IMAZAMOX

First draft prepared by
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Explanation

Imazamox is the International Organization for Standardization (ISO)–approved common name for (+)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-(methoxymethyl) nicotinic acid (International Union of Pure and Applied Chemistry) (Chemical Abstracts Service No. 114311-32-9). Imazamox is an imidazolinone herbicide used pre- or post-emergence of weeds.

Imazamox has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed by the present Meeting at the request of the Codex Committee on Pesticide Residues.

This evaluation is based mainly on the study reports submitted by the sponsor. All critical studies contained statements of compliance with good laboratory practice (GLP), unless otherwise specified. However, GLP status was not specifically checked. In general, studies were conducted with technical material.

A literature search was conducted by the authors on 20 June 2014 in the databases PubMed and PubMedCentral (keyword: imazamox, no restriction for publication date). Forty-three and 16 references were retrieved, respectively. Articles appearing to be obviously non-relevant for a toxicological or human health evaluation were excluded from the results list based on their titles

and/or abstracts. For the remaining five references, the full articles were retrieved. One article (Peterson & Shama, 2005) did not include toxicological data and was not further considered. Another article (Fragiorge et al., 2008) investigated the effects of an imazamox-containing formulation on *Drosophila melanogaster* larvae and is therefore less relevant for the evaluation of the active ingredient. The remaining three articles were included in the evaluation and are described in the appropriate sections.

Evaluation for acceptable daily intake

1. Biochemical aspects

1.1 Absorption, distribution and excretion

The absorption, tissue distribution, metabolism (see section 1.2) and excretion (ADME) of [6-pyridine-^{14}C]imazamox or [6-pyridine-^{13}C]imazamox[1] were studied in male and female Sprague-Dawley rats administered either an intravenous or oral dose of these compounds (Chiu, 1995). Forty-eight rats were placed on test, including four preliminary-phase animals (two of each sex), four control animals and 40 test animals (five of each sex for each of the following four dose groups: low-dose intravenous 10 mg/kg body weight [bw]; low-dose oral 10 mg/kg bw; low-dose multiple oral 10 mg/kg bw; high-dose oral 1000 mg/kg bw). Urine and faeces were collected from all treated groups at prescribed intervals. Animals were terminated 7 days after administration of the radiolabelled dose. Selected tissue samples were collected, weighed and analysed for total radioactivity.

Imazamox was eliminated primarily via the urine and secondarily via the faeces (Table 1). Elimination occurred rapidly within 6 hours post-dosing. Radiolabelled imazamox equivalents in the tissues were generally below, or in a few cases only just slightly above, detection limits and accounted for at most about 0.007% of the actual administered dose for all treatment groups (Chiu, 1995).

In another ADME study, male and female Sprague-Dawley rats were administered an oral dose of [6-pyridine-^{14}C]imazamox or [6-pyridine-^{13}C]imazamox (see footnote 1 for chemical structure) (Chiu, 1996). Seventy-six animals were placed on test, including four preliminary-phase animals (two of each sex), four control animals and 68 test animals (four of each sex for each of low-dose oral 10 mg/kg bw and high-dose oral 1000 mg/kg bw for blood pharmacokinetics; nine of each sex for each of low-dose oral 10 mg/kg bw and high-dose oral 1000 mg/kg bw for tissue distribution/balance; four of each sex for each of low-dose oral 10 mg/kg bw and high-dose oral 1000 mg/kg bw for biliary excretion). The results of a further control group receiving sham treatment only are of little relevance for the present evaluation. Urine and faeces were collected from four of the five treated groups at prescribed intervals. Those rats were terminated 7 days after administration of the radiolabelled dose. Selected tissue and excreta samples were collected and analysed for total radioactivity.

Imazamox was eliminated primarily via the urine and secondarily via the faeces. Biliary excretion was not an important route of elimination (Table 2). Elimination was very efficient and occurred within 48 hours post-dosing. Maximum blood concentrations were reached within 0.5–1 hour, depending on the dose levels (Table 3); the terminal half-life was relatively fast (20 minutes to 1 hour) (Chiu, 1996).

[1] Chemical structure (* denotes the position of the ^{14}C or ^{13}C label):

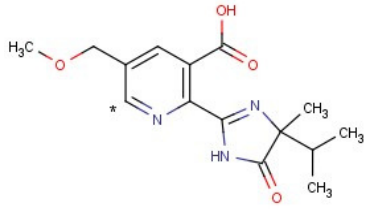


Table 1. Route of excretion and total recovery of imazamox in rat

Group	Target dose (mg/kg bw)	Route of administration	Sex of animal	% of radioactive dose ± standard deviation		
				Urine[a]	Faeces	Total
P (preliminary)	10	Single oral	M + F	68.6	19.9	88.5
A (low dose)	10	Intravenous	M	84.5 ± 10.9	2.7 ± 0.7	88.8[b] ± 10.3
			F	91.2 ± 7.0	1.9 ± 0.9	93.3[b] ± 6.4
B (low dose)	10	Single oral	M	74.5 ± 16.0	18.7 ± 10.7	93.2 ± 7.3
			F	74.4 ± 3.7	24.0 ± 2.8	98.3 ± 1.7
C (low dose)	10	Repeated oral	M	82.1 ± 11.3	17.2 ± 9.8	99.3 ± 1.8
			F	74.0 ± 10.6	24.2 ± 10.2	98.2 ± 1.0
D (high dose)	1 000	Single oral	M	80.2 ± 3.6	12.2 ± 3.7	92.4 ± 1.6
			F	79.3 ± 3.6	12.8 ± 3.7	92.1 ± 1.6

F: female; M: male

[a] Includes cage rinse, cage wash and cage wipe.

[b] Includes swab.

Source: Chiu (1995)

Table 2. Route of excretion and total recovery of imazamox in rat

Group	Target dose (mg/kg bw)	Route of administration	Sex of animal	% of radioactive dose			
				Urine	Faeces	Bile	Total
P (preliminary)	10	Single oral	M	74.9	21.8	NA	96.7
			F	77.6	16.6	NA	94.2
G (low dose)	10	Single oral	M	80.0	17.1	NA	97.1
			F	79.4	19.9	NA	99.3
H (high dose)	1 000	Single oral	M	88.1	11.5	NA	99.6
			F	79.6	17.2	NA	96.8
I (bile cannulation, low dose)	10	Single oral	M	67.6[a]	27.8	2.55	98.4
			F	68.5[a]	27.6	1.37	98.3
J (bile cannulation, high dose)	1 000	Single oral	M	67.1[a]	25.7	2.62	95.9
			F	75.5[a]	22.5	1.75	101.3

F: female; M: male; NA: not applicable

[a] Includes cage wash and cage wipe.

Source: Chiu (1996)

Table 3. Toxicokinetic parameters of imazamox in rat

Group	Target dose (mg/kg bw)	Route of administration	Sex of animal	T_{max} (h)	C_{max} (ppm)	$t_{½\ term}$ (h)	AUC_{0-t} (ppm·h)
E (low dose)	10	Single oral	M	0.53	4.59	0.36	6.40
			F	0.44	5.60	0.34	6.91
F (high dose)	1 000	Single oral	M	1.02	354	0.97	1 047
			F	1.03	342	1.00	1 099

AUC_{0-t}: area under the concentration–time curve from time 0 to time t; C_{max}: maximum concentration in blood; F: female; M: male; ppm: parts per million; $t_{½\ term}$: terminal half-life; T_{max}: time to reach C_{max}

Source: Chiu (1996)

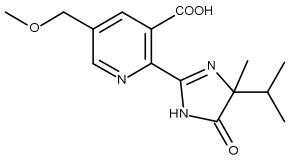
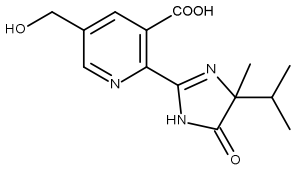
The toxicokinetic properties of ^{14}C-^{15}N-labelled imazamox[2] were investigated in male and female Wistar rats after application of a single oral dose of 500 mg/kg bw (Fabian & Landsiedel, 2012). The mean total recovery of radioactivity was found to be approximately 98% of the administered dose for male and female rats. The excretion via urine over the observation period of 168 hours amounted to 78% of the dose for males and 74% for females. The major part of the urinary excretion (73% of the administered dose for males and 65% for females) occurred within the first day after test substance administration. Smaller amounts of the test substance were excreted through faeces. These amounts accounted for 19% of the dose for males and 23% for females. After the observation period, the remaining radioactivity in the carcass amounted to 0.01% of the dose for both sexes, indicating fast excretion of the orally administered test substance. The absorbed dose (calculated as sum of percentage dose values in urine, cage wash, carcass and organs, with the exception of the gastrointestinal tract) showed similar values for both sexes and was estimated to be 78% and 75% of the administered dose for males and females, respectively.

In conclusion, orally dosed ^{14}C-^{15}N-labelled imazamox (500 mg/kg bw) was excreted mainly in the urine of male and female rats during the 1-week observation period. Under the test conditions, the estimated absorption of imazamox was comparable for both sexes and was determined to be about 75% of the administered dose (Fabian & Landsiedel, 2012).

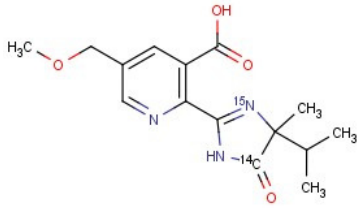
1.2 Biotransformation

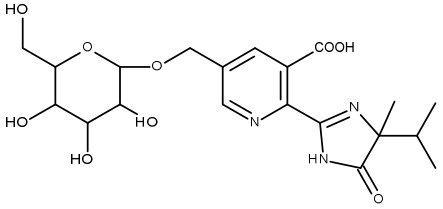
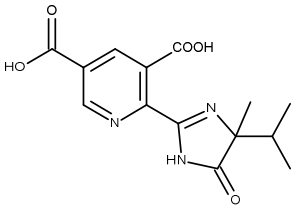
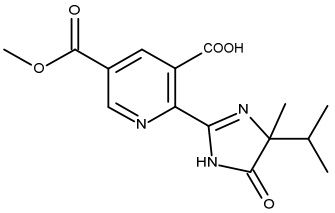
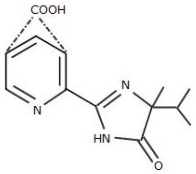
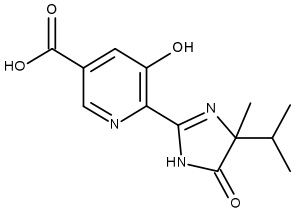
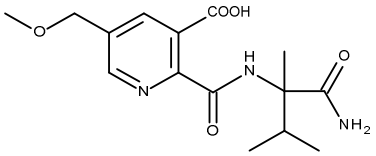
Selected excreta samples from the first ADME study (Chiu, 1995) were analysed for the presence and identity of parent compound and metabolites. Imazamox was primarily eliminated as unchanged test compound via the urine. The amount of total dose that was excreted via faeces consisted mostly of unchanged test compound plus minor amounts of the metabolites *O*-demethylated imazamox (CL 263284) and its subsequent carboxylic acid (CL 312622), together with likely trace amounts of the methyl ester of imazamox (CL 303190) and *N*-methyl-imazamox, in which the imidazole ring is *N*-methylated (Table 4, Fig. 1).

Table 4. Identity of selected substances

Codes	Structure
Imazamox BAS 720 H; CL 299263	
CL 263284; M715H001; 4110773	

[2] Chemical structure showing position of labels:

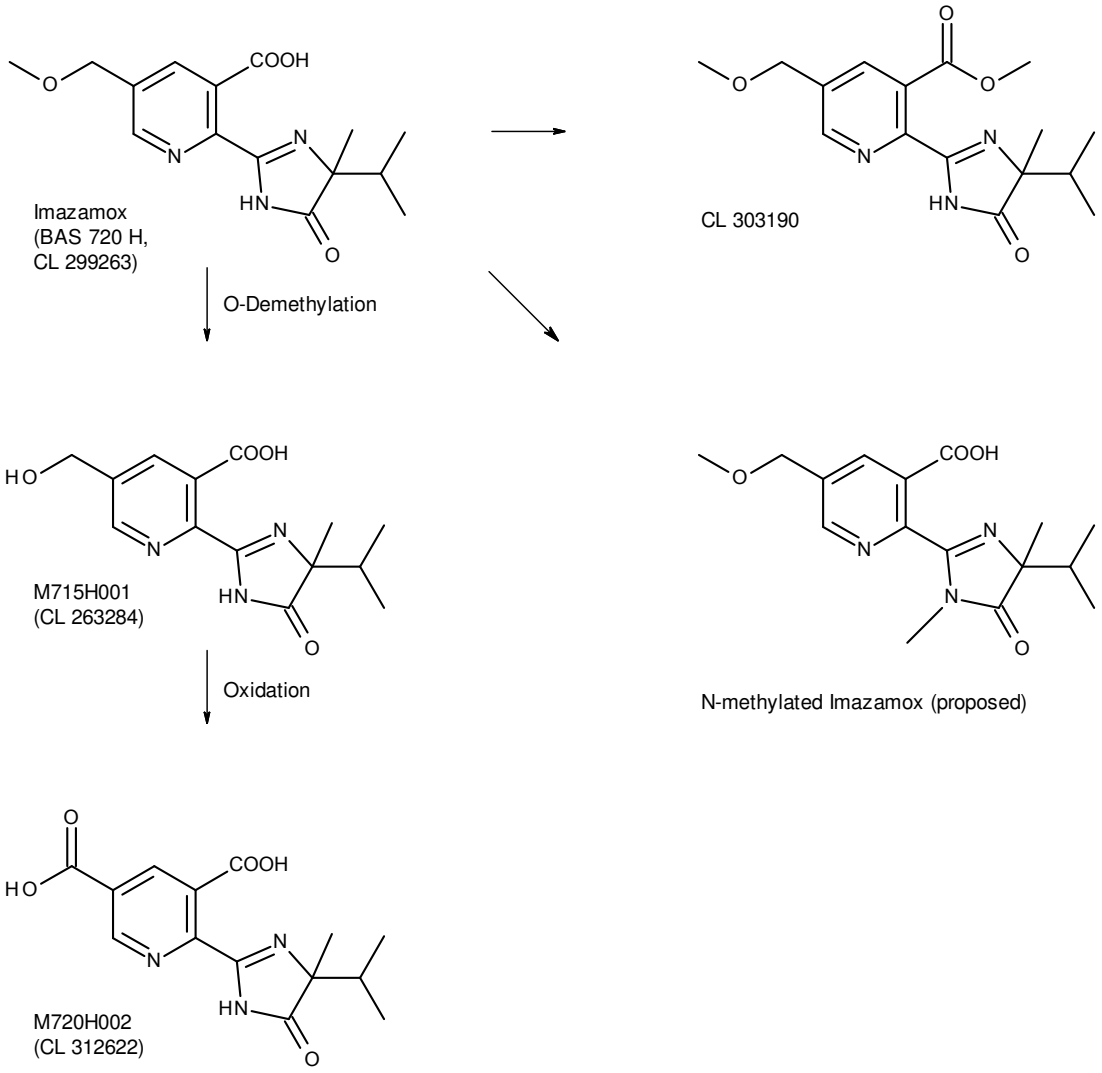


Codes	Structure
CL 189215; M715H002; 4110445	
CL 312622; M720H002; 4110542	
SES15698	
SES15996	
CL 354825	
CL 336554	

Source: Modified from Doi & Amouroux (2013)

Selected tissue and excreta samples from the second ADME study (Chiu, 1996) were analysed for the presence and identity of parent compound and metabolites. Imazamox was primarily eliminated as unchanged test compound via the urine and secondarily via the faeces. The amount of total dose that was excreted via urine, faeces and bile consisted mostly of unchanged test compound plus minor amounts of *O*-demethylated imazamox (CL 263284) and its subsequent carboxylic acid (CL 312622). The same metabolite profile was also found in liver, kidney and muscle extracts.

Fig. 1. Proposed metabolic pathway of imazamox in rats



Source: Doi & Amouroux (2013)

Urinary and faecal samples from the study by Fabian & Landsiedel (2012) were further analysed for the presence and identity of parent compound and metabolites (Thiaener & Lutz, 2012). In both sexes, imazamox was rapidly excreted via urine and faeces as the unchanged parent compound. About 73% (females) and 77% (males) of the applied dose were excreted within 96 hours as parent compound via urine. Additionally, about 21% (females, 0–72 hours) and 15% (males, 0–72 hours) of the dose were excreted as parent compound via faeces. Therefore, in total, 94% (females) and 92% (males) of the dose were excreted as imazamox via urine and faeces.

The *O*-demethylated imazamox (CL 263284), its subsequent carboxylic acid (CL 312622) and the respective ester (SES15698) (Table 4), which were identified in urine and faeces of both sexes, were already present as impurities in the dosing solution at a comparable order of magnitude. No significant increase in these components in rat excreta was observed, which could have been attributed to metabolism. Moreover, the isotope patterns of these components did not match those of the parent compound, which confirms the assumption that the amounts of CL 263284, CL 312622 and SES15698 detected in urinary and faecal samples were not formed by metabolism of imazamox in the rat. A further metabolite (SES15996) was detected in faeces, which is most probably a

decarboxylation product of CL 312622. As its isotope pattern also did not match that of the parent compound, it was likely not a rat metabolite of imazamox (Thiaener & Lutz, 2012).

2. Toxicological studies

2.1 Acute toxicity

(a) Lethal doses

Submitted studies on the median lethal dose (LD_{50}) values determined in experimental animals are summarized in Table 5.

Table 5. LD_{50} values determined in experimental animals

Route	Species, study design	Results	Source
Oral	Rat Similar to OECD TG 401	LD_{50} > 5 000 mg/kg bw	Fischer (1995a)
Oral	Mouse OECD TG 401	LD_{50} > 5 000 mg/kg bw	Bradley (1995a)
Dermal	Rabbit Similar to OECD TG 402	LD_{50} > 4 000 mg/kg bw	Fischer (1995c)
Inhalation	Rat OECD TG 403	LC_{50} > 6.3 mg/L (> 1.6 mg/L of respirable particles, i.e. size < 3 µm)	Hoffman (1994)

bw: body weight; LC_{50}: median lethal concentration; LD_{50}: median lethal dose; OECD TG: Organisation for Economic Co-operation and Development Test Guideline

(b) Dermal irritation

In a skin irritation study in rabbits (Fischer, 1995d), conducted similarly to Organisation for Economic Co-operation and Development (OECD) Test Guideline 404, very slight erythema was reported for 2/6 treated animals at the 24-hour observation time, which had resolved at the 48-hour observation time. No erythema was noted in the other animals at the 24-hour observation time or in any animals at all other observation times. No signs of oedema or other observations were reported in any animals at any observation time. No mortalities or systemic reactions occurred during the study period.

(c) Ocular irritation

In an eye irritation study (Fischer, 1996b) conducted according to OECD Test Guideline 405, 0.1 g of the test substance, imazamox technical, was instilled into the conjunctival sac of each of six female New Zealand White rabbits. After a 24-hour exposure period, treated eyes were rinsed with tap water. One hour after application, slight redness of the conjunctivae, slight to moderate chemosis and moderate ocular discharge were noted in all six rabbits. At the 24-hour observation time, all animals exhibited slight to moderate redness of the conjunctivae; four of six rabbits exhibited scattered and diffuse areas of corneal opacity, slight chemosis and a mild to moderate ocular discharge; and one of six rabbits exhibited mild iritis. By 48 hours, corneal opacities and iritis had resolved in all animals; however, all six animals continued to exhibit slight to moderate conjunctival redness, whereas 2/6 exhibited slight chemosis and slight ocular discharge. At 72 hours, all signs of irritation had resolved in 2/6 animals, with the remaining four rabbits still exhibiting slight conjunctival redness. All symptoms ceased after 7 days. No mortalities or systemic reactions occurred during the study period.

(d) Dermal sensitization

The skin sensitizing potential of imazamox was assessed according to the Buehler method in a study in which 10 guinea-pigs were treated with 0.2 g imazamox once per week for 3 weeks (Glaza, 1992). Upon challenge, no animal showed skin reactions. No mortalities or systemic reactions occurred during the study period. All guinea-pigs treated with the positive control substance, 2,4-dinitrochlorobenzene, developed skin reactions during both the induction and the challenge phases. It should be noted that a group size of 10 treated animals is too small to allow a firm conclusion to be reached; OECD Test Guideline 406 recommends a minimum of 20 animals per treatment group.

In another study, the skin sensitizing potential of imazamox was assessed in guinea-pigs using the maximization method of Magnusson and Kligman, according to OECD Test Guideline 406 (Glaza, 1996). In the induction phase, the test group received 0.1 mL intradermal injections of Freund's Complete Adjuvant (FCA), the test substance (5% weight per volume [w/v] suspension in mineral oil) and a mixture of FCA and the test substance (5% w/v suspension in a 50% solution of FCA in water) at posterior dorsal injection sites. Controls received FCA, 1:1 vehicle:FCA or vehicle alone, respectively. To induce skin irritation, the animals were dermally treated with 10% sodium lauryl sulfate after 7 days for 24 hours and then treated with a 25% weight per weight [w/w] mixture of imazamox or vehicle alone under occlusive conditions for 48 hours. Two weeks later, following a 24-hour occlusive topical challenge with the test substance or vehicle, the test sites were assessed. Upon challenge, none of the 20 treated guinea-pigs showed skin reactions. No mortalities or systemic reactions occurred during the study period. There was no effect on body weight gain. Although no concurrent positive control was included, in a separate study (same laboratory, same method, similar time frame), 10/10 guinea-pigs treated with hexylcinnamaldehyde showed skin reactions during the challenge phase.

2.2 Short-term studies of toxicity

(a) Oral administration

Mice

No short-term toxicity studies conducted with mice were submitted.

Rats

In a 28-day range-finding study, groups of five male and five female Sprague-Dawley rats received diets containing imazamox at a concentration of 0, 5000, 10 000 or 20 000 parts per million (ppm) (equal to 0, 607, 1248 and 2434 mg/kg bw per day for males and 0, 616, 1217 and 2441 mg/kg bw per day for females, respectively) (Fischer, 1996a). Rats were observed daily for signs of overt toxicity, morbidity and mortality. Detailed clinical observations, individual body weights and individual feed consumption were recorded weekly. At termination, all surviving rats were subjected to a gross necropsy, and selected organs were weighed. Samples of selected tissues were submitted for histopathological evaluation from all rats in the 0 and 20 000 ppm groups only.

No mortalities or treatment-related clinical signs were observed during the study period. Feed consumption values for treated males and females were generally similar to those of control rats at all measurement times. Body weights and body weight gains of males at all treatment levels were similar to, or in excess of, those of control rats at all measurement times. Body weights were slightly decreased in females of all treated groups at most measurement times, decreases attaining statistical significance among females of the 10 000 and 20 000 ppm groups during study week 3. Body weight gains were statistically significantly reduced among females of all dose groups during study week 1, resulting in overall body weight gain depressions of 7%, 10% and 8% in the 5000, 10 000 and 20 000 ppm groups, respectively. Decreases in body weight and body weight gain observed for treated females were not considered toxicologically significant, as no dose–response relationship was evident, similar findings were not observed in males and similar findings were not observed in females in the 13-week rat dietary toxicity study (see below) or during the first 4 weeks of treatment in the 2-year rat study (see below), at concentrations up to and including 20 000 ppm.

No haematology, blood chemistry, eye or urinary parameters were evaluated in this study. Absolute and relative (to body weight) liver weights were statistically significantly increased for males in the 10 000 ppm group only. These increases were not considered treatment related, given the absence of an effect at 20 000 ppm. No gross pathological or histopathological changes were reported.

The no-observed-adverse-effect level (NOAEL) was 20 000 ppm (equal to 2434 or 2441 mg/kg bw per day for males and females, respectively), based on the absence of adverse effects up to the highest dose level tested (Fischer, 1996a).

In a 13-week dietary toxicity study, groups of 10 male and 10 female Sprague-Dawley rats received diets containing imazamox at a concentration of 0, 1000, 10 000 or 20 000 ppm (equal to 0, 76, 785 and 1550 mg/kg bw per day for males and 0, 86, 880 and 1772 mg/kg bw per day for females, respectively) (Fischer, 1995b). Rats were observed daily for signs of overt toxicity, morbidity and mortality. Ophthalmological examinations were conducted on study day 0 and at termination. Detailed clinical observations, individual body weights and individual feed consumption were recorded weekly. Haematological, clinical chemistry and urine analysis determinations were performed on all surviving rats at termination of the study. At termination, all surviving animals were subjected to a gross necropsy, and selected organs were weighed. Samples of selected tissues from all test rats were submitted for histopathological evaluation.

No mortalities were observed during the 13-week study period. No clinical signs of toxicity were reported that were attributed to treatment with imazamox. Body weights were not adversely affected by treatment. Feed consumption values for treated males and females were comparable to or greater than those of control animals at all measurement intervals, attaining statistical significance in females at 1000 ppm during weeks 2, 3 and 13 of the study. No statistically significant changes were reported in haematological, clinical chemistry or urinary parameters for either sex at any treatment level. No indication of treatment-related ocular abnormalities were observed at the termination of the study. Changes in some absolute organ weights (liver, kidney, heart and spleen) observed in females of the low-dose group were considered not adverse due to the lack of a dose–response relationship and corroborating findings. No gross pathological or histopathological changes were attributed to treatment with imazamox.

The NOAEL was 20 000 ppm (equal to 1550 or 1772 mg/kg bw per day for males and females, respectively), based on the absence of adverse effects up to the highest dose level tested (Fischer, 1995b).

Dogs

In a 90-day dietary toxicity study, groups of four male and four female Beagle dogs received diets containing imazamox at a concentration of 0, 1000, 10 000 or 40 000 ppm (equal to 0, 34, 329 and 1333 mg/kg bw per day for males and 0, 36, 381 and 1403 mg/kg bw per day for females, respectively) (Kelly, 1994). Physical observations, ophthalmoscopic examinations, body weight and feed consumption measurements, haematology, clinical chemistry and urine analyses were performed on all animals pretest and at selected intervals during the treatment period. After at least 90 days of treatment, all animals were terminated, selected organs were weighed and organ/body weight and organ/brain weight ratios were calculated. Complete gross postmortem examinations and histopathological evaluation of selected tissues were conducted on all animals.

No mortalities were reported during the 13-week study period. No clinical signs of toxicity were attributed to treatment with imazamox. Feed consumption and feed efficiency values as well as body weights and body weight gains were similar between control and treated animals. A haematological evaluation performed during study week 6 revealed a statistically significant increase in absolute lymphocyte values for males fed 40 000 ppm imazamox. However, these values fell within historical control data ranges and were not statistically significantly different from those of controls at termination. Thus, this increase was not considered to be treatment related. Clinical chemistry, urine analysis and ophthalmological parameters did not indicate any adverse effects due to dietary

administration of imazamox. Absolute and relative organ weights were similar between control and treated animals, and there were no gross or microscopic findings attributed to treatment with this test material.

The NOAEL was 40 000 ppm (equal to 1333 and 1403 mg/kg bw per day for males and females, respectively), based on the absence of adverse effects up to the highest dose level tested (Kelly, 1994).

In a 12-month dietary toxicity study, groups of five male and five female Beagle dogs received diets containing imazamox at a concentration of 0, 1000, 10 000 or 40 000 ppm (equal to 0, 29, 283 and 1174 mg/kg bw per day for males or 0, 30, 282 and 1156 mg/kg bw per day for females, respectively) (Kelly, 1995b). Physical observations, ophthalmoscopic examinations, body weight and feed consumption measurements, haematology, clinical chemistry and urine analyses were performed on all animals pretest and at selected intervals during the treatment period. After at least 1 year of treatment, all animals were terminated, selected organs were weighed and organ/body weight and organ/brain weight ratios were calculated. Complete gross postmortem examinations and histopathological evaluation of selected tissues were conducted on all animals.

No mortalities occurred during the study period. No clinical signs of toxicity were attributed to treatment with imazamox. Feed consumption and feed efficiency values as well as body weights and body weight gains for treated and control animals were comparable. Haematological and urine analysis parameters evaluated at 3 and 6 months and at termination were also comparable between treated and control animals. Although sporadic instances of statistically significant differences in clinical chemistry parameters were observed for treated and control animals, values for treated animals were considered to be within normal biological limits, were not consistently observed at different time intervals and were not observed in both sexes. Thus, these differences were not attributed to administration of imazamox. At study termination, evaluation for ocular changes gave no indication of treatment-related effects. Absolute and relative organ weights were comparable for control and treated animals. Macroscopic and microscopic changes observed occurred sporadically among control and treated groups and were considered to be incidental findings and not treatment related.

The NOAEL was 40 000 ppm (equal to 1174 and 1156 mg/kg bw per day for males and females, respectively), based on the absence of adverse effects up to the highest dose level tested (Kelly, 1995b).

(b) Dermal application

Rats

In a dermal toxicity study, groups of five male and five female Sprague-Dawley rats were dermally administered imazamox at a dose level of 0, 250, 500 or 1000 mg/kg bw per day (6 hours/day, 5 days/week) for 28 days (Blaszcak, 1995). The test material was uniformly spread on a gauze dressing and moistened with 0.5 mL of 0.9% saline, and then the gauze was applied to the skin of the animals. Physical observations, ophthalmoscopic examinations and body weight and feed consumption measurements were performed on all animals pretest and at selected intervals during the treatment period. Haematology and clinical chemistry evaluations were performed on all animals at study termination. After 28 days of treatment, all animals were euthanized. Selected organs were weighed, and organ/body weight and organ/brain weight ratios were calculated. Complete macroscopic postmortem examinations were conducted on all animals. Histopathological evaluation of selected tissues was performed on all animals in the control and high-dose groups; macroscopic lesions were examined for animals in all dose groups at study termination.

No mortalities or clinical signs of toxicity could be attributed to treatment throughout the study period. In addition, no signs of dermal irritation were observed. Feed consumption and mean body weight and body weight gains for treated groups were comparable to those of the controls. Haematology and clinical chemistry values were also similar among treated and control animals. At

termination of the study, no test material–related ocular changes were reported. Absolute organ weights were unaffected by the administration of imazamox. Changes in relative brain weights observed in males of the low-dose group were considered not adverse due to the lack of a dose–response relationship and corroborating findings. There were no compound-related macroscopic or microscopic changes observed in any evaluated rat.

The NOAEL was 1000 mg/kg bw per day, based on the absence of adverse effects up to the highest dose level tested (Blaszcak, 1995).

(c) Exposure by inhalation

No short-term toxicity studies with inhalation exposure were submitted.

2.3 Long-term studies of toxicity and carcinogenicity

Mice

In a carcinogenicity study, groups of 55 male and 55 female CD-1 mice received diets containing imazamox at a concentration of 0, 500, 3500 or 7000 ppm (equal to 0, 73, 535 and 1053 mg/kg bw per day for males and 0, 96, 664 and 1348 mg/kg bw per day for females, respectively) for 18 months (Kelly, 1995a). Physical observations and body weight and feed consumption measurements were performed on all animals pretest and on all survivors at selected intervals during the treatment period. Haematology was performed on 10 mice of each sex per group at month 12 and at termination. After at least 18 months of treatment, all survivors were euthanized, selected organs were weighed and organ/body weight and organ/brain weight ratios were calculated. Complete macroscopic postmortem examinations were performed on all animals. Microscopic evaluation of selected tissues was conducted on all animals in the control and high-dose groups at termination as well as for all mice dying during the study. In addition, the kidneys, liver, lungs and gross lesions were examined for all low- and mid-dose mice euthanized at termination.

At study termination, survival was similar among the control and treated groups. Survival rates were 76%, 76%, 73% and 73% for males and 82%, 76%, 74% and 74% for females in the 0, 500, 3500 and 7000 ppm groups, respectively. Observed clinical signs of toxicity were not attributed to treatment with imazamox. Although statistically significant differences were occasionally observed for mean weekly, biweekly and monthly body weights, body weight gains and feed consumption, no consistent trend towards increases or decreases in these parameters for males or females in any treatment group was evident. No treatment-related haematological effects were noted either at the 12-month observation time or at study termination. Absolute and relative organ weights were comparable with those of controls at termination of the study. Macroscopic or microscopic findings of toxicological significance at any treatment level were considered not to be associated with dietary administration of imazamox because of the lack of a dose–response relationship.

No carcinogenic effects were reported for the test material up to the highest dose level tested.

The NOAEL was 7000 ppm (equal to 1053 and 1348 mg/kg bw per day for male and female mice, respectively), based on the absence of adverse effects up to the highest dose level tested (Kelly, 1995a).

Rats

In a long-term toxicity and carcinogenicity study, groups of 65 male and 65 female Sprague-Dawley rats received diets containing imazamox at a concentration of 0, 1000, 10 000 or 20 000 ppm (equal to 0, 52, 528 and 1068 mg/kg bw per day for males and 0, 63, 626 and 1284 mg/kg bw per day for females, respectively) for 2 years (Fischer & Hess, 1995). The rats were observed daily for signs of overt toxicity, morbidity and mortality. Detailed clinical observations were recorded weekly during the 24-month study period. Ophthalmological examinations were done on all test animals on study day 2 and on all surviving animals at termination (24 months). Individual body weights and feed consumption data were recorded weekly during the first 14 weeks of the study, at biweekly intervals

from weeks 14 to 26 and monthly for the remainder of the 24-month study period. Samples for haematological, clinical chemistry and urine analysis determinations were collected from 10 rats of each sex per dose level at 6-month intervals during the study period. At termination, all surviving animals were subjected to a gross necropsy, and selected organs were weighed (10 rats of each sex per dose level). Gross necropsies were also performed on unscheduled deaths (found dead, euthanized moribund, accidental deaths) that occurred during the study. Samples of selected tissues were submitted for histopathological evaluation from all surviving test animals and from any unscheduled deaths that occurred during the study.

Survival was unaffected by dietary administration of the test material. Survival rates (excluding accidental deaths) were 28%, 28%, 31% and 27% for males and 33%, 26%, 31% and 33% for females in the 0, 1000, 10 000 and 20 000 ppm groups, respectively. None of the clinical signs of toxicity observed were attributed to treatment with imazamox technical. Feed consumption for both male and female rats at all treatment levels was generally comparable to or greater than that of controls. Body weights for male rats administered imazamox in the diet were comparable with those of controls at most measurement intervals. Slight decreases in body weights noted for females fed 20 000 ppm were not considered treatment related, given that they occurred late in the 24-month study period (from week 74), were observed in only one sex and were not statistically significant. Although weekly weight gains for both sexes fed the test diet were generally comparable with those of controls, overall body weight gains over the 24-month study period for males fed treated diets were slightly increased, whereas overall body weight gains for females treated at 20 000 ppm were slightly decreased (8.7%, Table 6). This slight decrease in overall body weight gain observed for females in the high-concentration group was considered unrelated to treatment, as it likely reflected the slight decrease in body weight observed for that group beginning at week 74. Moreover, total body weight gain for females in the 20 000 ppm group for the majority of the study period (from weeks 1 to 66) was comparable with that of controls.

Table 6. Body weight gains in treated rats

	Body weight gain (g, mean ± SD)							
	Males				**Females**			
Weeks	**0 ppm**	**1 000 ppm**	**10 000 ppm**	**20 000 ppm**	**0 ppm**	**1 000 ppm**	**10 000 ppm**	**20 000 ppm**
0–14	468.2 ± 55.86	469.3 ± 55.28	470.4 ± 63.90	468.1 ± 53.41	233.3 ± 33.38	227.9 ± 40.50	230.4 ± 38.88	229.6 ± 34.16
0–104	613.3 ± 124.30	725.9 ± 154.99	678.4 ± 160.13	730.5 ± 130.05	440.5 ± 167.13	457.3 ± 144.90	409.6 ± 115.96	402.0 ± 139.81
		(+18.4%)	(+10.6%)	(+19.1%)		(+3.8%)	(−7.0%)	(−8.7%)

ppm: parts per million; SD: standard deviation

Source: Fischer & Hess (1995)

No treatment-related haematological, clinical chemistry or urine analysis effects were noted at the 6-, 12- or 18-month observation times or at study termination (24 months). Ophthalmoscopic examination at study termination revealed no treatment-related findings. Absolute kidney weights as well as kidney/brain weight and kidney/body weight ratios for male rats fed 10 000 ppm were significantly increased compared with controls. Given the absence of a dose–response relationship and the lack of a similar response in corresponding females, this increase was not considered toxicologically significant. No other significant changes were observed in either absolute or relative organ weights for males or females at any treatment level. No macroscopic or microscopic findings of toxicological significance at any treatment level were attributed to dietary administration of imazamox technical.

No carcinogenic effects were induced by the test material; however, owing to the low survival, the power of the study design regarding this end-point is limited. The study did not include groups designated for an interim termination to allow a toxicological evaluation after 1 year.

The NOAEL was 20 000 ppm (equal to 1068 and 1284 mg/kg bw per day for males and females, respectively), based on the absence of adverse effects up to the highest dose level tested (Fischer & Hess, 1995).

2.4 Genotoxicity

Results of the submitted genotoxicity/mutagenicity studies are summarized in Table 7.

Table 7. Results of submitted genotoxicity/mutagenicity studies

End-point	Test object	Concentration	Purity (%)	Result	Reference
In vitro					
Bacterial mutagenicity test (similar to OECD TG 471)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* WP2 uvrA	0, 100, 500, 1 000, 2 500 and 5 000 µg/plate	98.2	Negative	Mulligan (1995a)
Chromosome aberration test (similar to OECD TG 473)	Chinese hamster ovary cells	0, 417, 833, 1 667 and 3 333 µg/mL	97.1	Negative[a]	Kumaroo (1994)
Hgprt locus mutation assay (similar to OECD TG 476)	Chinese hamster ovary cells	0, 50, 100, 500, 1 000, 2 000 and 4 000 µg/mL	98.2	Negative[a]	Sharma (1993b)
In vivo					
Micronucleus assay (similar to OECD TG 474)	Mouse	0, 1 250, 2 500 and 5 000 mg/kg bw (single dose administration)	98.2	Negative[b]	Sharma (1993a)

Hgprt: hypoxanthine–guanine phosphoribosyltransferase; OECD TG: Organisation for Economic Co-operation and Development Test Guideline

[a] Top dose limited by solubility but not by toxicity.
[b] No signs of toxicity (including changes in the proportion of polychromatic erythrocytes) were reported.

2.5 Reproductive and developmental toxicity

(a) Multigeneration studies

Groups of 30 male and 30 female Sprague-Dawley rats were fed diets containing imazamox at a concentration of 0, 1000, 10 000 or 20 000 ppm (equal to 0, 76, 770 and 1554 mg/kg bw per day for males and 0, 88, 892 and 1826 mg/kg bw per day for females, respectively, during the premating period) for two generations (Schroeder, 1995). Both parental generations were treated during a premating period of 10–11 weeks, and treatment continued during both a 20-day mating period and a post-mating period. Mated females continued to be treated during the ensuing gestation, lactation and post-weaning periods until termination. Parental animals (P, F_1) were observed twice daily for

mortality and unusual findings, and each animal received a detailed physical examination weekly; vaginal smear samples were evaluated daily for parental females (P, F_1) to evaluate estrous cycling for a 2-week period prior to initiation of mating. Body weights and feed consumption for the parental animals were recorded weekly during the premating treatment periods, and these parameters continued to be recorded weekly for males during the post-mating period until termination. Body weights and feed consumption were recorded for females at regular intervals during the gestation and lactation periods. Each parental generation produced a single litter, and pups were weaned on lactation day 21. On lactation day 4, litters with more than eight pups were culled to that number so as to equalize sex distributions (four of each sex) when possible; litters with eight or fewer pups on lactation day 4 were not adjusted. During lactation, litter size, pup weights and pup sex distribution data were recorded, and several pup developmental landmarks (pinna detachment, eye opening, hair growth and incisor eruption) were scored as achieved. Randomly selected pups from the F_1 litters (at least one pup of each sex per litter) were chosen to become the F_1 parental generation. Preputial separation and vaginal opening were scored for F_1 pups retained after the day 28 selections to eventually become the F_1 parental animals.

At termination, parental animals were given a gross postmortem examination, and reproductive tissues and pituitary glands were taken and preserved in 10% neutral buffered formalin; gross lesions were also taken and preserved for all parental animals. Reproductive tissues were evaluated histomorphologically for P and F_1 control and high-dose animals, and gross lesions were evaluated for all animals. The unselected F_1 pups were terminated soon after the day 28 weighing interval and evaluated for external irregularities; pups with external findings were also evaluated internally, and abnormal tissues were saved (10% neutral buffered formalin). Additionally, at day 21 or soon thereafter, one pup of each sex per litter per group for each litter interval was selected at random and given a detailed macroscopic evaluation, and abnormal tissues were saved.

No treatment-related mortality occurred. During the premating treatment period, mean weekly feed consumption for males and females of both parental generations was either comparable with or slightly higher than that of controls (10 000 and 20 000 ppm groups only). Additionally, no adverse effects on feed consumption were reported from treatment of either P or F_1 males with imazamox technical during the post-mating periods. No adverse effect of treatment was indicated by maternal feed consumption during the gestation and lactation intervals for both parental generations as well.

Mean weekly body weights for treated males and females of both parental generations were comparable with those of controls during the premating treatment period; mean body weights for treated males of both parental generations were also comparable with those of controls during the mating and post-mating periods. Mean weight gains for P and F_1 males and females treated with 1000 and 10 000 ppm and for P and F_1 males treated with 20 000 ppm were comparable with those of controls during the premating period (Table 8). Although P females in the 20 000 ppm group exhibited mean weight gains that were similar to those of controls during the premating period, F_1 females exhibited a statistically significant decrease (−11.3%) in mean weight gain over this period. Given the absence of similar decreases for P females or for P or F_1 males at 20 000 ppm, this slight decrease in mean weight gain was considered unlikely to be of biological significance. No treatment-related effects on maternal body weight or weight gain during the gestation and lactation intervals were observed for either parental generation.

Reproductive performance (estrous cycle data, mating indices, pregnancy rates, male fertility indices, gestation indices and parturition indices) was unaffected by treatment with imazamox technical. F_1 litter size was statistically significantly lower in the top-dose group, but stayed within the laboratory's historical control range. Mean litter size data both pre-cull (prior to neonatal day 4) and throughout the remainder of lactation for the treated groups were comparable with those for 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 lactation and on neonatal day 28; pup sex distribution; pup developmental landmarks; or the number of dead pups at birth or during the 21-day lactation period. 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 with control data for each litter interval and was also similar to the mean total number of

respective pups born. No microscopic compound-related changes were observed. In summary, the types and frequencies of observations/lesions seen among the treated animals were similar to those seen commonly in the performing laboratory for the strain of rats used.

Table 8. Premating body weight gains in treated rats

	Body weight gain (g, mean ± SD)							
	Males				**Females**			
	0 ppm	**1 000 ppm**	**10 000 ppm**	**20 000 ppm**	**0 ppm**	**1 000 ppm**	**10 000 ppm**	**20 000 ppm**
P generation (weeks 0–10)	304.0 ± 36.5	300.9 ± 32.9	295.1 ± 33.8	291.4 ± 25.4	110.9 ± 15.1	113.4 ± 17.9	111.6 ± 13.1	105.0 ± 15.0
F_1 generation (weeks 20–31)	304.0 ± 49.6	300.9 ± 43.7	312.4 ± 58.0	289.1 ± 52.0	127.5 ± 16.6	118.2 ± 19.1	122.1 ± 23.3	113.1* ± 19.0

F_1: first filial; P: parental; ppm: parts per million; SD: standard deviation; *: $P \leq 0.05$

Source: Schroeder (1995)

In summary, the NOAEL for adverse effects on parental animals, offspring and reproduction was 20 000 ppm (equal to 1554 and 1826 mg/kg bw per day for males and females, respectively), based on the absence of adverse effects up to the highest dose level tested (Schroeder, 1995).

(b) Developmental toxicity

Rats

In a developmental toxicity study, groups of 25 pregnant Sprague-Dawley rats were treated with an imazamox dose of 0, 100, 500 or 1000 mg/kg bw per day via gavage (Foss, 1994). The treatment period was gestation days 6–15. Current test guidelines require daily administration from implantation to the day prior to scheduled caesarean section; hence, the study design may have been less sensitive than required according to current standards. All rats were euthanized by carbon dioxide asphyxiation on day 20 of presumed gestation. The uterus of each rat was excised, weighed and examined for pregnancy, number and distribution of implantations, live and dead fetuses, and early and late resorptions. The number of corpora lutea was recorded for each dam. Each fetus was weighed and examined for sex, gross external alterations and soft tissue or skeletal alterations.

No mortalities, abortions or premature deliveries occurred during the study; no clinical signs were observed that were attributed to treatment. Absolute and relative feed consumption values for the entire dosing and post-dosing periods tended to be reduced in the 1000 mg/kg bw per day dose group (Table 9); however, none of these reductions was statistically significant. Reflecting these findings, body weights tended to be reduced in the 1000 mg/kg bw per day dose group on days 8 through 20 of gestation (Table 9). A statistically significant reduction in body weight gain during days 6–12 of gestation was observed for animals in the 1000 mg/kg bw per day dose group compared with controls; however, body weight gains were comparable among the four dose groups for the remainder of the dosing period as well as for the post-dosing period. 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.

Fetal/litter evaluations occurred on day 20 of gestation following caesarean sectioning of the dams. Litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal weights, per cent resorbed conceptuses and per cent male fetuses were comparable among the four dose groups. Similarly, no gross external, soft tissue or skeletal malformations or variations were observed in fetuses that were caused by treatment of the dams with imazamox at doses as high as 1000 mg/kg bw per day. One fetus from the high-dose group, but none of the fetuses

from the other groups, was reported to have short, broad, bent ribs. As a result of this low incidence, this finding was considered not to be an adverse treatment-induced finding.

Table 9. Selected findings in treated pregnant rats

	Finding (mean ± SD)			
	0 mg/kg bw per day	**100 mg/kg bw per day**	**500 mg/kg bw per day**	**1 000 mg/kg bw per day**
Number of rats tested	25	25	25	25
Number of pregnant rats	24	24	25	25
Feed intake (absolute: g/day; relative: g/kg bw per day)				
Absolute, GDs 6–16	28.2 ± 2.6	28.7 ± 3.3	28.0 ± 2.6	27.0 ± 3.3
Absolute, GDs 16–20	33.1 ± 4.0	32.8 ± 2.3	32.2 ± 2.9	31.7 ± 3.5
Relative, GDs 6–16	88.6 ± 4.6	90.8 ± 6.9	88.7 ± 5.3	86.6 ± 6.1
Relative, GDs 16–20	82.6 ± 5.6	82.4 ± 4.4	81.9 ± 4.4	81.5 ± 5.5
Body weight (g)				
Maternal body weight, GD 8	293.8 ± 14.3	290.8 ± 12.7	292.7 ± 18.0	288.4 ± 17.7
Maternal body weight, GD 12	325.9 ± 18.8	322.4 ± 15.4	321.9 ± 18.6	315.2 ± 22.0
Maternal body weight, GD 16	363.2 ± 20.6	362.0 ± 20.3	358.7 ± 19.2	353.8 ± 26.2
Maternal body weight, GD 20	439.0 ± 30.5	436.4 ± 20.8	430.1 ± 31.0	426.4 ± 34.2
Gravid uterine weight	87.8 ± 9.7	88.2 ± 6.4	81.8 ± 20.2	84.3 ± 20.7
Body weight gain, GDs 6–12	44.0 ± 9.0	43.0 ± 7.4	38.4 ± 12.8	33.8* ± 14.0
Body weight gain, GDs 6–16	81.3 ± 10.2	82.6 ± 11.1	75.3 ± 13.8	72.4 ± 19.0
Body weight gain, GDs 16–20	75.8 ± 15.0	74.4 ± 6.8	71.4 ± 15.0	72.6 ± 13.0
Body weight gain, GDs 6–20	157.1 ± 23.2	157.0 ± 11.7	146.7 ± 25.8	145.0 ± 28.1

bw: body weight; GD: gestation day; SD: standard deviation; *: $P \leq 0.05$

Source: Foss (1994)

The NOAEL for adverse effects on maternal animals was 500 mg/kg bw per day, based on reduction of body weight gain and feed intake at 1000 mg/kg bw per day. The NOAEL for adverse effects on offspring was 1000 mg/kg bw per day, based on the absence of adverse effects up to the highest dose level tested (Foss, 1994).

Rabbits

In a developmental toxicity study, groups of 20 pregnant New Zealand White rabbits were treated with imazamox at a dose of 0, 300, 600 or 900 mg/kg bw per day via gavage (Hoberman, 1995). The treatment period was gestation days 7–19. Current test guidelines require daily administration from implantation to the day prior to scheduled caesarean section; hence, the study design may have been less sensitive than required according to current standards. All rabbits were observed for viability at least twice each day of the study and for general appearance several times during acclimation and on day 0 of presumed gestation. The rabbits were also examined for clinical observations of effects of the test substance, abortions, premature deliveries and deaths immediately before and after intubation (days 7 through 19 of presumed gestation). These observations were also made once daily during the post-dosing period (days 19 through 29 of presumed gestation). Body weights were recorded on days 0 and 7 through 29 of presumed gestation. Feed consumption values

were recorded daily throughout the study. The rabbits were terminated on day 29 of presumed gestation and necropsied. The number of corpora lutea in each ovary was recorded. The uterus was excised, weighed and examined for pregnancy, number and distribution of implantations, early and late resorptions, and live and dead fetuses. Each fetus was weighed, sexed and examined for gross external, soft tissue and skeletal alterations.

No mortalities or abortions occurred during the study. One doe in the 900 mg/kg bw per day group prematurely delivered a litter on day 29 of gestation; eight of the 10 conceptuses were live pups, and two of the 10 conceptuses were presumed cannibalized. This premature delivery was considered a possible effect of the test substance, as this doe had exhibited reduced body weight and feed consumption after day 11 of gestation. No other doe prematurely delivered a litter. No clinical signs were observed that were considered related to test substance intake.

Although absolute and relative feed consumption values for the entire dosing period were reduced in all treatment groups compared with control values (Table 10; 3% for 300 mg/kg bw per day, 12–13% for 600 mg/kg bw per day and 15–16% for 900 mg/kg bw per day), these effects were considered biologically significant only in the 600 and 900 mg/kg bw per day dose groups. For the majority of the dosing period (900 mg/kg bw per day) or for the entire dosing period (600 mg/kg bw per day), the pattern of decreased feed consumption increased with continued dosing. In addition, statistically significant reductions in absolute and relative feed consumption values were observed for the intermediate- and high-dose groups on days 7–29 of gestation. The reductions in feed intake were observed after a few days of dosing only. A statistically significant reduction in relative feed intake was observed in low-dose rabbits between gestation days 7 and 29. However, the mean relative feed consumption value was well within 10% of the control group value; thus, the change in the low-dose group was not considered biologically significant.

Table 10. Selected findings in treated pregnant rabbits

	Finding (mean ± SD)[a]			
	0 mg/kg bw per day	**300 mg/kg bw per day**	**600 mg/kg bw per day**	**900 mg/kg bw per day**
Number of rabbits tested	20	20	20	20
Number of pregnant rabbits	20	18	15	20
Feed intake (absolute: g/day; relative: g/kg bw per day)				
Absolute, GDs 7–20	181.4 ± 2.5 (*n* = 17)	175.7 ± 13.6	158.0 ± 20.9	152.4** ± 23.4 (*n* = 19)
Relative, GDs 7–20	49.1 ± 3.2 (*n* = 17)	47.8 ± 3.7	43.4** ± 5.6	41.5** ± 5.6 (*n* = 19)
Absolute, GDs 7–29	175.9 ± 5.7	167.2 ± 15.1	157.2** ± 17.5	155.5** ± 17.8 (*n* = 19)
Relative, GDs 7–29	46.7 ± 3.0	44.1* ± 2.6	42.2** ± 4.7	41.6** ± 4.5
Body weight gain (kg)				
GDs 7–20	0.27 ± 0.10	0.31 ± 0.06	0.24 ± 0.12	0.22 ± 0.14
GDs 20–29	0.24 ± 0.10	0.20 ± 0.08	0.21 ± 0.11	0.19 ± 0.09 (*n* = 19)
GDs 7–29	0.51 ± 0.12	0.51 ± 0.10	0.45 ± 0.16	0.44 ± 0.12 (*n* = 19)

bw: body weight; GD: gestation day; SD: standard deviation; **: $P \leq 0.01$

[a] *n* is given in parentheses wherever the value is not based on the total number of pregnant rabbits in the group.

Source: Hoberman (1995)

No statistically significant differences were observed in body weights or body weight gains for the entire dosing and post-dosing periods for treated rabbits compared with controls. However, a biologically significant reduction in body weight gain was noted during the dosing period (19%) and post-dosing period (21%) for does dosed at 900 mg/kg bw per day. Gravid uterine weights were not affected by administration of imazamox technical in any dose group. Gross necropsy findings for the does were considered unrelated to test substance intake.

Fetal litter evaluations for all remaining pregnant does occurred on day 29 of gestation following caesarean sectioning of the does. Litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal weights and per cent male fetuses were comparable among the four dose groups. The incidences of absent intermediate lung lobules and of vertebral malformations (thoracic hemivertebrae, cervical hemivertebrae) were increased in animals treated with 600 or 900 mg/kg bw per day (Table 11). The study report did not include a more detailed description of these findings. No further fetal gross external, soft tissue or skeletal malformations or variations observed were considered effects of the test substance.

Table 11. Incidence of selected findings in offspring

	Number of affected fetuses/number of affected litters			
	0 mg/kg bw per day	**300 mg/kg bw per day**	**600 mg/kg bw per day**	**900 mg/kg bw per day**
Number of litters evaluated	20	18	14	19
Number of live fetuses evaluated	160	148	116	160
Soft tissue alterations				
Lungs: absent intermediate lobe[a]	1/1 (0.6%/5.0%)	0/0	2/2 (1.7%/14.3%)	6**/4 (3.8%/21.0%)
Skeletal alterations				
Vertebral malformations	0/0	0/0	2/2 (1.7%/14.3%)	4/2 (2.5%/10.5%)
Vertebra, cervical hemivertebra	0/0	0/0	1/1 (0.9%/7.1%)	3/2 (1.9%/10.5%)
Vertebra, thoracic hemivertebra	0/0	0/0	1/1 (0.9%/7.1%)	2/1 (1.2%/5.3%)

bw: body weight; **: $P \leq 0.01$

[a] According to the report, the absence of other lung lobes was not observed in this study.

Source: Hoberman (1995)

Historical control data from the performing laboratory regarding the findings “lungs, one or more lobes partially or complete agenesis”, “vertebra, cervical hemivertebra” and “vertebra, thoracic hemivertebra” are summarized in Table 12. It should be noted that these historical control data on “lungs, one or more lobes partially or complete agenesis” also include findings in addition to the specific finding observed in fetuses in this study; hence, they may be of less relevance.

The NOAEL for adverse effects on maternal rabbits was 300 mg/kg bw per day, based on reduction of feed intake at 600 mg/kg bw per day, which was considered to be of equivocal toxicological relevance. The NOAEL for adverse effects on offspring was 300 mg/kg bw per day, based on an increased incidence of both absent intermediate lung lobes and hemivertebrae at 600 mg/kg bw per day (Hoberman, 1995).

Table 12. Historical control data on selected findings in rabbit fetuses

	Historical control data (range)		
	1990 to June 1992	**June 1992 to June 1995**	**June 1994 to June 1996**
Number of studies	49 (soft tissue and skeletal)	36 (soft tissue) 35 (skeletal)	17 (soft tissue) 18 (skeletal)
Number of litters examined	790 (soft tissue and skeletal)	593 (soft tissue) 586 (skeletal)	297 (soft tissue) 316 (skeletal)
Number of live fetuses examined	5 892 (soft tissue) 5 891 (skeletal)	4 479 (soft tissue) 4 436 (skeletal)	2 425 (soft tissue) 2 544 (skeletal)
Lungs: one or more lobes, partial or complete agenesis			
Number of litters affected	0–6 (0–35.3%)	0–5 (0–29.4%)	0–5 (0–29.4%)
Number of fetuses affected	0–12 (0–8.7%)	0–13 (0–6.9%)	0–9 (0–6.9%)
Vertebral malformations	Alteration not mentioned	Alteration not mentioned	Alteration not mentioned
Vertebra, cervical hemivertebra			
Number of studies with alteration	1	Alteration not mentioned	Alteration not mentioned
Number of litters affected	0–1 (0–5.3%)		
Number of fetuses affected	0–1 (0–0.6%)		
Vertebra, thoracic hemivertebra			
Number of studies with alteration	11	7	3
Number of litters affected	0–1 (0–7.1%)	0–1 (0–7.7%)	0–1 (0–5.9%)
Number of fetuses affected	0–2 (0–1.5%)	0–1 (0–1.1%)	0–1 (0–0.8%)

Source: Hoberman (1995)

2.6 Special studies

(a) Toxicity of metabolites

Submitted studies on the LD_{50} values determined in experimental animals and the genotoxicity studies conducted with metabolites CL 312622 (2-(4-isopropyl-4-methyl-5-oxo-3*H*-imidazol-2-yl)pyridine-3,5-dicarboxylic acid), CL 263284 (5-(hydroxymethyl)-2-(4-isopropyl-4-methyl-5-oxo-3*H*-imidazol-2-yl)pyridine-3-carboxylic acid) and CL 189215 (2-(4-isopropyl-4-methyl-5-oxo-3*H*-imidazol-2-yl)-5-({[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}methyl)pyridine-3-carboxylic acid) are summarized in Tables 13, 14 and 15, respectively. The chemical structures of these metabolites are reproduced in Table 4. In the assessment of these three metabolites using Toxtree software (version 2.6.6), they were assigned to Cramer class III, which is the same class as for the parent compound.

In a 28-day dietary toxicity study, groups of five male and five female Wistar rats received diets containing metabolite CL 263284 at a concentration of 0, 1200, 4000 or 12 000 ppm (equal to 0, 102, 333 and 1004 mg/kg bw per day for males and 0, 104, 339 and 1028 mg/kg bw per day for females, respectively) (Buesen et al., 2013). Rats were observed daily for signs of overt toxicity, morbidity and mortality. Detailed clinical observations, individual body weights and cage feed consumption were recorded weekly. Drinking-water consumption was monitored daily by visual inspection. Towards the end of the administration period, a functional observational battery was

Table 13. Results of submitted toxicity studies with metabolite CL 312622 (M720H002; Reg. No. 4110542)

Study	Species/test system	Findings	Reference
Oral LD_{50}	Sprague-Dawley rats	> 5 000 mg/kg bw (males and females)	Bradley (1995c)
Microbial mutagenicity assay (Ames)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538; *Escherichia coli* WP2 uvrA-	+S9: Negative −S9: Negative (at 0, 312.5, 625, 1 250, 2 500 and 5 000 µg/plate)	Mulligan (1995d)
In vitro/ micronucleus test	Chinese hamster lung V79 cells	+S9: Negative −S9: Negative (at 0, 4.5, 8.9, 17.9, 35.8, 71.6, 143.2, 286.4, 572.8, 1 145.5 and 2 291.0 µg/mL)	Bohnenberger (2013b)
Gene mutation assay (HPRT)	Chinese hamster ovary cells	+S9: Negative −S9: Negative (at 0, 218.8, 437.5, 875.0, 1 750.0 and 3 500.0 µg/mL and 0, 500.0, 1 000.0, 2 000.0 and 3 500.0 µg/mL [+S9 only])	Kapp & Landsiedel (2013)

bw: body weight; HPRT: hypoxanthine–guanine phosphoribosyltransferase; LD_{50}: median lethal dose; S9: 9000 × *g* supernatant fraction from rat liver homogenate

Table 14. Results of submitted toxicity studies with metabolite CL 263284 (M715H001; Reg. No. 4110773)

Study	Species/test system	Findings	Reference
Oral LD_{50}	CD-1 mice	> 5 000 mg/kg bw (males and females)	Bradley (1995b)
Microbial mutagenicity assay (Ames)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538; *Escherichia coli* WP2 uvrA-	+S9: Negative −S9: Negative (at 0, 312.5, 625, 1 250, 2 500 and 5 000 µg/plate)	Mulligan (1995c)
In vitro/ micronucleus test	Chinese hamster lung V79 cells	+S9: Positive −S9: Negative (at 0, 5.0, 10.0, 20.1, 40.2, 80.3, 100.0, 160.6, 200.0, 300.0, 321.3, 400.0, 500.0, 600.0, 642.5, 800.0, 1 200.0, 1 285.0, 1 400.0, 1 600.0, 2 000.0 and 2 570.0 µg/mL)	Bohnenberger (2013a,d)
In vivo/ micronucleus test	NMRI mice (bone marrow)	Negative (at 0, 500, 1 000 and 2 000 mg/kg bw)	Schulz & Mellert (2013)
28-day dietary study	Wistar rats	NOAEL: 333 mg/kg bw per day (M) 1 028 mg/kg bw per day (F) LOAEL: 1 004 mg/kg bw per day (M, bw and bw gain ↓) > 1 028 mg/kg bw per day (F)	Buesen et al. (2013)

bw: body weight; F: female; LD_{50}: median lethal dose; LOAEL: lowest-observed-adverse-effect level; M: male; NOAEL: no-observed-adverse-effect level; S9: 9000 × *g* supernatant fraction from rat liver homogenate

Table 15. Results of submitted toxicity studies with metabolite CL 189215 (M715H002; Reg. No. 4110445)

Study	Species/test system	Findings	Source
Microbial mutagenicity assay (Ames)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538; *Escherichia coli* WP2 uvrA-	+S9: Negative −S9: Negative (at 0, 312.5, 625, 1 250, 2 500 and 5 000 µg/plate)	Mulligan (1995b)
In vitro/ micronucleus test	Chinese hamster lung V79 cells	+S9: Negative −S9: Negative (at 0, 11.4, 22.8, 45.5, 91.1, 182.2, 364.4, 728.8, 1 457.5, 2 915.0 and 5 830.0 µg/mL)	Bohnenberger (2013c)

S9: 9000 × *g* supernatant fraction from rat liver homogenate

performed on all animals. Haematological, clinical chemistry and urine analysis parameters were determined in five animals of each sex per test group. At termination, all surviving rats were subjected to a gross necropsy, and selected organs were weighed. Samples of selected tissues from all rats in the 0 and 12 000 ppm groups only were submitted for histopathological evaluation.

Test material was distributed homogeneously within the diet and stable for 11 days at room temperature. The concentrations in diet achieved the expected range.

No mortalities or treatment-related clinical signs, including functional observational battery changes, were observed during the study period. Feed consumption values for treated males and females were generally similar to those of control rats at all measurement times. Body weights and body weight gains of females at all treatment levels were similar to those of control rats at all measurement times (Table 16). Body weights were decreased in males of the top-dose group on study days 21 and 28. Body weight gains were statistically significantly reduced among males of the top-dose group on study days 21 and 28. Body weight and body weight gain in males of the low- and mid-dose groups were similar to those of control rats at all measurement times.

Table 16. Selected body weight and body weight gains in rats treated with metabolite CL 263284 (M715H001; Reg. No. 4110773) in a 28-day study

	Body weight/body weight gain (g, mean ± SD)							
	Males				Females			
	0 ppm	1 200 ppm	4 000 ppm	12 000 ppm	0 ppm	1 200 ppm	4 000 ppm	12 000 ppm
Day 0	154.7 ± 5.7	154.7 ± 2.8	155.2 ± 4.8	155.2 ± 4.1	128.1 ± 3.2	125.9 ± 3.5	128.4 ± 1.3	125.9 ± 2.6
Day 28	288.1 ± 20.4	295.6 ± 6.7	292.1 ± 3.9	266.0 ± 21.4	185.5 ± 8.7	181.1 ± 8.3	188.5 ± 3.7	184.5 ± 5.8
Days 0–7	41.5 ± 4.8	43.4 ± 3.9	43.8 ± 2.8	38.4 ± 2.9	19.0 ± 2.4	16.1 ± 4.0	18.6 ± 1.1	20.9 ± 3.6
Days 0–15	84.3 ± 8.3	88.3 ± 6.6	84.9 ± 6.9	72.2 ± 8.3	32.8 ± 4.6	33.3 ± 6.8	29.0 ± 3.0	34.7 ± 8.0
Days 0–21	113.9 ± 13.8	120.5 ± 6.7	116.6 ± 7.8	93.6* ± 15.5	46.1 ± 8.1	46.1 ± 6.8	47.6 ± 2.7	48.7 ± 5.4
Days 0–28	133.4 ± 15.7	141.0 ± 8.8	136.9 ± 5.7	110.8* ± 18.5	57.4 ± 7.5	55.2 ± 5.9	60.1 ± 3.1	58.6 ± 5.1

ppm: parts per million; SD: standard deviation; *: $P < 0.05$

Source: Buesen et al. (2013)

Haematological, blood chemistry and urine analysis parameters either were comparable with those observed in control animals or did not show a dose–response relationship. Absolute and relative (to body weight) testes weights and absolute liver weights were statistically significantly increased for males in the 1200 ppm group only. These increases were not considered treatment related, given the absence of an effect at 4000 or 12 000 ppm. No adverse organ weight changes were reported in treated females. No gross pathological or histopathological changes were reported.

The NOAEL was 4000 ppm (equal to 333 mg/kg bw per day) for males, based on reduced body weights and body weight gains at 12 000 ppm (equal to 1004 mg/kg bw per day). The NOAEL was 12 000 ppm (equal to 1028 mg/kg bw per day) for females, based on the absence of adverse effects up to the highest dose level tested (Buesen et al., 2013).

(b) Other studies

Imazamox was tested for its ability to induce phototoxic effects in Balb/c 3T3 cells in vitro (Cetto & Landsiedel, 2012). The photo-cytotoxicity was estimated using the neutral red uptake (NRU) method. A single experiment was carried out, with and without irradiation with an ultraviolet A (UVA) light source. The test compound was tested at concentrations of 0, 4.6, 10.0, 21.5, 46.4, 100.0, 215.4, 464.2 and 1000.0 µg/mL.

In this study, no cytotoxicity in the absence or the presence of UVA irradiation was observed up to the highest required concentration indicated by the NRU method. The positive control chlorpromazine led to the expected cytotoxicity both with and without UVA irradiation, thus demonstrating the ability of the test system to detect phototoxicity.

Under the experimental conditions of this study, imazamox is considered not to be a phototoxic substance in the in vitro 3T3 NRU phototoxicity test using Balb/c 3T3 cells (Cetto & Landsiedel, 2012).

Technical imazamox was tested for its acute toxic potential in groups of three male and three female ICR mice when administered once intraperitoneally at a dose level of 0, 78.1, 313, 1250 or 5000 mg/kg bw (Futagawa, 1995). Additionally, groups of four male Japanese White rabbits were dosed once orally with technical imazamox at 0 or 5000 mg/kg bw. The behaviour of male and female mice was observed prior to administration, at 0.5, 1, 3 and 6 hours after administration and then once a day for 4 days. Clinical signs and cardiorespiratory parameters of male rabbits were measured before administration and at 0.5, 1, 3, 6 and 24 hours after administration.

Clinical signs in mice included decreases in awareness and motor activity, abnormal posture, lack of motor coordination, decreases in muscle tone and reflexes, and inhibitory abnormal autonomic signs at intraperitoneal doses of 1250 and 5000 mg/kg bw. These signs were noted 30 minutes following administration of the test material. Mortality occurred within 6 hours following administration for all mice in the 5000 mg/kg bw dose group. Animals in the 1250 mg/kg bw dose group recovered within 2 days after administration. No abnormal clinical signs were noted at a dose level of 313 mg/kg bw or lower.

Rabbits dosed orally with the test material at 5000 mg/kg bw exhibited no abnormal signs with regard to behaviour and somatic and autonomic profiles. No changes in respiration, blood pressure, electrocardiogram or heart rate were observed in male rabbits (Futagawa, 1995).

A comparison of the in vitro metabolism of imazamox in humans and those species that were used in in vivo toxicological testing was performed (draft report without signatures or quality assurance statement; Funk & Taraschewski, 2013) to investigate whether a metabolite occurs in human samples that might not be sufficiently covered by the animal testing.

^{14}C-^{15}N-labelled[3]/unlabelled imazamox mix was incubated with dog, rabbit, rat, mouse or human liver microsomes in the presence of a nicotinamide adenine dinucleotide phosphate (NADPH)–generating system. With 90% recovered radioactivity and above, only the parent molecule was detected in all test systems by high-performance liquid chromatographic analysis in fresh samples after the incubation. Under the conditions of the study, imazamox was not metabolized by liver microsomes of dogs, rabbits, rats, mice or humans. No unique human metabolite was detected. Under the conditions of the study, the positive control, testosterone, was metabolized by the microsome samples originating from different species (Funk & Taraschewski, 2013).

A summarizing article (Sipes et al., 2013) describes selected work conducted under the United States Environmental Protection Agency's (USEPA) ToxCast programme, but does not report primary data. According to the authors, two of 331 enzymatic and receptor signalling assays were affected by imazamox. In particular, human pregnane X receptor binding was indicated by the authors as being present at the lowest concentration tested.

In an in vitro study, male murine embryonic stem cells were treated with imazamox at a concentration of 0, 0.0125, 0.125, 1.25 or 12.5 µmol/L (Chandler et al., 2011). Cytotoxicity and changes in differentiation to cardiomyocytes were measured. The latter was assessed with antibodies against the α,β-cardiac myosin heavy chain. No change in differentiation was reported, whereas the top dose was cytotoxic to the cells (half maximal activity at 2.5 µmol/L).

In an in vitro study, human embryonic stem cells (WA09) were treated with imazamox at a concentration of 0, 1, 10 or 100 µmol/L (Kleinstreuer et al., 2011). Metabolomic changes were assessed by liquid chromatographic–mass spectrometric analysis. According to the authors, incubation did not induce cytotoxicity. Data were analysed with models to predict developmental toxicity, which were set up with data from (1) pharmaceutical agents or (2) selected pesticides from the USEPA's Toxicity Reference Database (ToxRefDB). Imazamox was predicted with a probability of approximately 0.7% to be a non-developmental toxicant. Considering the limited primary data included in the article, it is difficult to confirm the conclusions.

3. Observations in humans

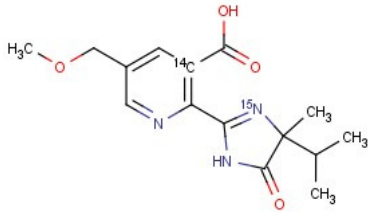
No information or data were provided on adverse health effects in workers involved in the manufacture or use of imazamox. No information on accidental or intentional poisoning in humans was submitted.

Comments

Biochemical aspects

In rats, imazamox was rapidly absorbed, and the oral absorption was approximately 75% of the administered dose. Urine was the major route of excretion (> 74%). Most of the elimination

[3] Chemical structure showing position of labels:



occurred within the first 24 hours after dosing, as unchanged parent compound. Smaller amounts of the test substance were excreted through faeces (> 19% in animals receiving 10 mg/kg bw and approximately 10–20% in animals receiving 1000 mg/kg bw). Only trace amounts of tissue residue were detected. Imazamox appears not to be metabolized. Trace levels of imazamox-related compounds detected in the urine and faeces were attributed to the presence of impurities in the dosing solution, not to rat metabolism.

A comparative in vitro metabolism study was performed in liver microsomes from mice, rats, rabbits, dogs and humans. Under the conditions of the study, no metabolites of imazamox were detected.

Toxicological data

Imazamox was of low acute toxicity after oral, dermal and inhalation exposure. The oral LD_{50} in rats was greater than 5000 mg/kg bw. The dermal LD_{50} in rabbits was greater than 4000 mg/kg bw, and the inhalation LC_{50} in rats was greater than 1.6 mg/L (value for respirable particles only). Imazamox was neither a skin irritant nor an eye irritant in rabbits. In a guinea-pig maximization test, no skin sensitization occurred.

In short-term toxicity studies in rats with dietary administration of imazamox over 28 and 90 days, no adverse effects were reported up to the top dose levels, which were at least 1500 mg/kg bw per day. Similarly, in 90-day and 1-year studies, no adverse effects were reported in dogs receiving imazamox in the diet up to the top dose levels, which were at least 1100 mg/kg bw per day. In long-term toxicity and carcinogenicity studies in mice and rats, no signs of systemic toxicity or treatment-related increases in neoplastic lesions were reported up to the highest dose levels tested, which were approximately 1000 mg/kg bw per day.

The Meeting concluded that imazamox is not carcinogenic in mice or rats.

Imazamox was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence of genotoxicity was found.

The Meeting concluded that imazamox is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that imazamox is unlikely to pose a carcinogenic risk to humans.

In a two-generation study in rats, there was no evidence of adverse effects on parental animals, offspring or reproduction up to the highest tested dietary imazamox concentration of 20 000 ppm (equal to 1554 mg/kg bw per day).

In a rat developmental toxicity study that tested imazamox doses of 0, 100, 500 and 1000 mg/kg bw per day, the NOAEL for maternal toxicity was 500 mg/kg bw per day, for reduced body weight gain and feed consumption at 1000 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

In a rabbit developmental toxicity study that tested imazamox doses of 0, 300, 600 and 900 mg/kg bw per day, the NOAEL for maternal toxicity was 300 mg/kg bw per day, for decreased feed intake during the dosing period at 600 mg/kg bw per day, which was of equivocal toxicological relevance. Effects on feed intake were not observed during the first days of dosing. The NOAEL for embryo and fetal toxicity was 300 mg/kg bw per day, based on an increased incidence of both absent intermediate lung lobes and hemivertebrae at 600 mg/kg bw per day.

The Meeting concluded that imazamox is teratogenic in rabbits, but not in rats.

Toxicological data on metabolites and/or degradates

The oral LD_{50}s of metabolites CL 312622 (2-(4-isopropyl-4-methyl-5-oxo-3*H*-imidazol-2-yl)pyridine-3,5-dicarboxylic acid) and CL 263284 (5-(hydroxymethyl)-2-(4-isopropyl-4-methyl-5-oxo-3*H*-imidazol-2-yl)pyridine-3-carboxylic acid) were greater than 5000 mg/kg bw in rats and mice, respectively. CL 312622 was tested for genotoxicity in an adequate range of assays in vitro.

No evidence of genotoxicity was observed. CL 263284 was tested for genotoxicity in an adequate range of assays in vitro and in vivo. It gave a positive response in the in vitro micronucleus assay, but was negative in the in vivo micronucleus assay. In a 28-day repeated-dose toxicity study in rats with CL 263284, which tested dietary concentrations of 0, 1200, 4000 and 12 000 ppm (equal to 0, 102, 333 and 1004 mg/kg bw per day for males and 0, 104, 339 and 1028 mg/kg bw per day for females, respectively), the NOAEL was 4000 ppm (equal to 333 mg/kg bw per day), based on lower body weights and significantly lower body weight gains observed in males treated with 12 000 ppm (equal to 1004 mg/kg bw per day). No effects were observed in females up to the highest tested dietary concentration of 12 000 ppm (equal to 1028 mg/kg bw per day). CL 189215 (2-(4-isopropyl-4-methyl-5-oxo-3*H*-imidazol-2-yl)-5-({[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}methyl)pyridine-3-carboxylic acid) was tested for genotoxicity in a range of assays in vitro, and there was no evidence of genotoxicity.

Human data

No information was provided on the health of workers involved in the manufacture or use of imazamox. No information on accidental or intentional poisoning in humans is available.

The Meeting concluded that the existing database on imazamox was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–3 mg/kg bw based on the NOAEL of 300 mg/kg bw per day for reduced feed intake in dams of equivocal toxicological relevance and an increased incidence of both absent intermediate lung lobes and hemivertebrae in the developmental toxicity study in rabbits, using a safety factor of 100.

The Meeting established an acute reference dose (ARfD) of 3 mg/kg bw based on the NOAEL of 300 mg/kg bw per day for an increased incidence of both absent intermediate lung lobes and hemivertebrae in the developmental toxicity study in rabbits, using a safety factor of 100. Considering the uncertainty as to whether the observed effects on prenatal bone development are also relevant for children's bone growth (bone remodelling), the ARfD is applicable to the whole population.

The plant metabolite CL 263284 is an *O*-demethylation product of imazamox and is a common metabolite with imazapic. Although there is some indication of slightly higher toxicity of this metabolite when compared with imazamox in a 28-day toxicity study in rats, the effects observed were mild changes in body weight gain in males only. Taking into account the close structural similarity to imazamox and the effects and effect levels observed in the developmental toxicity study in rats with imazamox, the Meeting concluded that CL 263284 is of similar toxicity to imazamox and would be covered by the ADI and ARfD for imazamox.

Levels relevant to risk assessment of imazamox

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of carcinogenicity[a]	Toxicity	7 000 ppm, equal to 1 053 mg/kg bw per day[b]	–
		Carcinogenicity	7 000 ppm, equal to 1 053 mg/kg bw per day[b]	–

Species	Study	Effect	NOAEL	LOAEL
Rat	Ninety-day study of toxicity[a]	Toxicity	20 000 ppm, equal to 1 550 mg/kg bw per day[b]	–
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	20 000 ppm, equal to 1 068 mg/kg bw per day[b]	–
		Carcinogenicity	20 000 ppm, equal to 1 068 mg/kg bw per day[b]	–
	Two-generation reproductive toxicity study[a]	Parental toxicity	20 000 ppm, equal to 1 554 mg/kg bw per day[b]	–
		Reproductive toxicity	20 000 ppm, equal to 1 554 mg/kg bw per day[b]	–
		Offspring toxicity	20 000 ppm, equal to 1 554 mg/kg bw per day[b]	–
	Developmental toxicity study[c]	Maternal toxicity	500 mg/kg bw per day	1 000 mg/kg bw per day
		Embryo and fetal toxicity	1 000 mg/kg bw per day[b]	–
Rabbit	Developmental toxicity study[c]	Maternal toxicity	300 mg/kg bw per day	600 mg/kg bw per day
		Embryo and fetal toxicity	300 mg/kg bw per day	600 mg/kg bw per day
Dog	Ninety-day and 1-year studies of toxicity[a,d]	Toxicity	40 000 ppm, equal to 1 333 mg/kg bw per day[b]	–

[a] Dietary administration.
[b] Highest dose tested.
[c] Gavage administration.
[d] Two or more studies combined.

Estimate of acceptable daily intake (ADI)

0–3 mg/kg bw

Estimate of acute reference dose (ARfD)

3 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to imazamox

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rats: T_{max} = 0.5–1 hour; extensive, ~75%
Dermal absorption	No data
Distribution	Widespread tissue distribution
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Excretion mainly via urine within 48 hours
Metabolism in animals	No metabolism
Toxicologically significant compounds in animals and plants	Parent compound
Acute toxicity	
Rat, LD_{50}, oral	> 5 000 mg/kg bw
Rabbit, LD_{50}, dermal	> 4 000 mg/kg bw
Rat, LC_{50}, inhalation	> 1.6 mg/L (respirable particles)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea-pig, dermal sensitization	Not sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	No adverse effects
Lowest relevant oral NOAEL	> 1 000 mg/kg bw per day, highest dose tested (rat and dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day, highest dose tested (rat)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	No adverse effects
Lowest relevant NOAEL	~1000 mg/kg bw per day, highest dose tested (rat and mouse)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans
Genotoxicity	
	Unlikely to be genotoxic
Reproductive toxicity	
Target/critical effect	No evidence of reproductive toxicity (rat)
Lowest relevant parental NOAEL	1 554 mg/kg bw per day, highest dose tested
Lowest relevant offspring NOAEL	1 554 mg/kg bw per day, highest dose tested
Lowest relevant reproductive NOAEL	1 554 mg/kg bw per day, highest dose tested
Developmental toxicity	
Target/critical effect	Increased incidence of both absent intermediate lung lobes and hemivertebrae at maternally toxic doses (rabbits)
Lowest relevant maternal NOAEL	300 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	300 mg/kg bw per day (rabbit)

Neurotoxicity	
Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data
Toxicological studies on CL 312622 (plant metabolite)	
Rat LD_{50}, oral	> 5 000 mg/kg bw
Genotoxicity	Unlikely to be genotoxic
Toxicological studies on CL 263284 (plant metabolite)	
Mouse LD_{50}, oral	> 5 000 mg/kg bw
Genotoxicity	Unlikely to be genotoxic in vivo
Twenty-eight day, rat	NOAEL: 333 mg/kg bw per day (based on reduced body weight and body weight gain in males)
Toxicological studies on CL 189215 (plant metabolite)	
Genotoxicity	Unlikely to be genotoxic
Medical data	
	No data

Summary

	Value	Study	Safety factor
ADI	0–3 mg/kg bw	Developmental toxicity study (rabbit)	100
ARfD	3 mg/kg bw	Developmental toxicity study (rabbit)	100

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