Committee for Risk Assessment

RAC

Annex 1

Background document

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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

5 December 2019

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification: Imazamox (ISO); (*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid

EC Number: **Not available**

CAS Number: **114311-32-9**

Index Number: **613-208-00-7**

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Version number: 2 **Date: January 2019**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON IMAZAMOX (ISO); (RS)-2-(4-ISOPROPYL-4-METHYL-5-OXO-2-IMIDAZOLIN-2-YL)-5-METHOXYMETHYLNICOTINIC ACID

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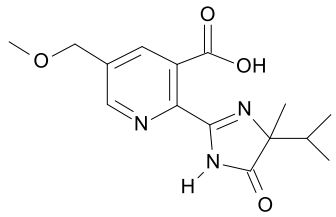
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	imazamox (ISO); (*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid
Other names (usual name, trade name, abbreviation)	**Chemical Name (CA)**: 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-5-(methoxymethyl)-3-pyridinecarboxylic acid
ISO common name (if available and appropriate)	Imazamox
EC number (if available and appropriate)	Not allocated
EC name (if available and appropriate)	Not allocated
CAS number (if available)	114311-32-9
Other identity code (if available)	619 (CIPAC)
Molecular formula	$C_{15}H_{19}N_3O_4$
Structural formula	
SMILES notation (if available)	COCc1cnc(C2=NC(=O)C(C)(N2)C(C)C)c(c1)C(O)=O
Molecular weight or molecular weight range	305.336 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Imazamox is a racemic mixture (1.1 ratio for R- and S-enantiomers)
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not relevant
Degree of purity (%) (if relevant for the entry in Annex VI)	950 g/kg

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
Imazamox	≥ 950 g/kg		

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Cyanide CN^-	max 5 mg/kg			

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Not relevant					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Proposed revisions to the harmonised classification and labelling of imazamox (ISO) according to the CLP criteria

	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	
Resulting entry in Annex VI if adopted by RAC and agreed by Commission	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	

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier	No
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Harmonised classification proposed **Reproductive toxicity Cat.2: H361d Suspected of damaging the unborn child**	**Yes**
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Harmonised classification proposed Aquatic Acute 1 : H400 **(acute M factor = 10)** Aquatic Chronic 1: H410 **(chronic M factor = 10)**	Yes
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Imazamox is currently classified and included in Annex VI of Regulation (EC) 1272/2008.

The existing entry on Annex VI of CLP Regulation is:

Aquatic Acute 1; H400 – Very toxic to aquatic life

Aquatic Chronic 1; H410 – Very toxic to aquatic life with long lasting effects.

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.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Imazamox is a pesticidal active substance originally included in Annex I of the EU Council Directive 91/414/EEC on 1st July 2003. The active substance was subsequently approved under regulation EC 1107/2009 via Implementing Regulation (EU) 540/2011. In accordance with Commission Regulation (EC) No 844/2012, BASF submitted on January 2014, a supplementary dossier to support and allow a decision on the renewal of the active substance Imazamox. France, acting as the Rapporteur Member State (RMS), evaluated all the aspects of the renewal dossier and produced a Renewal Assessment Report (RAR) which was sent to EFSA on April 2015. This RAR was the subject of an intensive peer review by the Co-RMS (Italie), European Member States and EFSA.

During the renewal peer review process, it was concluded that, based on observed developmental alterations (cervical hemivertebrae and absence of intermediate lobe of lung) in the developmental toxicity study in rabbits, a classification as Repr. 2 (H361d; Suspected of damaging the unborn child) may be warranted according to CLP criteria. This proposal for classification was reported in the RAR and in the EFSA conclusion (EFSA Journal 2016;14(03):4432).

The M-factors were also added to the proposed harmonized classification (Aquatic Acute 1 and Aquatic Chronic 1 with M-factors of 10) to be in accordance with the EFSA conclusion (EFSA Journal 2016;14(03):4432)

Given the discrepancy between the current harmonised classification and the outcomes of the European renewal peer review of the active substance, a target CLH proposal for the reproductive toxicity is presented in this document.

5 IDENTIFIED USES

Imazamox is a pesticide belonging to the imidazolinones class of herbicide. Imazamox is used solo or in mixture with other herbicide active substances for the control of mono and dicotiledon weeds in sunflower, oilseed rape and in various legume crops. It is also used in rice for weed

control. The application is mainly done in post emergence of the crop but also it is used in pre emergence.

Imazamox mode of action is described as the inhibition of the activity of the enzyme acetohydroxyacid synthase (AHAS) also known as acetolactate synthase (ALS). This enzyme is found in bacteria and plants, but not in animals and humans.

ALS is the first enzyme in the pathway for the biosynthesis of the essential branched-chain amino acids valine, leucine and isoleucine. The inhibition of ALS activity leads to amino acid starvation and the accumulation of toxic precursors. The primary effect following treatment of susceptible weeds with the herbicide is the restraint of new growth and cell development.

Imazamox has systemic properties.

6 DATA SOURCES

Please refer to the Renewal Assessment Report (RAR) for Imazamox publicaly available on the EFSA website http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-2323

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Pure substance: solide present as a fine white powder Technical substance: powdered solid	Kroehl T. 2013 a Patel, J., 1993 a	Visual assessment Pure substance 99.8% Tech. substance 98.2%
Melting/freezing point	166 °C	Kroehl T. 2013 a	OPPTS 830.7200, FP0091/002 (Differential scanning calorimetry/ thermogravimetry) Pure substance 99.8%
Boiling point			Not relevant
Relative density	From DAR: 1.39 at 20°C	Patel, J., 1993 a	EEC A.3 Pure substance 99.3%
Vapour pressure	$6.3*10^{-11}$ Pa at 20°C $2.1*10^{-10}$ Pa at 25°C	Kroehl T. 2013 a	EEC A.4, OECD 104 Pure substance 99.8%
Surface tension	51.9 mN/m at 20°C (90 % saturated solution)	Kroehl T. 2013 a	OEDC 115, EEC A.5 Pure substance 99.8%
Water solubility	21.53 g/L at 20°C (pH 4) >574 g/L at 20°C (pH 7) >505 g/L at 20°C (pH 9)	L.F.P.,Silva C.M. da 2014 a	OECD 105 Pure substance 99.8%
Partition coefficient n-octanol/water	log P_{OW} = -0.3 at 20°C (pH 4) log P_{OW} = <-2.9 at 20°C (pH 7) log P_{OW} = < - 3.0 at 20°C (pH 9)	L.F.P.,Silva C.M. da 2014 a	OECD 105 Pure substance 99.8%
Flash point			Not applicable
Flammability	Not flammable	Achhammer 2013 a	EEC A.10 Tech. substance 98.0%
Explosive properties	Not explosive	Achhammer 2013 a	OECD 113 Tech. substance 98.0%

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Self-ignition temperature	Not self-heating	Achhammer 2013 a	EEC A.16 Tech. substance 98.0%
Oxidising properties	Not oxidising	Achhammer 2013 a	EEC A.17 Tech. substance 98.0%
Granulometry			Not relevant for CLP
Stability in organic solvents and identity of relevant degradation products			No evidence of instability in organic solvents. Not required.
Dissociation constant	pKa = 2.3, 3.3, 10.8	Melcer, 1993 a	US EPA 63-10 Pure substance 99.5%
Viscosity			Not applicable for a solid

8 EVALUATION OF PHYSICAL HAZARDS

Not applicable, not addressed in this proposal

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not applicable, not addressed in this proposal.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Not applicable, not addressed in this proposal.

10.2 Acute toxicity - dermal route

Not applicable, not addressed in this proposal.

10.3 Acute toxicity - inhalation route

Not applicable, not addressed in this proposal.

10.4 Skin corrosion/irritation

Not applicable, not addressed in this proposal.

10.5 Serious eye damage/eye irritation

Not applicable, not addressed in this proposal.

10.6 Respiratory sensitisation

Not applicable, not addressed in this proposal.

10.7 Skin sensitisation

Not applicable, not addressed in this proposal.

10.8 Germ cell mutagenicity

Not applicable, not addressed in this proposal.

10.9 Carcinogenicity

Not applicable, not addressed in this proposal.

10.10 Reproductive toxicity

Please note that AC 299,263 is a code name for imazamox.

10.10.1 Adverse effects on sexual function and fertility

Table 8: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Two generation reproduction Guideline EPA 83-4, OECD 416 GLP Oral (diet) Rat, Sprague-Dawley (Crl:CD®BR) 30/sex/group	Imazamox (AC 299,263, batch number AC 6935-63, purity 98.2-97.1% a.i.) Dose levels: 0, 1000, 10000 and 20000 ppm	**Parental toxicity** Up to 20000 ppm (1469 mg/kg bw/day): No effect ***Parental NOAEL 1469 mg/kg bw/day*** **Reproductive toxicity** Up to 20000 ppm (1469 mg/kg bw/day): No effect ***Reproductive NOAEL 1469 mg/kg bw/day*** **Offspring toxicity** Up to 20000 ppm (1469 mg/kg bw/day): No effect ***Offspring NOAEL 1469 mg/kg bw/day***	Anonymous (1995)

Anonymous (1995): A two generation reproduction study with AC 299,263 in rats; Report n° 92-4043; Study date: May 26, 1995.

Test method: The test procedure complied with US EPA Guideline 83-4 (test method equivalent to EEC Guideline 87/302/EEC, B, n° L 133/47-50), OECD Guideline n° 416 and JMAFF Guideline 59 NohSan n°4200, 1985.

GLP : This study was conducted in compliance with the GLP Regulation of :
- EPA, 40 CFR Part 160,
- OECD GLP, ISBN 92-64-12367-9,
- JMAFF Notification n° 3850.

Test system: Groups of 60 (30/sex/generation) Sprague Dawley rats (Crl:CD®BR strain) were administered dietary concentrations 0; 1000; 10000 and 20000 ppm (98.2%-97.1% a.i[1] ; lot n° AC 6935-63) through 2 generations; P1 and F1 generation animals rats were treated over a 10-w and 11-w premating period, respectively, and treatment continued during both a 20-d mating period and postmating period (males and unmated females) until sacrifice; mated females were treated during the ensuing gestation, lactation and post-weaning periods until sacrifice; the duration of treatment was 114-115 d and 134-135 d in the P1 males and females, respectively and 121-112 d and 141-142 d in the F1 males and females, respectively. Each parental

[1] The reference substance used was AC 299,263 (99.4% a.i.; lot n° AC7963-33; stable for at least 1 mo.) ; due to an improvement in the analytical methodology, its purity was lowered to 98.3%; this downward ajustment resulted in a change of the purity value of test material, lot n° AC 6935-63, from 98.2% to 97.1%. The amounts of test substance in diets were not adjusted for this change; however all values presented in data and tables were based on the purity value current at the time of analysis, rather than the original purity value.

generation produced a single litter (F1 and F2) and pups were weaned on lactation d-21. F1 parental animals were randomly selected (at least 1 pup/sex/litter) from the F1 litters on d-28 postpartum, pups receiving the same dose level as their parents until the last F1 litter was weaned and the F1 premating treatment initiated.

- Mating procedure: initially, a male was co-housed with the same female of the same treatment group until evidence of mating or for 10 consecutive days; day of evidence of mating (microsocopic observation of sperm in the vaginal smear and/or copulation plug) was defined as d-0 of gestation; unmated females were randomly redistributed to a male of the same treatment group which had previously mated a female. The same mating procedure was used for both parental generations. In the mating assignements of the F1 generation, brother-sister matings were avoided.

- Follow-up of adult generations: Parental animals (P1 & F1) were observed twice daily for mortality and signs of toxicity; detailed physical examinations were performed pretest (P1) or at initiation of the premating treatment period (F1) and weekly thereafter in both generations. Body weight and food consumption were recorded weekly during the premating treatment periods and postmating periods until sacrifice, and at regular intervals during gestation (d-0, d-7, d-14 and d-20) and lactation (d-0, d-4, d-7, d-4 and d-21) periods. For males sacrifice was performed after delivery of the last litter (P1) or approximately 3 w after completion of the mating period (F1); all males, including those found dead, were given a gross postmortem examination. All females (P1 and F1), including those that did not mate, those that mated but did no show any evidence of parturition and those that delivered and weaned a litter, were sacrificed after weaning of the last litter and given a gross postmortem examination, including a count of uterine implantations scars. Gross lesions, pituitary and reproductive organs (coagulating glands, prostate, seminal vesicles, testes with epididymes; cervix, ovaries, uterus, vagina) were evaluated histologically for all P1 and F1 adult of the control and high dose groups.

- Follow-up of offspring/litters: litter size, number of live and dead pups were recorded as soon as possible after delivery along with pups abnormalities, as well as during lactation d-0; d-4; d-7; d-14; d-21; individual pup bw and pup sex distribution (external sex determination) were recorded at the same time intervals during lactation (and at d-28 postpartum for F1 pups bw); physical development parameters (pinna unfolding, hair growth, tooth eruption, eye opening, vaignal opening and preputial sepration) were recorded. On lactation d-4, all litters with more than 8 pups were reduced to equalize sex distribution (4/sex) when possible (litters with fewer than 8 pups were not adjusted). Sacrifices were performed on d-21 of lactation for 1 male and 1 female pup from each litter (detailed external and internal examinations), on d-28 post partum for F1 pups not selected to become the F1 adult generation and on d-21 lactation for F2 pups. Those with external abnormalities were given an internal examination and viscera were preserved (those without external irregularities were discarded). Pups found dead during lactation, stillborn pups or those culled at d-4 were weighed and also given gross external and internal examination.
For each test diet prepared in the mixing phase, samples were taken at 3 locations of the mixer in order to determine the homogeneity of the diet preparation. After combining the remaining diet at each level, samples were put in appropriate containers for storage in the animal room and bulk storage for a period of 7; 14 and 21 d. In addition, freezer storage stability was determined. During each w of the study, one representative sample from each test diet at each level was taken and stored (never longer that the demonstrated period of freezer stability i.e. 45 w) in a freezer at approximately - 10°C until analyzed (HPLC-UV method).

Results

Mixing study conducted at 1000 and 20000 ppm demonstrated that the mixing procedure produced homogeneous diets over the desired dosage range; stability of the test material in diets dosed at low and high dose levels was demonstrated in animal room conditions and under bulk storage conditions for 7, 14 and 21 days; results of analysis of diet samples indicated that diets contained the intended amounts of test material during the test period.

Table 10.10.1-1 Summary of homogeneity, stability and diet analysis data

	Sampling	Nominal	Overall average & cv

		dose (ppm)	(% nominal)
Homogeneity (d-0)	2 x 3 locations	1000	103.1 ± 1.4
		20000	104.5 ± 1.9
Stability			
„Bulk" feed storage	2 at d-7, d-14 & d-21	1000	103.7 ± 2.7
		20000	98.0 ± 5.5
„Animal room"		1000	106.1 ± 1.9
		20000	102.9 ± 2.9
„Freezer"	2 at 45w	1000	101.6
		20000	100.3
Feed analysis	2-4 / w x 9 w & ≈ 4/mo. thereafter	1000	106.0 ± 6.3
		10000	103.5 ± 5.1
		20000	104.4± 3.2

- Parental generations: No deaths occured in the control and all treated groups of the P1 generation, nor in the control and low dose groups of the F1 generation; 2 deaths were observed in the F1 mid dose group: 1 male died from an unkown cause (no remarkable macroscopic findings) during the w-8 of the premating period and 1 non pregnant female died on d-8 of presumed gestation (enlarged spleen, liver and adrenals, discoloration of pleura, liver and mediastinal lymph nodes and no uterine implantations were seen at necropsy); 3 deaths occurred in the F1 high dose group: 1 male died during the mating period from complications of a mouth lesion, 1 non pregnant female died from an unkown cause on d-18 of presumed gestation (no unusual macroscopic findings and no uterine implantations seen at necropsy) and 1 other non pregnant female died from an uterine infection 5-w after mating (postmortem examination revealed yellow fluid in the abdominal cavity, discolored and enlarged uterus, enlarged lymph nodes, dilated renal pelvis, discolored thymus and ovaries and no fetus, nor placental tissue, nor uterine implantation scars). The low mortality rate and the non specific macroscopic findings in the F1 mid and high dose groups did not indicate a treatment related effect.
There were no clinical findings that could be attributed to treatement in any of the P1 and F1 parental animals.

Mean weekly body weight for both sexes of both parental generations were comparable (generally within 5%) to those of controls during the pre-mating, the mating and post-mating treatment periods. Mean body weight gains for P1 and F1 males and females of all dose groups were comparable to controls during the pre-mating period, except for high dose F1 females which exhibited a statistically significant decrease (11.3%) in mean body weight gain over this entire 11-w period; however, there was no decreases in body weight gain in high dose P1 females nor in high dose P1 or F1 males and no dose-response relationship was apparent, so that there was no convincing evidence for relating to treatment such a slight decrease in mean body weight gain for only high dose F1 females during only the premating period. Maternal body weight or body weight gain for each recording interval during the gestation and lactation intervals for the treated groups in both parental generations were comparable to controls.

During the premating treatment period, mean weekly food consumption for males and females of both parental generations was either comparable to controls or slightly higher than controls (10000 and 20000 ppm groups only, in which the statistically significant differences were observed during most of the measurement intervals, particularly in females). In addition, there was no adverse effect on mean weekly food consumption from treatment of either P1 or F1 males during the postmating periods (values in P1

generation treated groups were slightly higher than control data, attaining statistical significance at the high dose level; in F1 generation treated groups, values were similar to control data, except in the high dose group at w-35, in which a small i.e. less than 5%, although statistically significant, reduction was seen). Mean maternal food consumption during the gestation and lactation intervals for both treated parental generations did not appear to be adversely affected by treatment, as no consistent time or dose trend were noticeable (a statistically significant increase, although slight i.e. 6%, in mean food consumption over the d-14-20 gestation was observed in the high dose P1 females; a statistically significant reduction (≈ 30%) in mean food consumption was noted in the low dose F1 females at d-1 lactation interval, but not at subsequent lactation intervals in this group, nor in higher dose groups at any lactation interval). Mean and ranges of weekly test substance intake values are summarized in Table 10.10.1-2.

Table 10.10.1-2 Test substance intake (mg/kg bw/d) (mean [range])

Dose (ppm)		1000		10000		20000	
		Males	**Females**	**Males**	**Females**	**Males**	**Females**
P1	Premating ❶	76 [57-114]	88 [72-110]	770 [574-1148]	892 [735-1159]	1554 [1168-2277]	1826 [1516-2278]
	Postmating ❸	53 [51-54]		530 [514-547]		1082 [1065-1105]	
	Gestation ❺		83 [80-87]		853 [819-901]		1745 [1714-1802]
	Lactation ❻		143 [89-186]		1487 [1217-1967]		3129 [2281-4102]
F1	Premating ❷	73 [53-120]	85 [67-121]	748 [526-1248]	867 [677-1287]	1469 [1039-2370]	1705 [1334-2487]
	Postmating ❹	50 [49-51]		497 [485-511]		984 [692-1001]	
	Gestation ❺		78 [76-82]		790 [769-802]		1539 [1517-1555]
	Lactation ❻		131 [93-181]		1280 [777-1750]		2667 [1570-3784]

❶ mean of 10 mean weekly values (study w 1-10)
❷ mean of 11 mean weekly values (study w 1-10)
❸ mean of 3 weekly values (study w 14-16)
❹ mean of 3 weekly values (study w 35-37)
❺ mean of mean values for the 3 recording intervals (d 0-7, d 7-14, d 14-20)
❻ mean of mean values for the 5 recording intervals (d1, d4, d7, d10 d14)

Reproductive performance (estrous cycle data, mating indices for both males and females, pregnancy rates, male fertility indices, gestation indices and parturition indices) was unaffected by treatment and these indices for the control and treated groups were generally within the range of historical control data for F1 and F2 pregnancies from reproduction studies conducted in the performing laboratory[2]. For both generations, the mean gestation length for the treated groups was comparable to control data and gestation indices were 100 % in any groups (Table 10.10.1-3).

[2] The male mating index (70%) and the pregnancy rate (75%) for the F1 control group were lower than usually achieved and just outside the range of recent historical data of the laboratory i.e.72-92% and 71.4-100%, respectively. The reason for the poorer mating performance of F1 control males and the reduction in the pregnancy rate in F1 females was unexplained.

Table 10.10.1-3 Reproductive indices

Dose levels (ppm)		**0**		**1000**		**10000**		**20000**	
Generations		**P1**	**F1**	**P1**	**F1**	**P1**	**F1**	**P1**	**F1**
Mating									
Males ❶	n°	30/30	21/30	29/30	28/30	26/30	26/29	29/30	23/30
	%	100.0	70.0	96.7	93.3	86.7	89.7	96.7	76.7
Females ❷	n°	30/30	28/30	30/30	30/30	30/30	30/30	30/30	29/30
	%	100.0	93.3	100.0	100.0	100.0	100.0	100.0	96.7
Historical range ❻		*Males = 70.8-100% (mean = 88.2%) ; females = 84.0-100% (mean = 97.4)*							
Males Fertility ❸	n°	29/30	19/21	29/29	26/28	26/26	26/26	25/29	22/23
	%	96.7	90.5	100.0	92.9	100.0	100.0	86.2	95.7
Historical range ❻		*76.2-100.0% (mean = 91.1%)*							
Pregnancy ❹	n°	29/30	21/28	30/30	27/30	29/30	27/30	26/30	26/29
	%	96.7	75.0	100.0	90.0	96.7	90.0	86.7	89.7
Gestation index ❺									
	n°	29/29	21/21	30/30	27/27	29/29	27/27	26/26	26/26
	%	100.0	100	100.0	100.0	100.0	100.0	100.0	100.0
Gestation lenght (d)		22.0±0.3	22.3±0.6	21.9±0.3	22.0±0.7	21.9±0.4	22.1±0.6	21.9±0.4	22.0±0.4
Historical range ❻		*Pregnancy rate = 71.4 - 100.0% (mean = 89.4%)* *Gestation lenght = 21.9-22.6 d (mean = 22.1 d)*							
Mean n° of uterine implantation scars		14.6±2.9	14.7±2.0	14.2±2.2	13.6±4.0	14.0±2.2	14.0±1.9	13.5±3.4	13.7±2.3

❶ number of males for which mating was confirmed in at least 1 female
❷ number of females showing evidence of mating (plug ±sperm ± pregnancy ± uterine implantation scars)
❸ number of males mated with at least 1 female for which pregnancy was evident
❹ number of females showing evidence of pregnancy (parturition uterine implantation scars)
❺ number of females delivering litters containing viable pups/number of pregnant females
❻ 12 mutigeneration reproduction studies CD rat (1987-1991), 36 litter intervals

- Pup data: The mean pup live birth indices for the treated groups were also comparable to controls for both litter intervals, except for the F1 litter high dose group, in which the mean number of liver pups at birth was significantly lower than control values; however, this decrease was within the range of the recent historical control data of the laboratory and the mean number of live pups in the control group during the same litter interval reached the upper range of this historical data; therefore there was no clear evidence of a a treatment related effect, the observed difference being most likely related to the low number of dead pups recovered in the control group. Mean litter size data both pre-cull (prior to neonatal d-4) and throughout the remainder of lactation (d-7, d-14 and d-21) for the treated groups was comparable to controls for both litter intervals. There were no treatment-related effects during either litter interval concerning: litter or pup survival indices; mean pup weights at birth, during each recording intervals of lactation, and on neonatal d- 28; pup sex distribution; pup developmental landmarks (pinna detachment, upper incisor eruption, eye opening, fur growth, mean day to completion for vaginal opening and preputial separation for the selected F1 pups); or the mean pup viability and weaning indices, representing pup survival over the d 0-4 and d 4-21 lactation intervals (Table 10.10.1-4).

Table 10.10.1-4 Litter data (mean ± SD)

Dose levels (ppm)	**0**		**1,000**		**10,000**		**20,000**	
Generations	**P1**	**F1**	**P1**	**F1**	**P1**	**F1**	**P1**	**F1**
Litters	**F1**	**F2**	**F1**	**F2**	**F1**	**F2**	**F1**	**F2**
Mean n° of pups at birth	14.4±1.5	13.0±2.8	14.1±1.6	13.1±3.6	14.5±2.0	13.6±1.7	12.3±3.6	12.8±2.3
Live	14.3±1.6	12.9±2.7	13.8±1.7	12.6±3.7	14.2±2.0	13.1±2.1	12.0±3.5*	12.7±2.3
Dead	0.0±0.2	0.1±0.4	0.2±0.5	0.5±1.1	0.3±0.6	0.5±0.8	0.3±0.7	0.1±0.3
Historical range ❹ Means	*total n°of pups: 13.3 (11.1-14.8); live pups: 13.0 (10.8-14.4) ; dead pups: 0.3 (0.0-1.0)*							
Pup live birth index ❶	99.7±1.5	99.1±2.3	98.3±3.5	95.3±9.3	98.2±3.9	96.2±6.7	98.1±5.1*	99.1±2.4
Litter survival								
d-4	13.8±1.6	12.2±3.1	13.8±1.7	12.1±3.5	13.6±1.8	12.5±2.1	11.8±3.4	12.4±2.3
d-7	8.0±0.0	7.6±0.8	7.9±0.3	7.6±1.3	8.0±0.2	8.0±0.2	7.5±1.3	7.9±0.4
d-14	7.9±0.3	7.6±0.8	7.9±0.3	7.6±1.3	7.9±0.4	8.0±0.2	7.4±1.4	7.9±0.4
d-21	7.9±0.3	7.6±0.8	7.9±0.3	7.5±1.3	7.9±0.4	7.8±0.8	7.4±0.4	7.9±0.4
Historical range ❹ Means	*Pups survival indices : d0-4 : 96.3% (88.4-99.4%); d4-21 : 98.1% (92.9-100.0%)* *Litter survival indices : 98.3% (86.4-100.0%)*							
Pup viability index ❷	96.2±8.2	94.3±13.4	99.5±2.0	96.4±7.4	96.2±6.6	95.4±5.7	98.1±4.6	92.6±20.5
Pup weaning index ❸	99.1±3.2	98.8±3.8	99.2±3.2	99.1±3.3	99.1±4.6	97.7±9.8	97.8±7.2	100.0±0.0
Pup sex ratio								
d-0	1.2	1.0	0.9	1.0	1.1	1.0	1.1	1.0
d-21	1.0	1.0	1.0	1.0	1.1	1.0	0.9	0.9
Pup weights (g)								
d-0	5.7±0.4	6.1±0.7	5.9±0.4	5.9±0.6	5.6±0.3	6.0±0.5	5.9±0.4	5.8±0.5
d-21	46.9±5.3	46.7±5.6	47.9±5.0	46.9±4.9	46.0±6.7	46.9±6.8	44.9±7.8	45.8±4.9

❶ [total pups born alive / total pups born] / x 100
❷ [total pups alive on d-4 - precull / total pups born alive] x 100
❸ [total pups alive on d-21 / total pups alive on d-4] x 100
❹ 12 mutigeneration reproduction studies CD rat (1987-1991), 36 litter intervals

No gross macroscopic findings were observed for either parental or pup generations. The mean number of uterine implantation scars in the treated groups was considered comparable to control data for each litter interval and was also similar to the mean total number of pups at birth within the same groups for each litter interval.There were no microscopic compound-related changes observed.

Conclusions

No adverse effects were indicated from the evaluation of parental or neonatal parameters and no treatment related effects on reproductive performance were noted at dietary levels up to and including 20000 ppm. The NOAEL for parental, offspring and reproductive toxicity was determined to be 20000 ppm (1469 mg/kg bw/day).

Table 5: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No human data				

Table 10: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

A 2-generation reproductive toxicity study in Sprague-Dawley rats was conducted on imazamox. Imazamox did not affect reproductive performance in this study, nor was there evidence of significant pre- or postnatal effects up to the highest dose tested, resulting in a NOAEL at 20000 ppm (1469 mg/kg bw/d) for parental, reproductive and offspring toxicity.

The 2-generation study was designed to meet requirements established for the following: US EPA Guideline (Subdivision F, 83-4), OECD Guideline 416 and Japanese MAFF Guideline (No. 59 NohSan No. 4200, January 28, 1985 for "Reproduction studies"). The study, performed in 1995, was conducted according to the old OECD 416 guideline. The major deviations to the current OECD guideline 416 (updated in 2001) comprise the following: no sperm parameters were assessed; no functional investigations of the F1 offspring were performed; no organ weights were reported, however histology was done on relevant reproductive organs (coagulating glands, prostate, seminal vesicles, testes with epididymes; cervix, ovaries, uterus, vagina). Though this study was not conducted according to the current OECD guideline, it has been performed in compliance with the OECD guideline 416 which was in place and standard at that time and is still considered to be acceptable and valid.

10.10.3 Comparison with the CLP criteria

The CLP criteria for adverse effects on sexual function and fertility stated the following:

Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

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 20000 ppm (1469 mg/kg bw/d). Moreover, reproductive organs were not shown to be target organs of imazamox up to the highest tested doses in the whole toxicity database. 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, based on the available data, no classification for adverse effects on sexual function and fertility is warranted for imazamox.

10.10.4 Adverse effects on development

Table 61: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Developmental toxicity Guideline EPA 83-3, OECD 414 (1981) GLP Oral (gavage) Rat, Sprague-Dawley (Crl:CD®BR VAF/Plus®) 25 presumed pregnant females per group	Imazamox (AC 299,263, batch number AC 6935-63, purity 98.2-97.1% a.i.) Dose levels: 0, 100, 500 and 1000 mg/kg bw/day Dosing on gestation days 6-15 Vehicle: 0.5% w/v carboxymethylcellulose	**Maternal toxicity** 1000 mg/kg bw/day: ↓ body weight, ↓ body weight gain (23% GD6-12, 11% GD6-16), ↓ food consumption 500 and 100 mg/kg bw/day: No effect ***Maternal NOAEL 500 mg/kg bw/day*** **Developmental toxicity** Up to 1000 mg/kg bw/day: No effect ***Developmental NOAEL 1000 mg/kg bw/day***	Anonymous (1994)
Developmental toxicity Guideline EPA 83-3, OECD 141 (1981) GLP Oral (gavage) Rabbit, New Zealand White (Hra:(NZW)SPF) 20 presumed pregnant females per group	Imazamox (AC 299,263, batch number AC 6935-63, purity 98.2% a.i.) Dose levels: 0, 300, 600 and 900 mg/kg bw/day Dosing on gestation days 7-19 Vehicle: 0.5% w/v carboxymethylcellulose	**Maternal toxicity** 900 mg/kg bw/day: ↓ body weight gain (19% GD7-20, 21% GD20-29), ↓ food consumption (15-16% GD7-20) 600 mg/kg bw/day: ↓ food consumption (12-13% GD7-20) 300 mg/kg bw/day: No effect ***Maternal NOAEL 300 mg/kg bw/day*** **Developmental toxicity** 900 mg/kg bw/day: fused digits in the hindpaw, cervical vertebrae findings (small arch, reduced number), thoracic vertebrae findings (hemivertebrae), sacral vertebrae findings (unossified arch), unossified ribs 600 mg/kg bw/day: cervical vertebra malformation (hemivertebrae), absent intermediate lobe of the lungs 300 mg/kg bw/day: No effect ***Developmental NOAEL 300 mg/kg bw/day***	Anonymous (1995)

STUDY 1 - RAT

Anonymous (1994): An oral developmental toxicity (embryo-fetal toxicity/teratogenicity) study with AC 299,263 in rats; Report n° 101-020; Study date: March 29, 1994.

Test method: The study was conducted in compliance with the EPA Pesticide Assessment Guideline Subdivision F, 83-3 (test method equivalent to EEC Guideline 87/302/EEC, Part B, No. L133/24-26), OECD 414 (1981), JMAFF 59 NohSan No. 4200.

GLP: This study was conducted according to the:

- EPA (FIFRA) „GLP Standards, 40 CFR Part 160,
- OECD GLP in the Testing of Chemicals (ISBN 92-64-12367-9),
- EC Commission Directive - Annexes A and B (No. L 11/37-50),
- JMAFF GLP Standards, Notification n° 3850.

Deviations: None.

Test system: Groups of 25 presumed pregnant Crl:CD®BR VAF/Plus® (Sprague-Dawley) rats were administered 0; 100; 500 and 1000 mg/kg bw/day of AC 299263 technical (98.2-97.1 % a.i[3]. ; lot n° AC 6935-63) in an aqueous suspension[4] of 0.5% w/v carboxymethylcellulose (CMC), by oral gavage once daily, on d-6 through d-15 of presumed gestation[5]. Suspensions of test substance in CMC were prepared weekly during the study at concentrations of 0; 10, 50 and 100 mg/ml; homogeneity and stability analysis of low and high dose solutions were conducted before the study and at the beginning of the dosage period; confirmation analysis of test material content in each dosage preparations were conducted on the first and on the last day of the dosing period. Rats were observed for mortality twice daily throughout the dosing period; clinical observations were performed pretest, on d-0, d-6 of presumed gestation and daily during the dosing and postdosing periods (d-16 through d-20 of presumed gestation); bw and food consumption were determined pretest, on d-0 of presumed gestation and daily thereafter until termination of the postdosing period. All rats were sacrificed on d-20 of presumed gestation; uteri were weighed and examined for pregnancy and gross lesions of the thoracic and abdominal cavities, number of corpora lutea in each ovary, number and distribution of implantations, early and late resorptions, and live and dead fetuses were recorded. Each fetus was weighed and examined for sex and gross external alterations; approximately one half of the fetuses in each litter were examined for soft tissues alterations and the remaining examined for skeletal alterations.

Statistics: Maternal body weight and body weight changes, food consumption data, uterine weights and litter averages for percent male fetuses, percent resorbed conceptuses, fetal bw, fetal anomaly average data and fetal ossification site data were analyzed using Bartlett's test of homogeneity of variances and the analysis of variances when Bartlett's test was not significant at the 0.05 level. When ANOVA was significant at the 0.05 level, Dunnett's test was used to identify the statistical significance of the individual groups; if the ANOVA was not appropriate, the Kruskal-Wallis test was used when ≤ 75% ties were present; when this latter test was significant, Dunn's method of multiple comparisons was used to identify the statistical significance of the individual groups; if there were > 75% ties, Fisher's exact test was used. Count data observed at Caesarean sectioning of the dams were evaluated using the above procedures for the Kruskal-Wallis test.

Results

Assays of low and high dose suspensions indicated a good homogeneity and a good freezer storage stability; results of confirmation analysis showed that tests rats were properly dosed (Table 10.10.4-1).

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[3] The purity which was initially determined as 98.2.%, was subsequently lowered to 97.1%, when reassayed using changes of the analytical standard (improvements made to the analytical method which resulted in a decrease in the purity of the analytical standard from 99.4% to 98.3%). The amount of test material used to prepare the test diet was not adjusted for this change and analytical results were not recalculated.

[4] Dosage volume of 10 mL/kg adjusted daily on the basis of individual bw recorded before intubation

[5] 140 healthy virgin females rats were placed in cohabitation with 140 breeder male rats (1 male per female). Females rats with spermatozoa in a vaginal smear or a copulatory plug were considered to be at d-0 of presumed gestation and returned to individual housing.

Table 10.10.4-1 Summary of homogeneity, stability and diet analysis data

	Sampling	Nominal concentation (mg/mL)	Overall average & cv (% nominal)
Homogeneity (d-0)	triplicate	10	98 ± 1
		100	88 ± 5
Stability „Freezer“	after 17 days	10	101± 2
		100	87 ± 4
Feed analysis	1 at first and last day of dosing	10	96-106
		50	94-108
		100	92-122
		average	103 ± 11

No mortalities, abortions or premature deliveries occurred during the study, and there were no clinical signs observed that were attributed to treatment, nor gross lesions identified at necropsy. Absolute and relative feed consumption values for the entire dosage and postdosage periods were reduced (not statistically significant) in the high dose group. The body weight gain value for the entire dosage period (d-6 to d-16 gestation) tended also to be reduced in the high dose group and this was related to an early significantly reduced body weight gain on d-6 to d-12 of gestation. Body weight gains were comparable among all groups for the remainder of the dosing period (d-12 to d-16 of gestation) and postdosing period (Table 10.10.4-2). Gravid uterine weights were not affected by administration of the test compound at any dose level, and there were no gross lesions identified at necropsy.

Table 10.10.4-2 Mean (± SD) body weight changes (g)

Dose group (mg/kg bw/d)	0	100	500	1000
days 6-12	+ 44.0 ± 9.0	+ 43.0 ± 7.4	+ 38.4 ± 12.8	+ 33.8 ± 14.0*
days 12-16	+ 37.3 ± 6.2	+ 39.6 ± 6.9	+ 36.8 ± 9.3	+ 38.6 ± 11.0
days 16-20	+ 75.8 ± 15.0	+ 74.4 ± 6.8	+ 71.4 ± 15.0	+ 72.6 ± 13.0
days 6-16	+ 81.3 ± 10.2	+ 82.6 ± 11.1	+ 75.3 ± 13.8	+ 72.4 ± 19.0
days 0-20	+ 202.6 ± 28.3	+ 200.5 ± 15.2	+ 194.2 ± 29.9	+ 190.9 ± 30.3
days 0-20 corrected #	+ 114.8 ± 21.6	+ 112.3 ± 12.7	+ 112.4 ± 19.8	+ 106.6 ± 20.0

* $p \leq 0.05$
# corrected maternal body weight (d-20 of gestation body weight minus the gravid uterine weight)

Pregnancy occurred in 24 or 25 of the 25 presumed pregnant females of each group. No caesarean-sectioning or litter parameters were affected by the test substance at any dosage level. Litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weight, percent resorbed conceptuses and percent male fetuses were comparable among the 4 dosage groups. No dam had a litter consisting of only resorbed conceptuses and there were no dead fetuses (Table 10.10.4-3).

Table 10.10.4-3 Summary of Caesarean-sectioning observations (Mean ± SD)

Dose group (mg/kg bw/d)	0	100	500	1000
Rats pregnant (n°)	24	24	25	25
Corpora lutea	17.8 ± 1.9	18.8 ± 2.5	18.2 ± 3.2	17.8 ± 3.0
Implantations	15.8 ± 1.4	16.2 ± 1.6	15.2 ± 3.6	15.1 ± 4.0
Litter size Live fetuses Dead fetuses	15.2 ± 1.5 15.2 ± 1.5 0.6 ± 0.8	15.4 ± 1.4 15.4 ±1.4 0.8 ± 1.3	14.4 ± 3.7 14.4 ±3.7 0.8 ± 1.1	14.6 ± 3.8 14.6 ± 3.8 0.5 ± 0.8
Resorptions Early Late	0.6 ± 0.8 0.5 ± 0.6 0.0 ± 0.2	0.8 ± 1.3 0.8 ± 1.3 0.0 ± 0.0	0.8 ± 1.1 0.8 ± 1.1 0.0 ± 0.2	0.5 ± 0.8 0.5 ± 0.8 0.0 ± 0.0
Live male fetuses/litter	47.6 ± 13.8	52.5 ± 14.8	48.4 ± 17.2	45.2 ± 17.3
Live fetal bw (g)/litter Males females	3.64 ± 0.24 3.75 ± 0.26 3.53 ± 0.22	3.52 ± 0.26 3.62 ± 0.28 3.42 ± 0.28	3.50 ± 0.30 3.66 ± 0.26 3.40 ± 0.27	3.63 ± 0.22 3.74 ± 0.25 3.55 ± 0.22
% Resorbed conceptuses/litter	3.7 ± 4.7	4.3 ± 606	5.4 ± 8.5	3.1 ± 4.3

There were no fetal gross external, soft tissue or skeletal malformations or variations observed that were considered caused by treatment of the dams with imazamox at dosages as high as 1000 mg/kg/day (Table 10.10.4-4).

Table 10.10.4-4 Summary of fetal alterations

Dose group (mg/kg/d)	0	100	500	1000
Litters evaluated (n°)	**24**	**24**	**25**	**25**
Fetuses evaluated Live Dead	364 364 0	371 371 0	361 361 0	365 365 0
Litters with fetuses with any alterations observed N(%)	6 (25.0%)	10 (41.7%)	12 (48.0%)	11 (44.0%)
Fetuses with any alteration observed N (%)	11 (3.0%)	22 (5.9%)	24 (6.6%)	16 (4.4%)
% fetuses with any alteration/litter	2.99 ± 6.68	6.18 ± 10.35	6.34 ± 9.30	4.37 ± 5.86

- Fetal gross external alterations

No fetal gross external alterations were observed.

- Fetal soft tissue alterations

One control group fetus and one 1000 mg/kg bw/d dosage group fetus had moderate dilation of the pelvis of one or both kidney. Therefore, as this was the only finding observed, occurring also in the control group, no fetal soft tissue alteration was considered treatment-related.

- Fetal skeletal alterations

One 1000 mg/kg bw/d dosage group fetus had malformed ribs (short, broad, bent) (fetal incidence: 0.5%, litter incidence: 4%). These alterations were not considered as treatment related because they were seen in only one fetus and their incidence were within the laboratory historical control data provided in the study report.

Some fetal skeletal variations occurred in all groups, including the control group, but were not considered treatment related since they also occurred in the control group and/or no dose relationship was observed.

Conclusion

The maternal NOAEL was set at 500 mg/kg bw/d, based on decreased body weights, body weight gains and food consumption observed at the dose level of 1000 mg/kg bw/d at the beginning of the treatment period (statistically significant decrease of -23% compared to the control group during days 6-12 of gestation) and during the whole treatment period (-11% compared to the control group during days 6-16 of gestation).

Based on the absence of adverse effect, the developmental NOAEL was 1000 mg/kg bw/d, the highest dose tested.

STUDY 2 – RABBIT (pilot study)

Anonymous (1995): An oral developmental toxicity (embryo-fetal toxicity/teratogenicity) pilot study with AC 299,263 in rabbits; Report n° 101-021P; Study date: May 10, 1995.

Test method: The study was conducted in compliance with the EPA Pesticide Assessment Guideline Subdivision F, 83-3 (test method equivalent to EEC Guideline 87/302/EEC, Part B, No. L133/24-26).

GLP: This study was conducted according to the:

- EPA (FIFRA) „GLP Standards; Final Rule“ (40 CFR Part 160),
- OECD „GLP in the Testing of Chemicals“ (ISBN 92-64-12367-9),
- EC Commission Directive - Annexes A and B (No. L 11/37-50),
- JMAFF „GLP Standards“, Notification n° 3850.

Deviations: None

Test system: Groups of 8 artificially inseminated New Zealand White rabbits were administered orally, via stomach tube, 0 (vehicle); 500; 750 and 1000 kg/bw/d of AC 299,263 technical (98.2% a.i.; lot n° AC 6935-63) in an aqueous suspension of 0.5% w/v carboxymethylcellulose (CMC) on d-7 through d-19 of presumed gestation. Suspensions of test substance in CMC were prepared weekly during the study at concentrations of 0; 50; 75 and 100 mg/ml and were assayed for confirmation analysis of test material content on the first and on the last day of the dosing period. All rabbits were examined daily during the dosing and postdosing periods, for viability, clinical signs, abortions,premature deliveries, body weight and food consumption. All surviving animals were sacrificed on d-29 presumed gestation and a gross necropsy was performed as well as in animals dying prematurely: uteri were weighed and examined for pregnancy, and number and distribution of implantations, live and dead fetuses, early and late resorptions and number of corpora lutea in each ovary were recorded. Each fetus was weighed and examined for viability, gross external alterations and sex (internal examination).

Results

The death of one high dose doe which occurred on d-22 of gestation, was considered as treatment related because of the following findings prior to death: abnormal feces (d-15 through 21 of gestation), weight loss and reduced food consumption (from d-7 of gestation); postmortem examination revealed ulcerations in the gallbladder, hemorrhagic lungs, parovarian cysts and a late resorption found in the vaginal canal and this doe had a litter of 3 early resorptions and 5 late resorptions. No deaths occured in the other does and there were no abortions or premature deliveries. Although commonly observed in rabbits, soft or liquid feces could be related to the test substance since it occurred in 2 of 8 does of the high dosage group only. There were no

other treatment related clinical or necropsy findings, the observation of dried feces and red substance in cage pan being considered at incidental (Table 10.10.4-5).

Table 10.10.4-5 Summary of clinical observations

Dose group (mg/kg bw/d)	**0**	**500**	**750**	**1000**
Rabbits examined	8	8	8	8
Found dead	0	0	0	1
Feces [b] soft/liquid dried	 0 / 0 0 / 0	 0 / 0 5 / 1	 0 / 0 0 / 0	 4 / 2 [a] 2 / 1 [a]

[a] : occurred in the doe found dead on d-22 gestation
[b] : total n° of observation : n° of rabbits with this osbervation

In the high dose group, absolute and relative feed consumption values and mean body weight and body weight gains were reduced during the entire dosing period, and were comparable to those of controls during the postdosage period; gravid uterine weights were also reduced and this was related to a smaller live litter size (Table 10.10.4-6). Gross necropsy findings were noted only for the doe in the high dose group that was found dead.

Table 10.10.4-6 Mean (± SD) bw (kg), bw changes (g), gravid uterine weights (g)

Dose group (mg/kg/d)	**0**	**500**	**750**	**1000**
Body weight (kg)				
d-0	3.56 ± 0.26	3.56 ± 0.17	3.58 ± 0.23	3.60 ± 0.17
d-7	3.76 ± 0.24	3.75 ± 0.18	3.77 ± 0.17	3.80 ± 0.22
d-19	3.88 ± 0.30	3.82 ± 0.18	3.87 ± 0.12	3.67 ± 0.28
d-29	4.06 ± 0.30	3.90 ± 0.25	4.07 ± 0.21	3.92 ± 0.22 [a]
Body weight gain (kg)				
d 0 - 7	+ 0.19 ± 0.10	+ 0.19 ± 0.08	+ 0.19 ± 0.07	+ 0.20 ± 0.11
d 7 - 20	+ 0.14 ± 0.10	+ 0.08 ± 0.06	+ 0.14 ± 0.10	- 0.13 ± 0.24
d 20 - 29	+ 0.16 ± 0.10	+ 0.07 ± 0.18	+ 0.16 ± 0.12	+ 0.19 ± 0.09
Gravid uterus weight (g)	413.0 ± 113.7	470.7 ± 97.2	538.9 ± 168.7	351.5 ± 194.3

[a] : exclude values for the high dose doe dead on d-22 gestation

Fetal litter evaluations for all remaining pregnant does occurred on d-29 of gestation following cesarean sectioning of the does. Absolute and group mean litter size was reduced and the percent resorbed conceptuses per litter was increased in the high dose group. These findings were considered possible effects of the test substance because they occurred at the highest dosage tested. Litter averages for corpora lutea, implantations, fetal body weight and percent male fetuses were comparable among the 4 dosage groups.

Similarly, there were no gross external fetal malformations observed that were caused by treatment of the does with AC 299,263 at dosages as high as 1000 mg/kg bw/d (Table 10.10.4-7).

Table 10.10.4-7 Summary of Caesarean-sectioning observations (Mean ± SD)

Dose group (mg/kg bw/d)	**0**	**500**	**750**	**1000**
Rats pregnant (n°)	**6**	**6**	**7**	**6**
Corpora lutea	10.7 ± 2.0	10.8 ± 1.8	11.7 ± 1.5	10.2 ± 2.2
Implantations	6.5 ± 2.0	8.7 ± 2.4	8.3 ± 2.6	6.0 ± 1.9
Litter size Live fetuses Dead fetuses	6.3 ± 1.9 6.3 ± 1.9 0	7.8 ± 1.7 7.8 ± 1.7 0	7.8 ± 2.5 7.8 ± 2.5 0	4.8 ± 2.8 4.8 ± 2.8 0
Resorptions Early Late	0.2 ± 0.4 0.2 ± 0.4 0.0 ± 0.0	0.8 ± 1.6 0.7 ± 1.6 0.2 ± 0.4	0.4 ± 0.5 0.4 ± 0.5 0.0 ± 0.0	1.2 ± 1.1 1.2 ± 1.1 0.0 ± 0.0
Does with any resorptions	1	2	3	4
Fetuses evaluated	38	47	55	24
Live male fetuses/litter	46.1 ± 15.5	44.6 ± 24.0	57.3 ± 14.4	42.1 ± 32.0
Live fetal bw (g)/litter	46.57 ± 3.534	41.97 ± 4.00	45.86 ± 5.05	48.22 ± 1.63
% Resorbed conceptuses/litter	2.1 ± 5.1	7.4 ± 13.4	4.9 ± 6.3	25.5 ± 28.8

Conclusion
Based on maternal toxicity (reduced body weight, body weight gains and feed consumption) as well as embryo-fetal mortality (increased resorptions) at 1000 mg/kg bw/d, dosages of 300, 600 and 900 mg/kg bw/d were selected for use in the definitive study.

STUDY 3 - RABBIT

Anonymous (1995): An oral developmental toxicity (embryo-fetal toxicity/teratogenicity) definitive study with AC 299,263 in rabbits; Report n° 101-021; Study date: May 10, 1995.

Test method: The study was conducted in compliance with the EPA Pesticide Assessment Guideline Subdivision F, 83-3 (test method equivalent to EEC Guideline 87/302/EEC, Part B, No. L133/24-26), OECD 414 (1981), JMAFF 59 NohSan No. 4200.

GLP: This study was conducted according to the:
- EPA (FIFRA) GLP Standards, 40 CFR Part 160,
- OECD GLP in the Testing of Chemicals (ISBN 92-64-12367-9),
- EC Commission Directive - Annexes A and B (No. L 11/37-50),
- JMAFF GLP Standards, Notification n° 3850.

Deviations: None.

Test system: Groups of 20 presumed pregnant New Zealand White [Hra:(NZW)SPF] rabbits were administered orally (via stomach tube) once daily, 0 (vehicle); 300; 600 and 900 kg/bw/d of AC 299,263 technical (98.2% a.i.; lot n° AC 6935-63) in an aqueous suspension of 0.5% w/v carboxymethylcellulose (CMC) on d-7 through d-19 of presumed gestation. Suspensions of test substance in CMC were prepared

daily during the study at concentrations of 0; 30; 60 and 90 mg/ml and were assayed for homogeneity, stability at study initiation and confirmation analysis of test material content on the first and on the last day of the dosing period. All rabbits were examined for viability, clinical signs, abortions,premature deliveries twice daily during the dosing period and daily during the postdosing period (d-19 through d-29 of presumed gestation). Body weights were recorded on d-0 and d-7 through d-19 and food consumption was recorded daily throughout the study. All surviving animals were sacrificed on d-29 presumed gestation and a gross necropsy was performed: uteri were weighed and examined for pregnancy, number and distribution of implantations, early and late resorptions and live and dead fetuses; the number of corpora lutea in each ovary were recorded. Each fetus was weighed, examined for gross external, and internally to identify sex, soft tissue and skeletal alterations.

Statistics: Maternal body weight and body weight changes, food consumption data, uterine weights and litter averages for percent male fetuses, percent resorbed conceptuses, fetal bw, fetal anomaly average data and fetal ossification site data were analyzed using Bartlett's test of homogeneity of variances and the analysis of variances when Bartlett's test was not significant at the 0.05 level. When ANOVA was significant at the 0.05 level, Dunnett's test was used to identify the statistical significance of the individual groups; if the ANOVA was not appropriate, the Kruskal-Wallis test was used when ≤ 75% ties were present; when this latter test was significant, Dunn's method of multiple comparisons was used to identify the statistical significance of the individual groups; if there were > 75% ties, Fisher's exact test was used. Count data observed at Caesarean sectioning of the dams were evaluated using the above procedures for the Kruskal-Wallis test.

Results

Assays of low and high dose suspensions indicated a good homogeneity and a good freezer storage stability; results of confirmation analysis showed that tests rabbits were properly dosed (Table 10.10.4-8)

Table 10.10.4-8 Summary of homogeneity, stability and diet analysis data (range finding and definitive studies)

	Sampling	**Nominal concentation (mg/mL)**	**Overall average & cv (% nominal)**
Homogeneity (d-0)	triplicate	50	94 ± 2
		100	95 ± 5
Stability „Freezer"	after 17 days	50	92± 2
		100	92 ± 4
Feed analysis	Range finding assay (dosing suspensions) 1 at first and last day* of dosing	50	94 ± 2 162*

		75	117 ± 4 157*
		100	56± 7 112*
	Definitive assay (dosing suspensions) d-1	30	100 ± 2
		60	99± 2
		90	97 ± 2
	Definitive assay (dosing suspensions) 20 d-freezer storage	30	98 ± 2
		60	97± 1
		90	92 ± 4
	Definitive assay (dosing suspensions) last day	30	96
		60	92
		90	96
	Overall mean (excluding freezer stability)		96 ± 4
	Fortification recoveries (overall mean)		99 ± 4

No mortalities or abortions occurred during the study. One high dose doe prematurely delivered, on d-29 of gestation, a litter of 10 conceptuses among which 8 were live pups that appeared normal for their developmental age and 2 were presumed cannibalized. This premature delivery was considered a possible effect of the test substance because this doe exhibited reduced body weight and food consumption after day 11 of gestation and abnormal feces on d-21 through d-29 gestation. No other doe prematurely delivered a litter. There were no clinical signs observed that were considered related to test substance intake.

There were no statistically significant differences in body weight or body weight changes for the entire dosage and postdosage periods for treated animals when compared to controls. Body weight changes were slightly affected in the mid dose group, but no differences were noted when body weight changes were calculated from d-7 through d-20 gestation excluding does with unilateral pregnancies i.e. 4 control does and 2 mid-dose does. In addition, a non statistically significant reduction in body weight gain was noted during the dosage period (19%) and postdosage period (21%) for does dosed at 900 mg/kg bw/d. Gravid uterine weights and d-29 body weight corrected for gravid uterine weights were not affected in any dose group by administration of AC 299263 technical (Table 10.10.4-9)

Table 10.10.4-9 Mean (± SD) body weight (kg), body weight changes (kg), gravid uterine weights (g)

Dose group (mg/kg bw/d)	**0**	**300**	**600**	**900**
n° pregnant/n° tested	**20/20**	**18/20**	**15/20**	**20/20**
Body weight (kg)				
d-0	3.44 ± 0.28	3.47 ± 0.26	3.47 ± 0.25	3.45 ± 0.31
d-7	3.53 ± 0.26	3.53 ± 0.27	3.50 ± 0.23	3.52 ± 0.31
d-20	3.80 ± 0.28	3.84 ± 0.30	3.75 ± 0.28	3.74 ± 0.36

d-29	4.04 ± 0.28	4.04 ± 0.34	3.95 ± 0.26	3.95 ± 0.38 [a]
Body weight gain (kg)				
d 0 - 7	+ 0.09 ± 0.08	+ 0.06 ± 0.10	+ 0.03 ± 0.07	+ 0.07 ± 0.08
d 7 - 20	+ 0.27 ± 0.10	+ 0.31 ± 0.06	+ 0.24 ± 0.12	+ 0.22 ± 0.14
d 20 - 29	+ 0.24 ± 0.10	+ 0.20 ± 0.08	+ 0.21 ± 0.11	+ 0.19 ± 0.09 [a]
Gravid uterus weight (g)	518.4 ± 111.6	538.8 ± 83.8	493.3 ± 176.7	525.6 ± 91.4 [a]
[a] : exclude values for the high dose doe which prematurely delivered on d-29 gestation				

The absolute and relative feed consumption values for the entire dosage period were reduced in all treatment groups compared to control values (3% for low dose group, 12-13% for mid-dose group and 15-16% for high dose group); the differences were significant ($p \leq 0.01$) in the mid and high dose groups, in which the pattern of decreased feed consumption increased with continued dosing for the majority of the dosing period (high dose level) or for the entire dosing period (mid-dose level); exclusion of the values for the 6 does with unilateral pregnancies did not affect the results. For the low dose group, only relative feed consumption was statistically significantly reduced ($p \leq 0.05$) during the dosing period, but this value was not longer significant after exclusion of the values for does with unilateral litters and the mean relative feed consumption value was well within 10% of the control group value (Table 10.10.4-10).

Table 10.10.4-10 Maternal absolute (g/d) and relative (g/kg bw/d) feed consumption values (mean ± SD)

Dose group (mg/kg bw/d)	**0**	**300**	**600**	**900**
n° pregnant/n° tested	**20/20**	**18/20**	**15/20**	**20/20**
Absolute feed consumption (g/d)				
d 7-10	181.5 ± 4.58	177.6 ± 15.0	174.8 ± 14.1	173.1 ± 14.6
d 7-20	181.4 ± 2.5	175.7 ± 13.6	158.0 ± 20.9	152.4 ± 23.4** [a]
d 20-29	168.2 ± 12.5	154.9 ± 23.8	155.9± 20.2	154.1 ± 21.3 [b]
d 7-29	175.9 ± 5.7	167.2 ± 15.1	157.2 ± 17.5**	155.5 ± 17.8** [b]
Relative feed consumption (g/kg bw/d)				
d 7-10	51.0 ± 3.3	49.9 ± 4.4	49.5 ± 5.5	48.6 ± 4.2
d 7-20	49.1 ± 3.2	47.8 ± 3.7	43.4 ± 5.6**	41.5 ± 5.6** [a]
d 20-29	43.0 ± 4.0	39.2 ± 4.2	40.6 ± 5.8	40.1 ± 6.0 [b]
d 7-29	46.7 ± 3.0	44.1 ± 2.6*	42.2 ± 4.7**	41.6 ± 4.5 ** [b]
* : $p \leq 0.05$ ** : $p \leq 0.01$ [a] : exclude values associated with spillage or wet feed [b] : exclude values for the high dose doe which prematurely delivered on d-29 gestation				

There were 20, 18, 15 and 19 pregnant does Caesarean-sectioned on d-29 gestation in the control, low dose, mid dose and high dose groups respectively; the significant reduction ($p \leq 0.01$) in pregnancy in the mid dose group was considered as incidental since it was not dose dependent. Gross necropsy findings for the does were considered unrelated to test substance intake. Litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weight and percent male fetuses were comparable among the 4 dosage groups (only a mid dose doe had a litter consisting only of 2 early resorptions: this event was not considered as treatment related since it was within historical range values of the laboratory and was not dose dependent) (Table 10.10.4-11).

Table 10.10.4-11 Summary of Caesarean-sectioning observations (Mean ± SD)

Dose group (mg/kg/d)	**0**	**300**	**600**	**900**
Rats pregnant (n°) **Prematurely delivered**	**20** **0**	**18** **0**	**15**** **0**	**20** **1**
Corpora lutea	10.2 ± 2.1	10.2 ± 1.8	9.5 ± 2.8	10.4 ± 1.9
Implantations	8.4 ± 2.0	8.6 ± 1.4	8.0 ± 2.8	8.7 ± 1.5
Litter size Live fetuses Dead fetuses	8.0 ± 2.0 8.0 ± 2.0 0	8.2 ± 1.4 8.2 ± 1.4 0	7.7 ± 3.0 7.7 ± 3.0 0	8.4 ± 1.6 8.4 ± 1.6 0
Resorptions Early Late	0.4 ± 0.7 0.4 ± 0.7 0.0 ± 0.0	0.3 ± 0.5 0.3 ± 0.5 0.0 ± 0.2	0.3 ± 0.6 0.2 ± 0.6 0.1 ± 0.2	0.3 ± 0.4 0.2 ± 0.4 0.0 ± 0.2
Does with any resorptions Does with all conceptuses resorbed	5 0	6 0	3 1	5 0
Litters evaluated Fetuses evaluated	20 160	18 148	14 116	19 160
Live male fetuses/litter	53.9 ± 18.1	48.9 ± 19.0	51.9 ± 30.2	46.9 ± 18.0
Live fetal bw (g)/litter	47.07 ± 4.32	47.12 ± 3.28	45.94 ± 4.71	44.58 ± 4.11
% Resorbed conceptuses/litter	3.8 ± 7.4	4.0 ± 6.0	1.6 ± 4.1	3.2 ± 5.7
Litters with fetuses with any alterations n/%	18 (90%)	16 (88.9%)	11 (78.6%)	17 (89.5%)
Fetuses with alterations n/%	39 (24.4%)	34 (23.0%)	32 (27.6%)	39 (24.4%)
% fetuses with any alteration/litter	25.36 ± 14.17	22.57 ± 16.23	26.06 ± 21.18	23.18 ± 17.04
** : $p \leq 0.01$				

Some fetal alterations have been observed during this study. Historical control data (HCD) for the developmental toxicity study in rabbits have been submitted by the applicant. All studies included in the HCD have been conducted using Hazleton research New Zealand White rabbits. Three files have been provided covering three different periods: studies performed from June 1992 to June 1995, from June 1994 to June 1996 and from June 1997 to June 1999. The experimental phase of the study with imazamox being performed in October-November 1993 (study report dated May 1995), only the two first files have been considered of adequate relevance in terms of covering period (1992-1995 and 1994-1996).
It should nevertheless be noted that the relevance of the provided HCD could be questionable. The studies included in the HCD were performed by several routes of administration (oral, intravenous, intramuscular,

intradermal, intraperitoneal, dermal, subcutaneous) and different vehicles were administered during different time periods (GD 6-18, GD 6-15, GD 6-28, GD 7-19, GD 7-18). The C-section was generally performed on Day 29 (2 studies on Day 18 and 1 study on Day 19). The HCD also included dosage-range studies using very few animals (i.e. 5 tested females). **The available HCD are thus considered of low relevance.** It is nevertheless considered that they can give information on the rarity of an alteration and are therefore reported in the following tables.

- Fetal gross external alterations

Two fetuses from the high dose group were externally malformed. One fetus had a short tail. The other fetus had fused first and second digits in the left hindpaw, the fusion being restricted to the soft tissue. This finding is considered as a malformation (by the study author and in the DevTox database).

Table 10.10.4-12 Fetal gross external alterations

Dose group (mg/kg bw/d)		**0**	**300**	**600**	**900**	**HCD 1992-1995 60 studies**		**HCD 1994-1996 37 studies**	
Litter evaluated	**N**	**20**	**18**	**14**	**19**	**701**		**405**	
Foetuses evaluated	**N**	**160**	**148**	**116**	**160**				
Live foetuses	**N**	**160**	**148**	**116**	**160**	**5264**		**3329**	
Dead foetuses	**N**	**0**	**0**	**0**	**0**				
						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)

- Fetal soft tissue alterations

The incidences of diaphragmatic hernia and absent gallbladder were not considered related to treatment as these isolated findings occurred without any dose-relationship.

One high-dose fetus, which also present skeletal alterations, presented ectopic and close-set kidneys.

A dose-related increased incidence of absent intermediate lobe of the lungs was observed in the mid- and high-dose groups, the fetal incidence reaching a statistical significance at 900 mg/kg bw/d. The HCD provided by the applicant (and reported in Table 10.10.4-13) included not only fetuses with agenesis of the intermediate lobe of the lung but included also foetuses with partial or complete agenesis of one or more lobe and therefore the comparison to the finding of absent intermediate lobe of the lungs was not possible.

To address this concern, the applicant provided a position paper reviewing 60 developmental toxicity studies in rabbits conducted between 1992 and 1997 in order to examine the incidence of agenesis of the intermediate lobe of the lung only. Of these 60 studies, agenesis of the intermediate lobe of the lung occurred in the control group in 49 studies. The incidence range was 0 to 13 fetuses from 0 to 6 litters. Overall 8227 fetuses from 1073 litters were observed in these 60 studies. There were 108 (10.0%) litters and 140 (1.7%) fetuses with this finding (Table 10.10.4-14). Despite the fact that incidences of agenesis of the intermediate lobe of the lung lied within ranges of HCD at both the mid- and high-dose levels, they exceeded the mean value of HCD. Considering the dose-response relationship and the low relevance of the provided HCD (see above), it cannot be excluded that this effect was treatment-related.

Table 10.10.4-13 Fetal soft tissue alterations

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**	
Foetuses evaluated	**N**	**160**	**148**	**116**	**160**				
Live foetuses	**N**	**160**	**148**	**116**	**160**	**4479**		**2425**	
Dead foetuses	**N**	**0**	**0**	**0**	**0**				
						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]
						Total	*Range/study*	*Total*	*Range/study*
Diaphragm									
Diaphragmatic hernia									
Litter incidence	N (%)	1 (5.0)	1 (5.0)	0	0	3 (0.51)	0-1 (0-7.1)	2 (0.67)	0-1 (0-5.9)
Fetal incidence	N (%)	1 (0.6)	1 (0.7)	0	0	3 (0.07)	0-1 (0-1.1)	2 (0.08)	0-1 (0-0.8)
						Total	*Range/study*	*Total*	*Range/study*
Kidneys									
Ectopic									
Litter incidence	N (%)	0	0	0	1 (5.3)	1 (0.17)	0-1 (0-6.2)	-	-
Fetal incidence	N (%)	0	0	0	1 (0.6)[a]	1 (0.02)	0-1 (0-0.8)	-	-
Close-set									
Litter incidence	N (%)	0	0	0	1 (5.3)	-	-	-	-
Fetal incidence	N (%)	0	0	0	1 (0.6)[a]	-	-	-	-
						Total	*Range/study*	*Total*	*Range/study*
Gallbladder									
Absent									
Litter incidence	N (%)	0	1 (5.6)	0	0	1 (0.17)	0-1 (0-5.3)	-	-
Fetal incidence	N (%)	0	1 (0.7)	0	0	1 (0.02)	0-1 (0-0.7)	-	-

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

[a] Same fetus 23555-6, which also had other alterations.

[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)

Table 10.10.4-14 Incidence of absent intermediate lobe in historical control data based on a review of the control data by the applicant

Dose group (mg/kg bw/d)		**HCD 1992-1997 60 studies**	
Litter evaluated	**N**	**1073**	
Live foetuses	**N**	**8227**	
		Total	*Range/study*
Lung			
Intermediate lobe, absent			
Litter incidence	N (%)	108 (10)	0-6 (0-31.2)
Fetal incidence	N (%)	140 (1.70)	0-13 (0-6.4)

- Fetal skeletal alterations

Several skeletal alterations were observed in rabbit fetuses. Selected findings are reported in Table 10.10.4-15.

The fetal incidence of displaced nasal suture was statistically significantly increased in the mid-dose group. Nevertheless, this effect was considered unrelated to treatment as no dose-relationship was observed .

The main effects on cervical and thoracic vertebrae consisted of effects described as follows:
One 600 mg/kg bw/day dose group fetus (23546-2) had scrambling of the cervical vertebra (hemivertebra present in the 4th cervical vertebra and fused centra of the 3rd trought 5th cervical vertebra). Another fetus from this group (23543-1) showed only thoracic hemivertebrae.

Three 900 mg/kg bw/d dosage group foetuses had cervical vertebral malformations:
- One (23560-10) had a hemivertebra present as the 2nd cervical vertebra and fused centra in the 5th and 6th cervival vertebra; this fetus also had interrelated vertebral-rib malformations: assymetric centrum in the second thoracic vertebra; fused bases of the 2nd and 3rd and 4th and 5th right ribs (the 4th and 5th right ribs were fused from the bases to the medial portions).
- Another (23555-7) had hemivertebra present as the 5th cervical vertebra, only 6 cervical vertebrae present; fused centra (left) in the 2nd and 3rd thoracic vertebra, assymetric centrum in the 4th thoracic vertebra, hemivertebra present as the 5th thoracic vertebra and an unossified first left thoracic rib.
- Another (23555-3) had hemivertebra (right) as the 5th cervical vertebra, fused arches in the 1st and 2nd cervical vertebrae, centrum in the 4th cervical vertebra unilaterally (left) ossified, small arches in the 5th and 7th cervical vertebrae, fused centra in the 1st and 2nd cervical and in the 7th cervical and 1st thoracic vertebrae, hemivertebrae (left) as the 1st and 5th thoracic vertebra. Reflected by the short tail, the 4th through 8th and 11th through 14th caudal vertebrae were fused. Variations in sternal ossifications were also observed (fused 1st and 2nd vertebrae, 1st sternebrae incompletely ossified, 2nd vertebrae assymetric).

As shown in the table, the incidence of some findings exceeded the range of available (low relevant) HCD, or were not reported in these HCD. These included mainly vertebral findings (cervical, thoracic, sacral).
The following findings were not observed in the provided HCD : cervical hemivertebrae (1 fetus at 600 mg/kg bw/d and 3 fetuses from 2 litters at 900 mg/kg bw/d), small arch in cervical vertebrae (1 fetus at 900 mg/kg bw/d), only 6 cervical vertebrae present (1 fetus at 900 mg/kg bw/d), sacral arch not ossified (1 fetus at 900 mg/kg bw/d) and unossified rib (1 fetus at 900 mg/kg bw/d).
The fetal incidence of thoracic hemivertebrae (1 fetus at 600 mg/kg bw/d and 2 fetuses from 1 litter at 900 mg/kg bw/d) and the fetal and litter incidences of assymetric thoracic centrum (2 fetuses from 2 litters at 900 mg/kg bw/d) exceeded the range of HCD at the high dose level.
According to the DevTox database, cervical and thoracic hemivertebrae, as well as reduced number of cervical vertebrae, are considered as malformations, whereas small cervical arch, assymetric thoracic centrum, unossified sacral arch and unossified ribs are classified in the Grey Zone (i.e. no consensus on whether they should be considered as variations or malformations).

The applicant provided in a position paper further information on the HCD for the incidence of cervical hemivertebrae. The incidence of this finding was examined in 60 developmental toxicity studies in rabbits conducted in their facility between 1992 and 1997. Two fetuses presented this malformation. It is noted that the applicant proposed to examine incidences across all dose groups, which is not considered adequate: including all dose groups there were over 5300 litters and 47000 fetuses examined for skeletal malformations and seven fetuses from six studies were observed with this malformation (two of these foetuses being from a control group litter).
Amongst the HCD provided by the applicant in three different files, no occurrence of cervical hemivertebrae was observed in studies performed from June 1992 to June 1995 and from June 1994 to June 1996. This finding was observed in 2 studies performed by intravenous route from June 1997 to June 1999: one study from 1998 and one study from 1999[6], these HCD being not considered relevant considering the dates at which the studies were conducted and the route of exposure, in addition to their low relevance as described above (e.g. inclusion of dose-ranging studies). It is noted that this observation is contradictory with the 2 incidences of cervical hemivertebrae occuring between 1992 and 1997 as reported in the applicant position paper.
The very low number of observed cases in these HCD of low relevance highlights the fact that cervical hemivertebrae is a very rare malformation. Overall, it was considered that this dose-related finding, which was confirmed to be a very rare malformation according to the available (low relevant) HCD, was treatment-related and toxicologically relevant from the dose level of 600 mg/kg bw/d.

Table 10.10.4-15 Selected fetal skeletal alterations

[6] HCD from June 1997 to June 1999, 38 studies, 712 litters examined, 5884 fetuses examined. Cervical hemivertebrae, litter incidence: Total n=2 (0.28%) Range 0-1 (0-5.0%); fetal incidence: Total n=2 (0.03%) Range 0-1 (0-0.6%).

Dose group (mg/kg bw/d)		**0**	**300**	**600**	**900**	**HCD 1992-1995 35 studies**		**HCD 1994-1996 18 studies**	
Litter evaluated	**N**	**20**	**18**	**14**	**19**	**586**		**316**	
Foetuses evaluated	**N**	**160**	**148**	**116**	**160**				
Live foetuses	**N**	**160**	**148**	**116**	**160**	**4436**		**2544**	
Dead foetuses	**N**	**0**	**0**	**0**	**0**				
Skull									
						Total	*Range/study*	*Total*	*Range/study*
Skull – irregular ossification									
Nasals, midline suture displaced									
Litter incidence	N (%)	8 (40.0)	8 (44.4)	8 (57.1)	10 (52.6)	270 (46.1)[a]	3-18 (16.7-75)[a]	68 (21.5)[a]	0-8 (0-41.2)[a]
Fetal incidence	N (%)	9 (5.6)	11 (7.4)	**17 (14.6)**** [d]	11 (6.9)[e]	401 (9.04)[a]	3-30 (1.8-18.3)[a]	78 (3.07)[a]	0-10 (0-7.7)[a]
						Total	*Range/study*	*Total*	*Range/study*
Skull – irregular ossification									
Interparietals, incompletely ossified									
Litter incidence	N (%)	0	0	0	1 (5.3)	1 (0.17)[b]	0-1 (0-6.2)[b]	-	-
Fetal incidence	N (%)	0	0	0	1 (0.6)[e]	1 (0.02)[b]	0-1 (0-0.8)[b]	-	-
						Total	*Range/study*	*Total*	*Range/study*
Skull – other alterations									
Parietal, contains a hole									
Litter incidence	N (%)	0	0	0	2 (10.5)	12 (2.05)	0-1 (0-7.1)	6 (1.90)	0-2 (0-12.5)
Fetal incidence	N (%)	0	0	0	2 (1.2)[e,j]	18 (0.41)	0-5 (0-5.2)	9 (0.35)	0-5 (0-4.1)
Vertebrae									
						Total	*Range/study*	*Total*	*Range/study*
Vertebrae									
Cervical, hemivertebra									
Litter incidence	N (%)	0	0	**1 (7.1)**	**2 (10.5)**	-	-	-	-
Fetal incidence	N (%)	0	0	**1 (0.9)[g]**	**3 (1.9)[h,i,k]**	-	-	-	-
						Total	*Range/study*	*Total*	*Range/study*
Vertebrae									
Cervical, centrum, unilateral ossification									
Litter incidence	N (%)	0	0	0	2 (10.5)	4 (0.68)	0-2 (0-11.8)	3 (0.95)	0-2 (0-11.8)
Fetal incidence	N (%)	0	0	0	2 (1.2)[e,i]	4 (0.09)	0-2 (0-1.5)	3 (0.12)	0-2 (0-1.5)
						Total	*Range/study*	*Total*	*Range/study*
Vertebrae									
Cervical, centra/arches, fused						Arches fused	Arches fused	Arches fused	Arches fused
Litter incidence	N (%)	0	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	0	1 (0.9)[g] (centra fused)	2 (1.2) (1 centra fused[h], 1 arches fused[i])	1 (0.02)	0-1 (0-0.8)	1 (0.04)	0-1 (0-0.8)
						Centra fused	Centra fused	Centra fused	Centra fused
Litter incidence	N (%)					1 (0.17)	0-1 (0-6.2)	-	-
Fetal incidence	N (%)					1 (0.02)	0-1 (0-0.8)	-	-
						Total	*Range/study*	*Total*	*Range/study*
Vertebrae									
Cervical, arch, small									
Litter incidence	N (%)	0	0	0	**1 (5.3)**	-	-	-	-
Fetal incidence	N (%)	0	0	0	**1 (0.6)[i]**	-	-	-	-
						Total	*Range/study*	*Total*	*Range/study*
Vertebrae									
Cervical, 6 present									
Litter incidence	N (%)	0	0	0	**1 (5.3)**	-	-	-	-
Fetal incidence	N (%)	0	0	0	**1 (0.6)[k]**	-	-	-	-
						Total	*Range/study*	*Total*	*Range/study*
Vertebrae									
Thoracic, hemivertebra									
Litter incidence	N (%)	0	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	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)
						Total	*Range/study*	*Total*	*Range/study*
Vertebrae									
Thoracic, centra, fused									
Litter incidence	N (%)	0	0	0	1 (5.3)	6 (1.02)[c]	0-2 (0-10.5)[c]	3 (0.95)[c]	0-1 (0-5.9)[c]
Fetal incidence	N (%)	0	0	0	1 (0.6)[k]	6 (0.14)[c]	0-2 (0-1.4)[c]	3 (0.12)[c]	0-1 (0-0.6)[c]

Dose group (mg/kg bw/d)	**0**	**300**	**600**	**900**	**HCD 1992-1995 35 studies**		**HCD 1994-1996 18 studies**	
					Total	*Range/study*	*Total*	*Range/study*
Vertebrae								
Thoracic, centrum, bifid								
Litter incidence N (%)	0	0	0	1 (5.3)	1 (0.17)	0-1 (0-5.3)	2 (0.63)	0-1 (0-5.3)
Fetal incidence N (%)	0	0	0	1 (0.6) [k]	1 (0.02)	0-1 (0-0.7)	2 (0.08)	0-1 (0-0.6)
					Total	*Range/study*	*Total*	*Range/study*
Vertebrae								
Thoracic, centrum, assymetric								
Litter incidence N (%)	0	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	0	**2 (1.2)** **[h,k]**	1 (0.02)	0-1 (0-0.8)	2 (0.08)	0-1 (0-0.8)
					Total	*Range/study*	*Total*	*Range/study*
Vertebrae								
Sacral, arch, not ossified								
Litter incidence N (%)	0	0	0	**1 (5.3)**	-	-	-	-
Fetal incidence N (%)	0	0	0	**1 (0.6)** [j]	-	-	-	-
					Total	*Range/study*	*Total*	*Range/study*
Vertebrae								
Caudal, fused								
Litter incidence N (%)	0	0	0	1 (5.3)	5 (0.85)	0-1 (0-7.1)	5 (1.58)	0-1 (0-5.9)
Fetal incidence N (%)	0	0	0	2 (1.2) [i,j]	8 (0.18)	0-4 (0-2.8)	7 (0.28)	0-3 (0-1.9)
					Total	*Range/study*	*Total*	*Range/study*
Vertebrae								
Caudal, misaligned								
Litter incidence N (%)	0	0	1 (7.1)	0	20 (3.41)	0-3 (0-17.6)	14 (4.43)	0-3 (0-17.6)
Fetal incidence N (%)	0	0	1 (0.9) [d]	0	22 (0.50)	0-3 (0-2.4)	14 (0.55)	0-3 (0-2.3)
Ribs								
					Total	*Range/study*	*Total*	*Range/study*
Ribs								
Not ossified								
Litter incidence N (%)	0	0	0	**1 (5.3)**	-	-	-	-
Fetal incidence N (%)	0	0	0	**1 (0.6)** [k]	-	-	-	-
					Total	*Range/study*	*Total*	*Range/study*
Ribs								
Fused								
Litter incidence N (%)	0	0	0	1 (5.3)	9 (1.54)	0-2 (0-10.5)	3 (0.95)	0-1 (0-5.9)
Fetal incidence N (%)	0	0	0	1 (0.6) [h]	9 (0.20)	0-2 (0-1.4)	3 (0.12)	0-1 (0-0.6)
Sternal Centra								
					Total	*Range/study*	*Total*	*Range/study*
Sternal centra								
Incompletely ossified								
Litter incidence N (%)	0	0	0	1 (5.3)	9 (1.54)	0-2 (0-11.8)	5 (1.58)	0-2 (0-11.8)
Fetal incidence N (%)	0	0	0	1 (0.6) [i]	10 (0.23)	0-3 (0-2.3)	6 (0.24)	0-3 (0-2.3)
					Total	*Range/study*	*Total*	*Range/study*
Sternal centra								
Fused								
Litter incidence N (%)	1 (5.0)	1 (5.6)	1 (7.1)	3 (15.8)	42 (7.17)	0-5 (0-27.8)	23 (7.28)	0-5 (0-27.8)
Fetal incidence N (%)	1 (0.6)	1 (0.7)	1 (0.9)	3 (1.9) [i]	48 (1.08)	0-6 (0-4.7)	26 (1.02)	0-6 (0-4.7)
					Total	*Range/study*	*Total*	*Range/study*
Sternal centra								
Assymetric								
Litter incidence N (%)	0	0	0	1 (5.3)	7 (1.19)	0-2 (0-11.8)	5 (1.58)	0-1 (0-5.9)
Fetal incidence N (%)	0	0	0	1 (0.6) [i]	8 (0.18)	0-2 (0-1.4)	5 (0.20)	0-1 (0-0.8)

[a] Displaced suture
[b] Interparietals and supraoccipitals: incompletely ossified
[c] Thoracic, Arches and/or centra fused
[d] Fetus 23543-7 also had other skeletal malformations
[e] Fetus 23559-6 also had other skeletal malformations
[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

Conclusion

The maternal NOAEL was set at 300 mg/kg bw/d based on reduced maternal feed consumption values in the 600 mg/kg bw/d group. The developmental NOAEL was agreed at 300 mg/kg bw per day, based on cervical vertebra malformation (hemivertebrae) and absent intermediate lobe of the lungs observed from 600 mg/kg bw/d.

Other fetal alterations (including malformations), observed at the highest tested dose of 900 mg/kg bw/d, were shown to be rare according to the the available HCD. They occurred in one or two fetuses each and included fused digits in the hindpaw, cervical vertebrae findings (small arch, reduced number), thoracic vertebrae findings (hemivertebrae (also one occurrence at 600 mg/kg bw/d), assymetric centrum), sacral vertebrae findings (unossified arch) and ribs (unossified).

Table 72: Summary table of human data on adverse effects on development

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No human data				

Table 83: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

The prenatal developmental toxicity of imazamox was investigated in the rat and in the rabbit. The developmental toxicity studies in rats and rabbits were designed to meet requirements established for the following: US EPA Guideline (Subdivision F, 83-3), OECD Guideline 414 and Japanese MAFF Guideline (No. 59 NohSan No. 4200, 1985). They were performed in 1994-1995 according to the OECD 414 guideline (1981) which was in place and standard at that time. The major deviation to the current OECD 414 guideline (updated in 2001) comprises that the treatment was done during organogenesis only (GD 6-15 in rats or GD 7-19 in rabbits).

In the developmental rat toxicity study, maternal toxicity was manifested as decreased body weights, body weight gains and food consumption observed at the dose level of 1000 mg/kg bw/d at the beginning of the treatment period (statistically significant decrease of -23% compared to the control group during days 6-12 of gestation) and during the whole treatment period (-11% compared to the control group during days 6-16 of gestation). No treatment-related adverse effect were observed on rat fetuses under the conditions of this study.

In the main developmental toxicity study in rabbits, developmental effects were observed from the intermediate dose level of 600 mg/kg bw/d onwards and consisted of cervical vertebra malformation (hemivertebrae) and absent intermediate lobe of the lungs. At the highest tested dose of 900 mg/kg bw/d, other fetal alterations (including malformations) were observed. They occurred in one or two fetuses each and included fused digits in the hindpaw, cervical vertebrae findings (small arch, reduced number), thoracic vertebrae findings (hemivertebrae (also one occurrence at 600 mg/kg bw/d), assymetric centrum), sacral vertebrae findings (unossified arch) and ribs (unossified). The available historical control data showed that these findings were very rare. In this study, maternal toxicity was present from the intermediate dose level of 600 mg/kg bw/d group onwards and consisted of reduced maternal feed consumption values. Decreased maternal body weight gains were only observed at the highest tested dose of 900 mg/kg bw/d: non

statistically significant reduction in body weight gain was noted during the dosage period (19%) and postdosage period (21%) in this group.

10.10.6 Comparison with the CLP criteria

The CLP criteria for adverse effects on development of the offspring stated the following:

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

In the main rat and rabbit developmental toxicity studies, no death of the developing organism was observed up to the highest tested doses (1000 mg/kg bw/d in rats, 900 mg/kg bw/d in rabbits), although increased resorptions occurred at the dose level of 1000 mg/kg bw/d in the rabbit pilot study.

In the rat, no treatment-related adverse effect on the development of the offsprings (either impaired fetal weight or fetal gross external, soft tissue or skeletal alterations) was observed up to 1000 mg/kg bw/d.

In the main rabbit study, fetal weight was not statistically significantly impaired compared to the control group up to 900 mg/kg bw/d. Nevertheless, fetal alterations have been observed during this study and are summarised below:

Agenesis of intermediate lobe of the lung
A dose-related increased incidence of absent intermediate lobe of the lungs was observed in the mid- (2 fetuses (1.7%) from 2 litters (14.3%)) and high-dose (6 fetuses (3.8%) from 4 litters (21%)) groups, the fetal incidence reaching a statistical significance at the highest tested dose of 900 mg/kg bw/d.
In a position paper provided by the applicant reviewing 60 developmental toxicity studies in rabbits conducted between 1992 and 1997, the percent incidence range of this finding was 0 to 6.4% fetuses (mean 1.7%) from 0 to 31.2% litters (mean 10%).
Despite the fact that incidences of agenesis of the intermediate lobe of the lung lied within ranges of historical control data at both the mid- and high-dose levels, they largely exceeded the mean value of historical control data. Considering the clear dose-response relationship and the low relevance of the provided historical control data (in terms of routes of exposure, administration period, dose-range finding studies examining low number of fetuses… - see above), it cannot be excluded that this effect was treatment-related from the intermediate dose level onwards.
According to the DevTox database, absent lung lobe is a finding classified in the Grey Zone (i.e. no consensus on whether it should be considered as a variation or a malformation).

Skeletal alterations (particularly cervical, thoracic and sacral vertebrae alterations)
Several skeletal alterations, including malformations, were observed in rabbit fetuses.
Cervical hemivertebrae were observed in one foetus in the intermediate dose group and in 3 foetuses from 2 litters in the high dose group. Cervical hemivertebrae is a very rare malformation and no occurrence of this finding was reported in the contemporary historical control data (studies performed from June 1992 to June 1995 and from June 1994 to June 1996). Therefore, considering also the dose-relationship of this finding, it is considered that cervical hemivertebrae were treatment-related and toxicologically relevant from the intermediate dose level onwards.

In addition to cervical hemivertebrae, thoracic hemivertebrae were observed in one foetus in the intermediate dose group (foetus different from the one presenting cervical hemivertebrae) and 2 foetuses from one litter in the high dose group (same foetuses than those presenting cervical hemivertebrae). The historical control data confirmed the rarity of this finding.
Another vertebral malformation (reduced number of cervical vertebrae) also occurred in one high-dose foetus presenting cervical and thoracic hemivertebrae. No occurrence of this finding was reported in the historical control data.
Other skeletal anomalies, not reported in the historical control data or with a low incidence demonstrating the rarity of these findings, were observed at the highest dose level and included: small cervical arch (one foetus), assymetric thoracic centrum (2 foetuses from 2 litters), unossified sacral arch (one foetus) and unossified ribs (one foetus). According to DevTox database, these anomalies are classified in the Grey Zone (i.e. no consensus on whether they should be considered as variations or malformations).

Fused digits
One foetus in the high dose group had fused first and second digits in the left hindpaw, the fusion being restricted to the soft tissue. No occurrence of this finding was reported in the available historical control data. This alteration is considered as a malformation according to the study author and to DevTox database.

According to Regulation (EC) No 1272/2008 a substance is classified for adverse effect on developemnt in one of the following categories:

Category 1: Known or presumed human reproductive toxicant
Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

- ***Category 1A: Known human reproductive toxicant***

The classification of a substance in Category 1A is largely based on evidence from humans.

- ***Category 1B: Presumed human reproductive toxicant***

The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Category 2: Suspected human reproductive toxicant
Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.
Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

In the absence of human data on reproductive toxicity potential of imazamox, category 1A is not triggered.

Fetal alterations were observed in the rabbit foetuses in the developmental toxicity study with imazamox.

Skeletal malformations were observed and consisted mainly of dose-related increased incidence of **cervical hemivertebrae**, which is considered a very rare malformation not reported in the historical control data. One foetus presented cervical hemivertebrae in the intermediate dose group and 3 fetuses from 2 different litters were affected at the highest dose level. In addition, two other skeletal malformations were reported:

- **thoracic hemivertebrae** in the intermediate (one foetus) and high (two foetuses) dose groups, in one litter in each group.
- **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 low relevant historical control data, were observed at the high dose level.

A fetal gross external malformation, i.e. **fused digits of the hindpaw**, was reported in one foetus in the high dose level. No occurrence of this finding was reported in the available historical control data.

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, maternal toxicity consisted of decreased food consumption in the intermediate dose group with no impact on body weight and body weight gains. At the highest tested dose, decreased maternal body weight gains were also observed (non statistically significant reduction in body weight gain during the dosage period (19%) and postdosage period (21%)).

Nevertheless, due to the nature of the fetal anomalies observed in the rabbit foetuses (i.e. malformations and alterations not considered as delayed development), it is considered that they were not secondary non-specific consequences of maternal toxicity. Therefore classification of imazamox for developmental toxicity is considered adequate.

Due to the rather slight incidences of each of the fetal anomalies in rabbits and the absence of developmental toxicity in rats, classification in category 1B seems not warranted.

Therefore, based on the fetal anomalies (cervical hemivertebrae and other skeletal malformations/alterations, as well as absence of the intermediate lobe of the lungs) observed at the dose levels of 600 and 900 mg/kg bw/d in the rabbit developmental toxicity only, imazamox needs to be classified as Repr 2 H361d according to Regulation (EC) No 1272/2008.

10.10.7 Adverse effects on or via lactation

Table 94: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Two generation reproduction Guideline EPA 83-4, OECD 416 GLP Oral (diet) Rat, Sprague-	Imazamox (AC 299,263, batch number AC 6935-63, purity 98.2-97.1% a.i.) Dose levels: 0, 1000, 10000 and 20000 ppm	**Parental toxicity** <u>Up to 20000 ppm (1469 mg/kg bw/day)</u>: No effect ***Parental NOAEL 1469 mg/kg bw/day*** **Reproductive toxicity**	Anonymous (1995)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Dawley (Crl:CD®BR) 30/sex/group		Up to 20000 ppm (1469 mg/kg bw/day): No effect ***Reproductive NOAEL 1469 mg/kg bw/day*** **Offspring toxicity** Up to 20000 ppm (1469 mg/kg bw/day): No effect ***Offspring NOAEL 1469 mg/kg bw/day***	

Table 105: Summary table of human data on effects on or via lactation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No human data				

Table 116: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant study				

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

In the 2-generation study performed with imazamox, no adverse effect was observed in the offsprings. There was no indication of impaired nursing behaviour or decreased pup viability during lactation. The results of the study do not indicate any direct, adverse effect on the offspring due to transfer of the chemical via the milk or to the quality of the milk.

10.10.9 Comparison with the CLP criteria

The classification is intended to indicate when a substance may cause harm due to its effects on or via lactation and is independent of consideration of the reproductive or developmental toxicity of the substance. There were no effects to warrant classification of imazamox for effects on or via lactation.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

The classification and labelling of imazamox for reproductive toxicity is proposed to be:

Repr 2 H361d Suspected of damaging the unborn child

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 Litter incidence N(%) Fetal incidence N(%)	 0 0	 **1 (7.1)** **1 (0.9)**	 **2 (10.5)** **3 (1.9)**[h,i,k]	*Total* - -	*Range/study* - -	*Total* - -	*Range/study* - -
Vertebrae Cervical, centra/arches, fused Litter incidence N (%) Fetal incidence N (%) Litter incidence N (%) Fetal incidence N (%)	 0 0 	 1 (7.1) 1 (0.9)[g] (centra fused) 	 2 (10.5) 2 (1.2) (1 centra fused[h], 1 arches fused[i]) 	*Total* Arches fused 1 (0.17) 1 (0.02) Centra fused 1 (0.17) 1 (0.02)	*Range/study* Arches fused 0-1 (0-5.9) 0-1 (0-0.8) Centra fused 0-1 (0-6.2) 0-1 (0-0.8)	*Total* Arches fused 1 (0.32) 1 (0.04) Centra fused - -	*Range/study* Arches fused 0-1 (0-5.9) 0-1 (0-0.8) Centra fused - -
Vertebrae Cervical, arch, small Litter incidence N (%) Fetal incidence N (%)	 0 0	 0 0	 **1 (5.3)** **1 (0.6)**[i]	*Total* - -	*Range/study* - -	*Total* - -	*Range/study* - -
Vertebrae Cervical, 6 present Litter incidence N (%) Fetal incidence N (%)	 0 0	 0 0	 **1 (5.3)** **1 (0.6)**[k]	*Total* - -	*Range/study* - -	*Total* - -	*Range/study* - -
Vertebrae Thoracic, hemivertebrae Litter incidence N (%) Fetal incidence N (%)	 0 0	 1 (7.1) 1 (0.9) [f]	 1 (5.3) **2 (1.2)**[i,k]	*Total* 7 (1.19) 7 (0.16)	*Range/study* 0-1 (0-7.7) 0-1 (0-1.1)	*Total* 3 (0.95) 3 (0.12)	*Range/study* 0-1 (0-5.9) 0-1 (0-0.8)
Vertebrae Thoracic, centrum, asymmetric Litter incidence N (%) Fetal incidence N (%)	 0 0	 0 0	 **2 (10.5)** **2 (1.2)**[h,k]	*Total* 1 (0.17) 1 (0.02)	*Range/study* 0-1 (0-6.2) 0-1 (0-0.8)	*Total* 2 (0.63) 2 (0.08)	*Range/study* 0-1 (0-6.2) 0-1 (0-0.8)

Vertebrae				*Total*	*Range/study*	*Total*	*Range/study*
Sacral, arch, not ossified							
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**.

10.11 Specific target organ toxicity-single exposure

Not applicable, not addressed in this proposal.

10.12 Specific target organ toxicity-repeated exposure

Not applicable, not addressed in this proposal.

10.13 Aspiration hazard

Not applicable, not addressed in this proposal.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 12: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Ready biodegradability **OECD 301B**	After 29 days, %$ThCO_2$ is 25-37 % for imazamox. Imazamox cannot be classified as readily biodegradable under the test conditions.	-	Gorman, M.; 1994a (please refer to Vol. 3 B.8.2.2.1 page 175 for detailed summary)
Ready biodegradability **OECD 301B**	After 28 days, %CO_2/$ThCO_2$ is <10% for imazamox. Imazamox cannot be classified as readily biodegradable under the test conditions.	-	Schwarz, H.; 2012a (please refer to Vol. 3 B.8.2.2.1 page 176 for detailed summary)
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, DT_{50} are 11.9 days at 50°C, 4.17 days at 60°C and 1.7 days at 70°C. Extrapolated DT_{50} at 25°C is 192 days and imazamox is therefore considered stable to hydrolysis at pH9.	-	Holman, J.; 1997a (please refer to Vol. 3 B.8.2.1.1 page 161 for detailed summary)

11.1.1 Ready biodegradability

Please refer to 11.1.

11.1.2 BOD_5/COD

No data available.

11.1.3 Hydrolysis

Please refer to 11.1.

11.1.4 Other convincing scientific evidence

Table 13: Summary of other convincing scientific evidence

Method	Results	Remarks	Reference
Photolysis **OECD 316** **US EPA OPPTS 835.2240**	Continuous irradiation by a Xenon arc lamp (wavelengths >290 nm, equivalent to natural sunlight at 40°N latitude) during 15 days. Imazamox is rapidly degraded under irradiated conditions with a DT50 of 0.2 day. No degradation is observed in dark control.	-	Singh, M.; 2013a (please refer to Vol. 3 B.8.2.1.2 page 166 for detailed summary)
Aerobic mineralisation **OECD 309**	Pelagic test system. Imazamox is not significantly degraded under the conditions of the test. After 63 days more than 95% AR is recovered as the unchanged active substance. Mineralization is ≤1% AR after 63 days.	-	Ebert, D.; 2013a (please refer to Vol. 3 B.8.2.2.2 page 177 for detailed assessment)
Water/sediment **BBA Part IV, Section 5-1**	2 systems: Mill stream pond and Iron Harch run-off. Imazamox is not degraded in total system to a level > 70 % within a 28-day period. After 103 days, imazamox amounts to 23.7-28.8%	-	McCullough, J. & Lewis, C.J.; 1997a (please refer to Vol. 3 B.8.2.2.3 page 181 for detailed assessment)

Method	Results	Remarks	Reference
	AR in the water phase, 26.7-33.9% AR in the sediment phase and 55.5-57.6% AR in total system. Maximum amount in sediment: 48.0% AR after 61 d. Mineralization: 3.6-4.0% AR after 103 days. DT50 in total system are 129-155 days (DT90: 430-516 days). DissT50 in water compartment are 67.1-76.4 days (DissT90: 194-206 days). DissT50 in sediment not determined.		Kinetic analysis presented in Donaldson 2013b (please refer to Vol. 3 B.8.2.2.3 page 197 for detailed assessment)
Water/sediment **OECD 308** **US EPA OPPTS 835.4300**	2 systems: Golden Lake and Goose River. Imazamox is not degraded in total system to a level > 70 % within a 28-day period. After 100 days, imazamox amounts to 31.0-71.6% AR in the water phase, 11.2-35.0% AR in the sediment phase and 61.4-83.4% AR in total system. Maximum amount in sediment: 35.0% AR after 100 d. Mineralization0.3-0.6% AR after 100 days. DT50 in total system are 283-525 days (DT90: 870->1000 days). DissT50 in water compartment are 135-441 days (DissT90: 358->1000 days). DissT50 in sediment not determined.	-	Wu, S.; 2013a (please refer to Vol. 3 B.8.2.2.3 page 182 for detailed assessment) Kinetic analysis presented in Donaldson 2013b (please refer to Vol. 3 B.8.2.2.3 page 197 for detailed assessment)

Conclusion on rapid degradability:

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 that imazamox is not degraded in the aquatic environment to a level > 70 % within a 28-day period. As a consequence, imazamox is considered not rapidly degradable.

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

No data available.

11.1.4.2 Inherent and enhanced ready biodegradability tests

Please refer to 11.1.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

Please refer to 11.1.4.

11.1.4.4 Photochemical degradation

Please refer to 11.1.4.

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant.

11.3 Environmental fate and other relevant information

No additional information. ,

11.4 Bioaccumulation

Table 14: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
United States EPA Pesticide Assessment Guideline, Subdivision N: Environmental Fate, Section 165-4	BCF < 1	A single treatment level was evaluated	Anonymous ,1995 (please refer to Vol. 3 B.9.2.2.3 page 23 for detailed summary)

11.4.1 Estimated bioaccumulation

Imazamox is estimated to have a low bioaccumulation potential, as the log Kow values are estimated to be 0.3 at 20°C (pH 4), < - 2.9 at 20°C (pH 7) and < - 3.0 at 20°C (pH 9). Moreover the BCF value is estimated to be below 1.

11.4.2 Measured partition coefficient and bioaccumulation test data

Please refer to 11.4.1.

11.5 Acute aquatic hazard

Table 15: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
OECD 203	*Oncorhynchus mykiss*	imazamox	LC_{50} (96 h) > 122 mg/L (measured concentration)	-	Anonymous ,1994a (please refer to Vol. 3 B.9.2.1.1 page 16 for detailed summary)
OECD 203	*Lepomis macrochirus*	imazamox	LC_{50} (96 h) > 119 mg/L (measured concentration)	-	Anonymous ,1994b (please refer to Vol. 3 B.9.2.1.2 page 17 for detailed summary)
EPA 40 CFR 158(E), EPA 72-3(a)	*Cyprinodon variegatus*	imazamox	LC_{50} (96 h) > 97 mg/L (nominal concentration)	-	Anonymous ,1998a (please refer to Vol. 3 B.9.2.1.3 page 17 for detailed summary)
OECD 202 Part A	*Daphnia magna*	imazamox	EC_{50} (48 h) > 122 mg/L (measured concentration)	-	Yurk J.J., Wisk J.D., 1994a (please refer to Vol. 3 B.9.2.4.1 page 24 for detailed summary)
OECD 202	*Daphnia magna*	imazamox	EC_{50} (48 h) > 100 mg/L (nominal	-	Dorner S., 2012b (please refer to Vol. 3 B.9.2.4.2 page 25

			concentration)		for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Anabaena flos-aquae*	imazamox	EC_{50} (120 h) > 0.038 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995a (please refer to Vol. 3 B.9.2.6.1 page 28 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Skeletonoma costatum*	imazamox	EC_{50} (120 h) > 0.039 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995b (please refer to Vol. 3 B.9.2.6.2 page 29 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Navicula pelliculosa*	imazamox	EC_{50} (120 h) > 0.037 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995c (please refer to Vol. 3 B.9.2.6.3 page 29 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Selenastrum capricornutum*	imazamox	EC_{50} (120 h) > 0.037 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995d (please refer to Vol. 3 B.9.2.6.4 page 30 for detailed summary)
OECD 201, EPA 850.4400	*Pseudokirchneriella subcapitata*	imazamox	E_rC_{50} (72 h) = 29.1 mg/L (nominal concentration)	-	Hoffmann F., 2012b (please refer to Vol. 3 B.9.2.6.5 page 30 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Lemna gibba*	imazamox	EC_{50} (14 d) = 0.011 mg/L (frond biomass; measured concentration) EC_{50} (14 d) = 0.014 mg/L (frond density; measured concentration)	-	Hoberg J. *et al.*, 1995e (please refer to Vol. 3 B.9.2.7.1 page 32 for detailed summary)
OECD 221, OECD 219, ASTM E 1913-04	*Myriophyllum aquaticum*	imazamox	EC_{50} (7 d) > 100 mg/L (total length, wet weight and dry weight; nominal concentration)	-	Backfisch K., 2013e (please refer to Vol. 3 B.9.2.7.2 page 33 for detailed summary)
OECD 221, EPA 850.4400, ASTM E 1415-91	*Lemna gibba*	imazamox	E_rC_{50} (7 d) = 0.021 mg/L (frond number; measured concentration) E_rC_{50} (7 d) = 0.050 mg/L (dry weight; measured concentration)	The reliability of the E_rC_{50} (dry weight) is questionable (only43% inhibition observed at the highest tested concentration (0.047 mg/L)) but this is a	Dorner S., 2013b (please refer to Vol. 3 B.9.2.7.3 page 35 for detailed summary)

				minor uncertainty as this endpoints is not the most sensitive one.	
OECD 221, EPA 850.4400, ASTM E 1415-91	*Lemna gibba*	imazamox	E_rC_{50} (7 d) = 0.022 mg/L (frond number; nominal concentration) E_rC_{50} (7 d) = 0.060 mg/L (dry weight; nominal concentration)	Static test with sediment	Dorner S., 2013c (please refer to Vol. 3 B.9.2.7.4 page 37 for detailed summary)
OECD 221, OECD 219, ASTM E 1913-04	*Spirodela polyrhiza*	imazamox	E_rC_{50} (11 d) = 0.085 mg/L (frond number; nominal concentration) E_rC_{50} (11 d) > 1.0 mg/L (dry weight; nominal concentration)	-	Backfisch K., 2013f (please refer to Vol. 3 B.9.2.7.5 page 39 for detailed summary)
OECD 221, OECD 219, ASTM E 1913-04	*Ceratophyllum demersum*	imazamox	E_rC_{50} (8 d) = 0.063 mg/L (total shoot length; nominal concentration) E_rC_{50} (8 d) = 0.050 mg/L (wet weight; nominal concentration) E_rC_{50} (8 d) > 1.0 mg/L (dry weight; nominal concentration) E_rC_{50} (8 d) = 0.074 mg/L (main shoot length; nominal concentration) E_yC_{50} (8 d) = 0.029 mg/L (side shoots length; nominal concentration) E_yC_{50} (8 d) = 0.021 mg/L (number of side shoots; nominal concentration)	No E_rC_{50} has been estimated for side shoot length and number of side shoots.	Backfisch K., 2013g (please refer to Vol. 3 B.9.2.7.6 page 41 for detailed summary)
OECD 221, OECD 219,	*Glyceria maxima*	imazamox	E_rC_{50} (10 d) = 0.032 mg/L	No E_rC_{50} has been estimated	Backfisch K., 2013h

ASTM E 1913-04			(total length; nominal concentration) E_rC_{50} (10 d) = 0.069 mg/L (wet weight; nominal concentration) E_rC_{50} (10 d) = 0.481 mg/L (dry weight; nominal concentration) E_yC_{50} (10 d) = 0.021 mg/L (number of leaves; nominal concentration)	for the number of leaves.	(please refer to Vol. 3 B.9.2.7.7 page 44 for detailed summary)
OECD 221	*Lemna gibba*	CL 312622	E_rC_{50} (7 d) = 6.3 mg/L (frond number; measured concentration) E_rC_{50} (7 d) = 59.0 mg/L (dry weight; measured concentration)	-	Baetscher R., 2007b (please refer to Vol. 3 B.9.2.7.8 page 47 for detailed summary)
OECD 221	*Lemna gibba*	CL 354825	E_rC_{50} (7 d) = 43.1 mg/L (frond number; measured concentration) E_rC_{50} (7 d) > 54.5 mg/L (dry weight; measured concentration)	-	Rzodeczko H., 2011b (please refer to Vol. 3 B.9.2.7.9 page 49 for detailed summary)

11.5.1 Acute (short-term) toxicity to fish

Imazamox does not seem to be acutely toxic for fish (please refer to 11.5).

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

Imazamox does not seem to be acutely toxic for aquatic invertebrates (please refer to 11.5).

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

The E_rC_{50} for *Pseudokirchneriella subcapitata* (29.1 mg/L) is higher than the EC_{50} values estimated for the other algae species but is considered to be the relevant endpoint to address the acute toxicity of imazamox for algae. Indeed the other EC_{50} values from old studies correspond to the highest tested concentrations and no significant effects were observed at these concentrations. The E_rC_{50} of 29.1 mg/L is above the trigger value of 1 mg/L for acute classification.

For aquatic plant, the lowest EC_{50} value of 0.011 mg/L estimated for *Lemna gibba* is not considered reliable for classification purpose since this EC_{50} is not based on growth rate but on frond biomass. Thus, the E_rC_{50} value of 0.021 mg/L estimated also for *Lemna gibba* is considered as the relevant toxicity value to address the acute toxicity of imazamox.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

No data available.

11.6 Long-term aquatic hazard

Table 16: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
OECD 204	*Oncorhynchus mykiss*	imazamox	NOEC (28 d) = 122 mg/L (measured concentration)	Chronic exposure of 28 d	Anonymous ,1995a (please refer to Vol. 3 B.9.2.2.1.1 page 19 for detailed summary)
OECD 210	*Oncorhynchus mykiss*	imazamox	NOEC (96 d) = 11.8 mg/L (measured concentration)	Early life stage toxicity test (96 d duration)	Anonymous ,1996 (please refer to Vol. 3 B.9.2.2.2.1 page 20 for detailed summary)
EPA 850.1400	*Cyprinodon variegatus*	imazamox	NOEC (35 d) = 1.22 mg/L (measured concentration)	Early life stage toxicity test (35 d duration)	Anonymous ,2013b (please refer to Vol. 3 B.9.2.2.2.2 page 20 for detailed summary)
OECD 202 Part B	*Daphnia magna*	imazamox	NOEC (21 d) = 137 mg/L (measured concentration)	-	Yurk J.J., Wisk J.D., 1995b (please refer to Vol. 3 B.9.2.5.1 page 27 for detailed summary
US EPA Subdivision J, Series 122-2 and 123-2	*Anabaena flos-aquae*	imazamox	NOEC (120 h) = 0.038 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995a (please refer to Vol. 3 B.9.2.6.1 page 28 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Skeletonoma costatum*	imazamox	NOEC (120 h) = 0.039 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995b (please refer to Vol. 3 B.9.2.6.2 page 29 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Navicula pelliculosa*	imazamox	NOEC (120 h) = 0.037 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995c (please refer to Vol. 3 B.9.2.6.3 page 29 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Selenastrum capricornutum*	imazamox	NOEC (120 h) = 0.037 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995d (please refer to Vol. 3 B.9.2.6.4 page 30 for detailed summary)
OECD 201, EPA 850.4400	*Pseudokirchneriella subcapitata*	imazamox	E_rC_{10} (72 h) = 5.1 mg/L (nominal concentration)	-	Hoffmann F., 2012b (please refer to Vol. 3 B.9.2.6.5 page 30 for detailed summary)
US EPA Subdivision J, Series 122-2 and 123-2	*Lemna gibba*	imazamox	NOEC (14 d) = 0.0045 mg/L (measured concentration)	-	Hoberg J. *et al.*, 1995e (please refer to Vol. 3 B.9.2.7.1 page 32 for detailed summary)
OECD 221, OECD 219, ASTM E 1913-04	*Myriophyllum aquaticum*	imazamox	NOEC (7 d) = 100 mg/L (total length, wet weight and dry weight; nominal	-	Backfisch K., 2013e (please refer to Vol. 3 B.9.2.7.2 page 33 for detailed summary)

			concentration)		
OECD 221, EPA 850.4400, ASTM E 1415-91	*Lemna gibba*	imazamox	E_rC_{10} (7 d) = 0.0067 mg/L (frond number; measured concentration) E_rC_{10} (7 d) = 0.0044 mg/L (dry weight; measured concentration)	-	Dorner S., 2013b (please refer to Vol. 3 B.9.2.7.3 page 35 for detailed summary)
OECD 221, EPA 850.4400, ASTM E 1415-91	*Lemna gibba*	imazamox	E_rC_{10} (7 d) = 0.0054 mg/L (frond number; nominal concentration) E_rC_{10} (7 d) = 0.0045 mg/L (dry weight; nominal concentration)	Static test with sediment	Dorner S., 2013c (please refer to Vol. 3 B.9.2.7.4 page 37 for detailed summary)
OECD 221, OECD 219, ASTM E 1913-04	*Spirodela polyrhiza*	imazamox	E_rC_{10} (11 d) = 0.016 mg/L (frond number; nominal concentration) E_rC_{10} (11 d) = 0.10 mg/L (dry weight; nominal concentration)	-	Backfisch K., 2013f (please refer to Vol. 3 B.9.2.7.5 page 39 for detailed summary)
OECD 221, OECD 219, ASTM E 1913-04	*Ceratophyllum demersum*	imazamox	NOE_rC (8 d) = 0.010 mg/L (total shoot length; nominal concentration) NOE_rC (8 d) = 0.010 mg/L (wet weight; nominal concentration) NOE_rC (8 d) = 1.0 mg/L (dry weight; nominal concentration) NOE_rC (8 d) = 0.010 mg/L (main shoot length; nominal concentration) NOE_YC (8 d) = 0.030 mg/L (side shoots length; nominal concentration) NOE_YC (8 d) = 0.030 mg/L (number of side shoots; nominal concentration)	No NOE_rC has been estimated for side shoot length and number of side shoots.	Backfisch K., 2013g (please refer to Vol. 3 B.9.2.7.6 page 41 for detailed summary)
OECD 221,	*Glyceria*	imazamox	NOE_rC (10 d) =	No NOE_rC has	Backfisch K., 2013h

OECD 219, ASTM E 1913-04	*maxima*		0.010 mg/L (total length; nominal concentration) NOE_rC (10 d) = 0.010 mg/L (wet weight; nominal concentration) NOE_rC (10 d) > 1.0 mg/L (dry weight; nominal concentration) NOE_yC (10 d) = 0.010 mg/L (number of leaves; nominal concentration)	been estimated for the number of leaves.	(please refer to Vol. 3 B.9.2.7.7 page 44 for detailed summary)
OECD 221	*Lemna gibba*	CL 312622	E_rC_{10} (7 d) = 1.1 mg/L (frond number; measured concentration) E_rC_{10} (7 d) = 0.79 mg/L (dry weight; measured concentration)	-	Baetscher R., 2007b (please refer to Vol. 3 B.9.2.7.8 page 47 for detailed summary)
OECD 221	*Lemna gibba*	CL 354825	E_rC_{10} (7 d) = 2.6 mg/L (frond number; measured concentration) E_rC_{50} (7 d) = 15.3 mg/L (dry weight; measured concentration)	-	Rzodeczko H., 2011b (please refer to Vol. 3 B.9.2.7.9 page 49 for detailed summary)

11.6.1 Chronic toxicity to fish

All the NOEC for fish are above the trigger value of 1 mg/L for chronic classification (please refer to 11.6).

11.6.2 Chronic toxicity to aquatic invertebrates

The NOEC value for aquatic invertebrates is above the trigger value of 1 mg/L for chronic classification (please refer to 11.6).

11.6.3 Chronic toxicity to algae or other aquatic plants

The NOEC for *Pseudokirchneriella subcapitata* (5.1 mg/L) is higher than the NOEC values estimated for the other algae species but is considered to be the relevant endpoint to address the chronic toxicity of imazamox for algae. Indeed the other NOEC values from old studies correspond to the highest tested concentrations.

For aquatic plant,. the lowest E_rC_{10} value of 0.0044 mg/L estimated for *Lemna gibba* is considered as the relevant toxicity value to address the chronic toxicity of imazamox.

11.6.4 Chronic toxicity to other aquatic organisms

No data available.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Adequate acute toxicity data are available for all three trophic levels (fish, crustacean, algae/aquatic plants). The E_rC_{50} value of 0.021 mg/L (measured concentration) estimated for the aquatic plant *Lemna gibba* is considered to be the key toxicity value for the comparison with CLP criteria for acute aquatic toxicity classification.
The criterion for classification as H400 "Very toxic to aquatic life" is a $L(E)C_{50} \leq 1$ mg/l. Thus, imazamox fulfils this criterion and has to be classified as Aquatic Acute 1, H400 with an acute M factor of 10 (considering 0.01 mg/L < $EC_{50} \leq 0.1$ mg/L).

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

- 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 that imazamox is not degraded in the aquatic environment to a level > 70 % within a 28-day period. As a consequence, imazamox is considered not rapidly degradable.
- Imazamox is estimated to have a low bioaccumulation potential, as the log Kow values are estimated to be 0.3 at 20°C (pH 4), < - 2.9 at 20°C (pH 7) and < - 3.0 at 20°C (pH 9). Moreover the BCF value is estimated to be below 1.
- Adequate chronic toxicity data are available for all three trophic levels (fish, crustacean, algae/aquatic plants). The E_rC_{10} value of 0.0044 mg/L (measured concentration) estimated for the aquatic plant *Lemna gibba* is considered to be the key toxicity value for the comparison with CLP criteria for chronic aquatic toxicity classification.
  For substances not fulfilling criteria for rapid degradation, the criterion for classification as H410 "Very toxic to aquatic life with long lasting effects" is EC_{10}/NOEC $\leq$ 0.1 mg/L. 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).

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Considering the availability of adequate acute and chronic toxicity data for all three trophic levels and that imazamox is a non-rapidly degradable substance, the following classification for the environment hazards can be concluded:

Aquatic Acute 1 with acute M factor = 10

Aqu

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 $\leqslant$ 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 ⩽ 0.1 mg/L (E_rC_{50} (7d)=0.021 mg/L), RAC supports an **M factor of 10** for aquatic acute toxicity.

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 ⩽ 0.01 mg/L (E_rC_{10} (7d) = 0.0044 mg/L), RAC supports an **M factor of 10**.

12 EVALUATION OF ADDITIONAL HAZARDS

Not applicable, not addressed in this proposal

13 ADDITIONAL LABELLING

[If relevant, please justify here the reason for supplemental hazard information in accordance with Annex II of the CLP Regulation.]

14 REFERENCES

ECHA (European Chemicals Agency), 2015. Guidance on the Application of the CLP Criteria; Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.1, June 2015. Reference: ECHA-15-G-05-EN; ISBN: 978-92-9247-413-3; available online: http://echa.europa.eu/documents/10162/13562/clp_en.pdf

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15 ANNEXES

Imazamox_RAR_08_Volume_3CA_B-6_2016-02

Imazamox_RAR_10_Volume_3CA_B-8_2015-12

Imazamox_RAR_11_Volume_3CA_B-9_2015-12