute and chronic studies are available, and representative studies that can be considered key studies are presented below*

Species	Method	Endpoint	Toxicity value	Reference
Acute studies				
Fish, *Oncorhynchus mykiss* (rainbow trout)	OECD TG 203, GLP, flow-through	LC_{50} (96h)	>122 mg/L (measured)	Anonymous, 1994
Invertebrate, *Daphnia magna*	OECD TG 202, GLP, static	EC_{50} (48h)	>122 mg/L (measured)	Yurk and Wisk, 1994
Algea, Pseudokirchneriella subcapitata	OECD TG 201, GLP, static	E_rC_{50} (72h)	29.1 mg/L	Hoffman, 2012
Aquatic plant, *Lemna gibba*	OECD TG 221, GLP, static	E_rC_{50} (7d) (frond number)	0.021 mg/L (measured)	Dorner, 2013
Chronic studies				
Fish, *Cyprinodon variegatus*	EPA 850.1400 flow-trough	NOEC (35d)	1.22 mg/L (measured)	Anonymous, 2013
Invertebrate, *Daphnia magna*	OECD TG 202, GLP, flow-through	NOEC (21d)	137 mg/L (measured)	Yurk and Wisk, 1995
Algea, *Pseudokirchneriella subcapitata*	OECD TG 201, GLP, static	E_rC_{10} (72h)	5.1 mg/L	Hoffman, 2012
Aquatic plant, *Lemna gibba*	OECD TG 221, GLP, static	E_rC_{10} (7d) dry weight frond number	(measured) 0.0044 mg/L 0.0067 mg/L	Dorner, 2013

Based on an $L(E)C_{50}$<1 mg/L, RAC supports classification with **Aquatic Acute 1, H400**, and since 0.01 < L(E)C 50 $\leqslant$ 0.1 mg/L (E_rC_{50} (7d)=0.021 mg/L), RAC supports an **M factor of 10**.

Since imazamox is not rapidly degradable, and the EC_{10}/NOEC is < 0.1 mg/L, imazamox should be **classified Aquatic Chronic 1, H410**. As the EC_{10}/NOEC falls within the interval 0.001 < NOEC $\leqslant$ 0.01 mg/L (E_rC_{10} (7d) = 0.0044 mg/L), RAC supports an **M factor of 10**.

Additional references

Stadler *et al*. 1983. Food Chem. Toxicol. 21(5):631-6

ANNEXES:

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 RAC (excluding confidential information).