5.23 IMAZAPYR (267)

TOXICOLOGY

Imazapyr is the ISO-approved name of 2-[(RS)-4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl]nicotinic acid (IUPAC), with CAS No. 81334-34-1. Imazapyr is a herbicide used for the control of grasses and broadleaf weeds in a variety of crops, including major uses in soya bean, sunflower, rice, maize, sugar cane, rape, wheat and non-crop areas such as vegetation management and forestry and minor uses in tobacco and oil palm. Imazapyr kills weeds by inhibiting the activity of the plant-specific enzyme acetohydroxyacid synthase, which catalyses the production of three branched-chain amino acids (valine, leucine and isoleucine) required for protein synthesis and cell growth.

Imazapyr has not previously been evaluated by JMPR and was reviewed by the present Meeting at the request of CCPR.

All critical studies contained statements of compliance with GLP.

Biochemical aspects

Imazapyr is quickly and extensively absorbed following oral administration to rats. There were no substantial sex differences in the absorption, elimination or distribution of radioactivity in rats receiving an oral dose of radiolabelled imazapyr. The majority of the administered dose was excreted in urine (68–95%) and, to a lesser extent, in faeces (5.5–33%). Most of the elimination occurred within the first 24 hours after dosing (57–91% in urine; 3–24% in faeces). The half-life of imazapyr in the rat was less than 1 day. Imazapyr was excreted mostly unchanged. Trace levels of polar and non-polar metabolites were formed and excreted in urine and faeces. Only trace amounts of tissue residues were detected in the liver and kidneys of the high-dose group, indicating no bioaccumulation.

Toxicological data

The oral LD_{50}s were greater than or equal to 5000 mg/kg bw in rats, rabbits and dogs, but some clinical signs were noted in dogs immediately after dosing. The dermal LD_{50}s in rats and rabbits were greater than 2000 mg/kg bw. Imazapyr appears to be of low acute inhalation toxicity, but characterization by this route was limited due to the high median particle sizes. Imazapyr was irritating to the eye but not irritating to the skin in rabbits. It was not a dermal sensitizer in guinea-pigs.

Repeated-dose toxicity studies in rats and dogs indicate no effects except for reduced body weight gain in a 28-day oral toxicity study in rats, in which there was decreased body weight gain in males at the highest dose tested, 10 000 ppm (equal to 1395 mg/kg bw per day). However, in two 13-week studies in rats, no treatment-related effects were observed up to 20 000 ppm (equal to 1740 mg/kg bw per day), and in a 1-year study in dogs, up to 10 000 ppm (equal to 282.1 mg/kg bw per day).

In two long-term oral toxicity and carcinogenicity tests in mice and rats (18 months in mice, 2 years in rats), no substance-related effects were observed. In the mouse study, no treatment-related effects occurred up to the highest dose tested (10 000 ppm, equal to 1301 mg/kg bw per day). Imazapyr did not show any carcinogenic potential. In rats, the NOAEL was the highest dose tested, 10 000 ppm (equal to 503 mg/kg bw per day). No compound-related tumours were observed. Three supplementary evaluations (two histopathological and one statistical) supported the results of the 2-year rat study.

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

Imazapyr was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. It showed no evidence of genotoxicity.

The Meeting concluded that imazapyr 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 imazapyr is unlikely to pose a carcinogenic risk to humans.

In a two-generation dietary reproductive toxicity study in rats, the NOAEL for parental and offspring toxicity was 10 000 ppm (equal to about 1471.8 mg/kg bw per day), the highest dose tested. There was also no effect on reproduction at the highest dose tested.

In a study of developmental toxicity in rats treated by gavage, salivation observed in 6 of 22 gravid females at 1000 mg/kg bw per day was considered to be due to the high dose and the irritating effect of the compound. The NOAEL for embryo and fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

In a pilot study for developmental toxicity in rabbits, treatment-related maternal toxicity, including death, was observed at 1000 mg/kg bw per day and above. This toxicity appears to have been due to local effects of the compound on the gastrointestinal tract. In the main study, the NOAEL for maternal and embryo and fetal toxicity was 400 mg/kg bw per day, the highest dose tested.

The Meeting concluded that imazapyr is not teratogenic in rats or rabbits.

In acute and subchronic neurotoxicity studies with imazapyr, there was no indication of neurotoxicity (including functional observational battery and motor activity measurements), with NOAELs of 2000 mg/kg bw and 924 mg/kg bw per day, respectively. Both doses were the highest doses tested.

The Meeting concluded that imazapyr is not neurotoxic.

In a 4-week dietary study in mice, no immunotoxic effects were seen up to the highest dose tested, 1668 mg/kg bw per day.

Toxicological data on metabolites and/or degradates

2,3-Pyridine dicarboxylic acid (PDC), a minor plant metabolite of imazapyr, is of low acute toxicity by the oral (LD_{50} > 5000 mg/kg bw) and dermal (LD_{50} > 2000 mg/kg bw) routes of administration. However, a greater number of clinical signs were observed post-dosing for the metabolite than for the parent. PDC is negative in the in vivo mouse micronucleus test. In a combined repeated-dose toxicity/reproductive and developmental toxicity study, in which rats were treated by gavage from 2 weeks premating through to 1 week post-mating in males and up to day 4 of lactation in females, the NOAEL for systemic and developmental toxicity was 1000 mg/kg bw per day, the highest dose tested.

Human data

No information is available on adverse health effects or poisoning in manufacturing plant personnel or in operators and workers exposed to imazapyr.

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

Toxicological evaluation

The Meeting established an ADI of 0–3 mg/kg bw, derived from a NOAEL of 282 mg/kg bw per day, the highest dose tested, from the 1-year study of oral toxicity in dogs. A safety factor of 100 was applied. Although imazapyr is generally of low toxicity, the Meeting concluded that an ADI was necessary because effects were observed at high doses in the 28-day oral toxicity study in rats.

The Meeting concluded that it was not necessary to establish an ARfD for imazapyr in view of its low acute toxicity and the absence of developmental toxicity and any other toxicological effects that would be likely to be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment of imazapyr

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	10 000 ppm, equal to 1301 mg/kg bw per day[b]	—
		Carcinogenicity	10 000 ppm, equal to 1301 mg/kg bw per day[b]	—
Rat	Short-term studies of toxicity[a,c]	Toxicity	20 000 ppm, equal to 1740 mg/kg bw per day[b]	—
	Two-year studies of toxicity and carcinogenicity[a,c]	Toxicity	10 000 ppm, equal to 503 mg/kg bw per day[b]	—
		Carcinogenicity	10 000 ppm, equal to 503 mg/kg bw per day[b]	—
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	10 000 ppm, equal to 1471.8 mg/kg bw per day[b]	—
		Parental toxicity	10 000 ppm, equal to 1471.8 mg/kg bw per day[b]	—
		Offspring toxicity	10 000 ppm, equal to 1471.8 mg/kg bw per day[b]	—
	Developmental toxicity study[d]	Maternal toxicity	1000 mg/kg bw per day[b]	—
		Embryo and fetal toxicity	1000 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity study[d]	Maternal toxicity	400 mg/kg bw per day[b,e]	—
		Embryo and fetal toxicity	400 mg/kg bw per day[b]	—
Dog	One-year study of toxicity[a]	Toxicity	10 000 ppm, equal to 282.1 mg/kg bw per day[b]	—

[a] Dietary administration.

[b] Highest dose tested.

[c] Two or more studies combined.

[d] Gavage administration.

[e] Maternal deaths occurred at higher doses in the pilot study, likely due to local effects.

Estimate of acceptable daily intake

0–3 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; absorption is ~80%
Dermal absorption	No data
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Rapid, 68–90% within 24 h, mainly via urine
Metabolism in animals	Minimal
Toxicologically significant compounds in animals, plants and the environment	Imazapyr
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	No reliable data
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Irritating
Dermal sensitization	Non-sensitizing (Magnusson and Kligman test)
Short-term studies of toxicity	
Target/critical effect	No effect at highest dose tested
Lowest relevant oral NOAEL	282 mg/kg bw per day, the highest dose tested (dog)
Lowest relevant dermal NOAEL	400 mg/kg bw per day, the highest dose tested (rabbit)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	No effects at highest dose tested
Lowest relevant NOAEL	503 mg/kg bw per day, the highest dose tested (rat)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Not genotoxic

Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects
Lowest relevant parental NOAEL	1471.8 mg/kg bw per day, the highest dose tested (rat)
Lowest relevant offspring NOAEL	1471.8 mg/kg bw per day, the highest dose tested (rat)
Lowest relevant reproductive NOAEL	1471.8 mg/kg bw per day, the highest dose tested (rat)
Developmental toxicity	
Developmental target/critical effect	None (but maternal deaths observed in pilot study, likely due to local effects)
Lowest relevant maternal NOAEL	400 mg/kg bw per day, the highest dose tested (rabbit)
Lowest relevant embryo/fetal NOAEL	400 mg/kg bw per day, the highest dose tested (rabbit)
Neurotoxicity	
	Not neurotoxic
Other toxicological studies	
Immunotoxicity	Not immunotoxic
Medical data	
	No information on health effects in manufacturing personnel

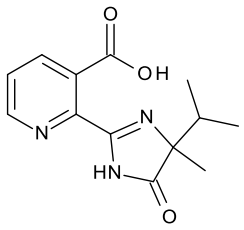
Summary

	Value	Study	Safety factor
ADI	0–3 mg/kg bw	One-year oral toxicity study (dogs)	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

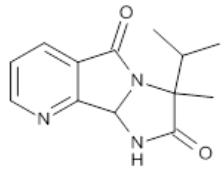
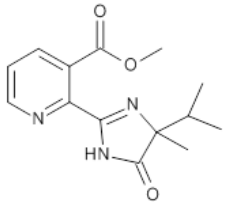
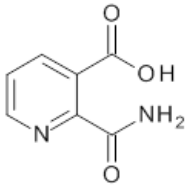
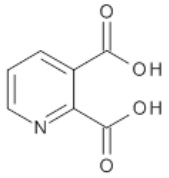
Residue and analytical aspects of imazapyr were considered for the first time by the present Meeting. The residue evaluation was scheduled for the 2013 JMPR by the Forty-fourth Session of the CCPR.

Imazapyr is a broad-spectrum herbicide in the imidazolinone family. Its primary use is as a post-emergence herbicide which is particularly effective on hard-to-control perennial grasses. It is non-selective, absorbed by foliage and rapidly translocated. The mode of action of imidazolinone herbicides is the inhibition of the enzyme acetohydroxyacid synthase (AHAS) which is a critical enzyme for the biosynthesis of branched chain amino acids necessary for cell growth and protein synthesis. The Meeting received information on identity, animal and plant metabolism, environmental fates in soil, rotational crops, analytical methods, storage stability, use patterns, supervised trials, farm animal feeding studies and fates of residues in processing.



2-[(*RS*)-4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl] nicotinic acid. Imazapyr is a 1:1 mixture of the enantiomers.

In this appraisal, the following abbreviated names were used for metabolites.

CL 247, 087	CL 240,000	CL 60,032	PDC
			
5*H*-imidazo [1',2':1,2] pyrrolo [3,4-b] pyridine -2(3*H*),5-dione, 1.9b α(β)-dihydro-3α- isopropyl-3-ethyl-	2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-3 -carboxymethyl pyridine	2-carbamoyl-nicotinic acid	Pyridine 2,3-dicarboxylic acid

Animal metabolism

The Meeting received animal metabolism studies with imazapyr in rats, lactating goats and laying hens. The metabolism and distribution of imazapyr in animals were investigated using the [^{14}C-carboxyl], [^{14}C-6-pyridine] and [^{14}C-5-imidazole]-labelled imazapyr.

Metabolism in rats was summarized and evaluated by the WHO panel of the JMPR in 2013.

Lactating goats were dosed with [pyridine-6-^{14}C]-imazapyr as a single daily oral dosage equivalent to a dietary level of 17.7 or 42.5 ppm for 7 consecutive days. Radioactivity was mainly excreted in the urine (65.3% and 60.4%) and faeces (16.1% and 19.0%) of the dose in the 17.7 ppm and 42.5 ppm dosed goats, respectively).

The TRR levels were < 0.01–0.01 mg equiv/kg and 0.01–0.02 mg equiv/kg in the milk samples of the 17.7 and 42.5 ppm dose goats, respectively. TRR levels for leg and loin muscles, liver, and fat were all less than the LOQ (0.05 mg equiv/kg) and these tissues were not analysed further. Detectable residues were found in the kidneys at 0.08 mg equiv/kg (17.7 ppm dose) and 0.11 mg equiv/kg (42.5 ppm dose).

Kidney residues were quantitatively extractable, with the majority (95.5%) isolated in a methanol/water fraction. The extracted ^{14}C residue in the milk and kidney was identified as unchanged imazapyr.

Lactating goats received [imidazole-5-^{14}C]-imazapyr at a dose equivalent to 47 ppm in the diet once daily for 7 consecutive days. After seven days, 58.7% and 34.4% of the administered radioactive dose were excreted in the urine and faeces, respectively. The TRR levels for the dosed goat were 0.014–0.015 mg equiv/kg for milk and 0.074 mg equiv/kg for kidney.

The major component in the milk (day-7) extract (65.6% of TRR, 0.01 mg/kg) was the parent compound (imazapyr). Polar unknowns (total 14.7% of TRR) were also present in the milk extract.

Since these fractions were 0.002 mg equiv/kg and contained multiple components, no further characterization was attempted. Imazapyr was the predominant radioactive residue (81.9% of TRR, 0.061 mg/kg) in the kidney. Polar unknowns (total 11.6% of TRR) were also present in the kidney extract. The concentration of the remaining radioactive components in the kidney and the milk was below 0.01 mg equiv/kg individually.

Laying hens were orally dosed with [pyridine-6-^{14}C]-imazapyr at the actual dietary dose equivalent to 2.0 or 9.7 ppm in the feed for 7 consecutive days. The majority of the dose was rapidly eliminated in the excreta. Elimination of ^{14}C via the excreta accounted for 90.5 and 91.7% of the total dose for the low and high dose, respectively.

During treatment, TRR in the egg samples was less than the LOQ (0.01 mg equiv/kg). Residues in skin with adhering fat, muscle, liver and kidney tissues were all less than the LOQ (0.01 mg equiv/kg). Parent compound or derived residues are excreted without retention or accumulation in eggs and edible poultry tissues.

In animal metabolism studies, imazapyr was the major component in milk and kidney of lactating goat, but no residue was found in eggs and all tissues of laying hens.

Plant metabolism

Imazapyr is used in three different situations:

- Directed sprays for weed control (crop not intentionally treated)
- Use for weed control with a crop (crop treated)
- Selective use in genetically modified imidazolinone-resistant crops (crop treated)

Plant metabolism studies were conducted with imazapyr to investigate these three situations.

The Meeting received plant metabolism studies performed on soya bean, maize, sugarcane, oil palm, clover and Bermuda grass with imazapyr [^{14}C] labelled in two positions ([^{14}C-3-pyridine] and [^{14}C-6-pyridine]).

Directed sprays to weeds

In a sugar cane metabolism study, [pyridine-6-^{14}C]-imazapyr was applied to the soil surface once as a pre-emergence application at a rate equivalent to 0.28 kg ai/ha. Stalk samples were taken at maturity approximately 14 months after the pre-emergence treatment. There were no detectable residues in the treated samples.

In an oil palm metabolism study, [pyridine-6-^{14}C]-imazapyr was applied to the ground beneath an actively fruiting oil palm at an application rate of 1.0 kg ai/ha. Fruit samples were collected from the oil palm as they ripened at 0 hour, 7, 30 and 62 days after treatment. Palm oil was extracted from the fruits using a hexane: water mixture (3:1, v/v). Residual radioactivity levels were below the LOQ (0.03 mg equiv/kg) at any given time in the palm oil, aqueous phase, fruit marc, kernel shell and kernel nut. The results indicate that imazapyr derived residues will not accumulate in the palm oil of an actively fruiting oil palm after application to the ground beneath the palm.

Weed control

In a clover metabolism study, [pyridine-6-^{14}C]-imazapyr was applied to clover at a rate of 1.68 kg ai/ha. Clover foliage was collected at 0, 4, 10, 15 and 21 days after treatment (DAT). Phytotoxic effects were apparent four days after application of the test material to the clover in the test plot. The phytotoxicity remained apparent until the final collection 21 days after treatment. The TRR levels in foliage ranged from 23–49 mg equiv/kg. The majority of the radioactivity was unchanged imazapyr ranging from 68–99% of TRR. The major metabolite was CL 247,087 with CL 240,000 as a minor metabolite (their sum accounting for 0.02–18% of TRR).

In a Bermuda grass metabolism study, [pyridine-6-^{14}C]-imazapyr was applied to Bermuda grass at a rate of 1.68 kg ai/ha. Bermuda grass foliage was collected 0, 4, 10, 15 and 21 days after treatment (DAT). Phytotoxic effects were apparent four days after application of the test material to the Bermuda grass in the test plot. The phytotoxicity remained apparent until the final collection 21 days after treatment. TRR levels in foliage were the highest at 0 DAT (64 mg equiv/kg), and then were 18 mg equiv/kg (4 DAT), 22 mg equiv/kg (10 DAT), 25 mg equiv/kg (15 DAT) and 48 mg equiv/kg (21 DAT). The majority of the radioactivity was unchanged imazapyr ranging from 78–97% of TRR. Three other identified radio-components were PDC, CL 247,087 and CL 240,000. The amount of PDC increased with time to 13% of TRR at 21 DAT. The amount of CL 247,087 plus CL 240,000 ranged from 0% to 10.5% of TRR between 4 DAT and 21 DAT.

Imidazolinone-resistant crops

In a soya bean metabolism study, [pyridine-3-^{14}C]-imazapyr (SL formulation) was applied once to the above ground portion of transgenic soya bean plants at BBCH growth stage 65 at an application rate of 0.11 kg ai/ha. The forage was harvested approximately one hour after application and the hay was harvested 35 days after application. Soya bean straw, pods and seeds were harvested when mature at 98 days after treatment.

The TRR of soya bean forage was 0.66 mg equiv/kg, soya bean hay was 0.25 mg equiv/kg, soya bean seed was 0.062 mg equiv/kg, soya bean straw was 0.079 mg equiv/kg and soya bean pod was 0.15 mg equiv/kg. Imazapyr was detected in all matrices and was the most abundant component of the residue in soya bean forage (0.60 mg/kg, 93.6% TRR), hay (0.094 mg/kg, 37.3% TRR), and seed (0.024 mg/kg, 34.2% TRR). Imazapyr was present in straw at 0.006 mg/kg (8.1% TRR) and pods at 0.018 mg/kg (12.7% TRR). A polar component M3 was the most abundant component in the pods (0.041 mg equiv/kg, 28.9% TRR). This component was also present in hay (0.028 mg equiv/kg, 11.1% TRR), straw (0.009 mg equiv/kg, 12.2% TRR) and seeds (0.0161 mg equiv/kg, 23.3% TRR), but was not detected in forage. This polar peak was isolated from the soya bean seeds, and shown to consist of multiple components, each present at ≤ 0.004 mg equiv/kg. M19 was present in the straw at 0.013 mg equiv/kg (17.6% TRR) and was also found in hay at 0.022 mg equiv/kg (8.7% TRR). This component had an intermediate polarity with a retention time of about 19 minutes and was not identified.

In a maize metabolism study, [pyridine-6-^{14}C]-imazapyr was applied to imidazolinone-resistant maize at the 3 to 4 leaf growth stage at treatment rates of 0.028 and 0.080 kg ai/ha. Samples of maize plants were harvested at 0 DAT (green plant), 14 DAT (green plant), 30 DAT (early forage), and 62 DAT (late forage). At maturity (114 DAT), the stalks, husks, and cobs with grain were collected.

For the 0 DAT, 96.3% (2.37 mg equiv/kg) of the TRR was extracted. For the 114 DAT fodder, 69.9% (0.020 mg equiv/kg) of the TRR was extracted and 30.1% (0.008 mg equiv/kg) remained in the PES. For the 114 DAT grain, 0.8 to 1.5% (< 0.002 mg equiv/kg) was extracted with hexane, 80.0 to 88.8% (0.023 to 0.076 mg equiv/kg) was extracted with methanol:water:hydrochloric acid (80:18:2, v/v/v), and 10.3 to 18.5% (0.005 to 0.009 mg equiv/kg) remained in the PES. Parent imazapyr constituted the major component of the extractable residue in the green plant, forage, fodder and grain (16.8 to 84.0% of extracted TRR, 0.003 to 2.0 mg/kg). The residue levels of the minor components in the 30 DAT to 114 DAT samples were all < 0.01 mg equiv/kg.

In the plant metabolism studies on soya bean (imidazolinone-resistant), maize (imidazolinone-resistant), sugarcane, oil palm, clover and Bermuda grass, Imazapyr is the major component of the residues found in soya bean, maize, clover, and Bermuda grass. CL 247,087 and PDC were also significant components of the residues in clover and Bermuda grass.

Environmental fate

The Meeting received information on aerobic soil metabolism, soil photolysis, rotational crop and hydrolysis.

In soil under the aerobic conditions, the DT_{50} ranged from 15 months–7.5 years at 20 °C–35 °C. At 12 months after application, imazapyr remained in soil was 60.5–89.3% of the applied radioactivity. Minor degradates were identified as PDC, CL 60,032 and CL 240,000.

In soil photolysis study, there was 11% degradation of imazapyr over the 28 days of continuous irradiation. There were at least five degradation products formed, none of which accounted for > 10% of the applied dose. The photodegradation half-life of imazapyr was 149 days at 25 °C.

In confined rotational crop study, rotational crops (wheat, radish, lettuce and soya bean) were planted at 120 days after treatment (DAT) for wheat, 271 DAT for radish, lettuce and soya bean, 420 DAT for radish and lettuce. The test substance was applied as a post-emergence application to imidazolinone-resistant maize plants at the 6-leaf stage at a rate of 0.028 kg ai/ha.

The TRR in wheat forage, straw and grain; lettuce; radish foliage and root; and soya bean forage, hay, and seed were all < 0.002 mg/kg, the limit of detection of the radio assay.

A series of rotational crops, namely carrot and lettuce were planted at 330 and 540 DAT, winter wheat planted at 359 DAT, spring wheat at 520 DAT. A single application of [^{14}C] imazapyr was made to the soil at a rate of 0.885 kg ai/ha which is 10 times the highest GAP rate for crops used in rotation.

The TRR in follow crops were at < 0.01 to 0.02 mg equiv/kg at the various plant back intervals. Residue in the rotational crops included the unchanged imazapyr which ranged from < 0.001 to 0.003 mg/kg. Metabolites were not detected (< 0.001 mg/kg). The Meeting noted that residues are not expected on rotational crops.

Imazapyr is used for paddy rice. In an hydrolysis study, imazapyr was stable in water (pH 5, 7 and 9) at 25 °C.

Methods of analysis

The Meeting received description and validation data for analytical methods for residues of imazapyr in plant and animal commodities.

In most of the methods for determination of imazapyr in plants, homogenized samples were extracted with acidic aqueous methanol or acidic aqueous acetone, and the extract was cleaned up with column chromatography using solid phase extraction and/or strong cation exchange cartridges. Residues were determined by HPLC with UV or MS/MS detection. The methods of analysis for a range of substrates were validated with LOQs of the 0.05 mg/kg for imazapyr.

In the methods for animal commodities, homogenized samples were extracted with acidic solvent, and the extract was cleaned up by solvent partition and solid phase extraction. Residue of imazapyr was determined by capillary electrophoresis with UV detection. The methods of analysis were validated with the LOQ of 0.01 mg/kg for milk and milk fat, and 0.05 mg/kg for tissues of cattle.

No multi-residue method was submitted.

Stability of residues in stored analytical samples

The Meeting received information on the freezer storage stability of imazapyr in plant (maize grain, forage and fodder and soya bean seed), their processed (soya bean meal and oil) commodities and animal products.

Storage stability results indicate that imazapyr residue was stable for at least 3 months in soya bean (seed, laminated soya bean, meal and oil), at least 6 months in milk, at least 8 months in muscle and liver, and at least 27 months in maize (grain, forage and fodder).

The periods of storage stability studies generally cover the sample storage intervals of residue trials.

Definition of the residue

In the lactating goat metabolism studies, TRRs in kidney (0.074–0.11 mg equiv/kg) was higher than those in milk (< 0.01–0.02 mg equiv/kg), liver (< 0.05 mg equiv/kg), muscle (< 0.05 mg equiv/kg) and fat (< 0.05 mg equiv/kg). Imazapyr is the major component of the residue in kidney (82% TRR) and milk (67% TRR). The concentration of the remaining radioactive components in the kidney and milk were below 0.01 mg/kg.

The Meeting decided that imazapyr is suitable analytes for enforcement purposes and dietary risk assessment in animal commodities.

The octanol/water coefficient (log P_{ow}) of imazapyr is –3.96 at 20 °C (pH 7). The Meeting considered the residue of imazapyr is not fat soluble.

In plant metabolism studies, parent imazapyr was a major component (8.1–99% TRR) in soya bean (forage, hay, seed, straw and pods), maize (forage, grain and fodder), clover and Bermuda grass. Imazapyr was a major compound in conventional and tolerant crops. Though PDC was found as a significant compound in Bermuda grass (13% TRR) which is a feed commodity, it may not be necessary to consider this compound for the definition of residue for food commodities.

The Meeting decided that parent imazapyr is a suitable analyte for enforcement purposes and dietary risk assessment in plant commodities.

The Meeting recommended the following residue definition:

For plants and animals the definition of the residue (for compliance with the MRL and for estimation of dietary intake): *Imazapyr*

The residue is not fat soluble

Results of supervised residue trials on crops

The Meeting received supervised trial data for the foliar application of imazapyr on lentils, soya bean, maize, rice, wheat, sugar cane, rape and sunflower. Residue trial data was made available from Argentina, Australia, Brazil, Canada, Uruguay and the USA.

Labels were available from Australia, Canada, Latin American countries and the USA describing the registered uses of imazapyr.

Pulses

Lentil (dry)

Data were available from supervised trials on imidazolinone-tolerant lentils in Canada.

The GAP for imidazolinone-tolerant lentil in Canada is a foliar application at a maximum rate of 0.0091 kg ai/ha with a PHI of 60 days.

Imazapyr residues in lentil seeds from independent trials in Canada matching GAP were (n=4): 0.06 (2) and 0.08 (2) mg/kg.

Based on the trials for lentils in Canada, the Meeting estimated a maximum residue level and an STMR value for imazapyr in lentil seeds of 0.3 and 0.07 mg/kg respectively.

Soya bean (dry)

Data were available from supervised trials on imidazolinone-tolerant soya beans in Brazil.

No GAP of Brazil was available for imidazolinone-tolerant soya beans.

The Meeting agreed that no recommendation could be made for soya beans.

Cereal grains

Maize

Data were available from supervised trials on imidazolinone-tolerant maize in Argentina, Brazil, Australia and the USA.

The GAP for imidazolinone-tolerant maize of Argentina is for a foliar application at a maximum rate of 0.025 kg ai/ha with the application timed before reaching 6th fully developed leaf stage.

Imazapyr residues in maize grains from trials in Argentina matching GAP were (n=7): < 0.05 (7) mg/kg.

Trials from Australia on maize were reported for a foliar application of a SL formulation (GAP: a foliar application at a rate of 0.018–0.022 kg ai/ha with a PHI not required when used as directed at the application timing at the 2–6 leaf stage of the crop). Imazapyr residue in maize grain from data in Australia at an exaggerated rate of 0.032 kg ai/ha (1.5 × GAP rate) were < 0.05 (2) mg/kg and at 0.048 kg ai/ha (2.2 × GAP rate) were < 0.05 (2) mg/kg.

The GAP on imidazolinone-tolerant maize of the USA is for a foliar application at a maximum rate of 0.016 kg ai/ha with a PHI of 45 days at the application timed at before the 6 leaf stage of the crop. However, imazapyr residue trials on maize in the USA did not match the GAP of the USA.

The Meeting decided to use the data of imazapyr residues in maize grain from the trials in Argentina.

Based on the trials for maize in Argentina, the Meeting estimated a maximum residue level, an STMR value for imazapyr in maize of 0.05 (*) and 0.05 mg/kg respectively.

Rice

Data were available from supervised trials on imidazolinone-tolerant paddy rice in Brazil.

The GAP for imidazolinone-tolerant rice of Brazil is two foliar applications at a maximum rate of 0.074 kg ai/ha with a PHI of 60 days.

Trials from Brazil on rice were reported for two foliar applications at a rate of 0.12 kg ai/ha with a PHI of 60 days. Imazapyr residues in rice grains from trials at a rate of 0.12 kg ai/ha in Brazil were (n=4): < 0.05 (3) and 0.05 mg/kg. However, the trials for rice in Brazil were considered insufficient to estimate a maximum residue level for the commodity.

The Meeting could not estimate a maximum residue level for imazapyr in rice.

Wheat

Data were available from supervised trials on imidazolinone-tolerant wheat in Australia.

The GAP on imidazolinone-tolerant wheat of Australia is for a foliar application at a rate of 0.004–0.007 kg ai/ha with a PHI not required for wheat grains when used as directed.

Imazapyr residues in wheat grains from trials in Australia matching GAP were (n=3): < 0.05 (3) mg/kg. Imazapyr residues in wheat grains from data in Australia at exaggerated rate of 0.014 kg ai/ha (2 × GAP rate) were < 0.05 (5) mg/kg and at 0.028 kg ai/ha (4 × GAP rate) were < 0.05 (5) mg/kg.

Based on the trials for wheat in Australia, the Meeting estimated a maximum residue level and an STMR value for imazapyr in wheat grain of 0.05 (*) and 0 mg/kg respectively.

Grasses for sugar or syrup production

Sugar cane

Data were available from supervised trials on sugar cane in Argentina and Brazil.

The GAP on sugar cane of Argentina is two applications with a spray to weeds at a maximum rate of 0.5 kg ai/ha, 30–45 days before planting. The GAP on sugar cane of Brazil is an application with a spray to weeds of a rate of 0.13–0.5 kg ai/ha with a PHI not required when used as directed.

Imazapyr residue in sugar cane from trials in Argentina matching GAP was (n=1): < 0.05 mg/kg. However, the trial for sugar cane in Argentina was insufficient to estimate a maximum residue level for the commodity.

The Meeting could not estimate a maximum residue level for imazapyr in sugar cane.

Oilseeds

Rape seed

Data were available from supervised trials on imidazolinone-tolerant rape from Australia and Canada.

The GAP on imidazolinone-tolerant rape of Canada is a foliar application at a maximum rate of 0.0091 kg ai/ha with a PHI of 60 days.

Imazapyr residues in rape seeds from independent trials in Canada matching GAP were (n=10): < 0.05 (10) mg/kg.

Trials from Australia on rape were reported for a foliar application of a WG formulation (GAP: a foliar application at a rate of 0.0045–0.011 kg ai/ha with a PHI not required when used as directed).

Imazapyr residues in rape seeds from trials in Australia matching GAP were (n=2): < 0.05 (2) mg/kg. Imazapyr residues in rape seeds from data in Australia at an exaggerated rate of 0.028 kg ai/ha (2.3 × GAP rate) were < 0.05 (2) mg/kg.

Based on the trials for rape seeds in Canada and Australia, the Meeting estimated a maximum residue level, an STMR value for imazapyr in rape seed of 0.05 (*) and 0 mg/kg respectively.

Sunflower seed

Data were available from supervised trials on imidazolinone-tolerant sunflower in Argentina and Uruguay.

The GAP on imidazolinone-tolerant sunflowers of Argentina and Uruguay is a foliar application at a maximum rate of 0.080 kg ai/ha with the application timing of early post emergence.

Imazapyr residues in sunflower seeds from trials in Argentina and Uruguay approximating GAP were (n=15): < 0.01 (10), 0.01, 0.03 (2) and < 0.05 (2) mg/kg.

Based on the trials for sunflower in Argentina and Uruguay, the Meeting estimated a maximum residue level and an STMR value for imazapyr in sunflower seed of 0.08 and 0.01 mg/kg respectively.

Animal feedstuffs

Maize fodder and forage

Data were available from supervised trials on imidazolinone-tolerant maize in Argentina, Australia and the USA.

Trials from Argentina on maize forage were reported for the foliar application of SC or WG formulation (GAP: a foliar application of a maximum rate of 0.025 kg ai/ha, the application timing before reaching 6th fully developed leaf status).

Trials from Australia on maize forage were reported for the foliar application of a SL formulation (GAP: a foliar application of a rate of 0.018–0.022 kg ai/ha at the application timing of 2–6 leaf stage of the crop, do not graze or cut for stock food for 4 weeks after application and not required for the harvest of grain when used directed).

Trials from the USA on maize fodder and forage were reported for the foliar application of ASU or WP formulation at a rate of 0.027 kg ai/ha (GAP: a foliar application of a maximum rate of 0.016 kg ai/ha, PHI of 45 days at the application timing of before 6 leaf stage for crop).

Maize fodder

In the residue trials for imazapyr on maize fodder in the USA, no samples were collected at 45 days after application, i.e., as per GAP. The Meeting could not estimate a maximum residue level for imazapyr in maize fodder.

Maize forage

Imazapyr residues in maize forage from trials in Argentina matching GAP were (n=4): < 0.05 (4) mg/kg on an as received basis. Imazapyr residues in maize forage from data in Argentina at exaggerated rate of 0.040 kg ai/ha (1.6 × GAP rate) were < 0.05 (4) mg/kg and 0.050 kg ai/ha (2 × GAP rate) were < 0.05 (4) mg/kg.

Imazapyr residues in maize forage from data in Australia at exaggerated rate of 0.032 kg ai/ha (1.5 × GAP rate) were < 0.05 (2) mg/kg and 0.048 kg ai/ha (2.2 × GAP rate) were < 0.05 (2) mg/kg.

Imazapyr residues in maize forage from trials in the USA at exaggerated rate of 0.027 kg ai/ha (1.7 × GAP rate) were < 0.05 (18) mg/kg on an as received basis.

Based on the residues in maize forage from trials in Argentina, Australia and the USA, the Meeting estimated a median residue value and a highest residue value for imazapyr in maize forage both at 0 mg/kg.

Wheat straw and forage

Data were available from supervised trials on imidazolinone-tolerant wheat in Australia.

Trials from Australia on wheat were reported for the foliar application of a SL formulation (GAP: a foliar application of a rate of 0.004–0.007 kg ai/ha, do not graze or cut for stock food for 4 weeks after application and not required to harvest for grains when used directed).

Wheat straw

Imazapyr residues in wheat straw from trials in Australia matching GAP were (n=3): < 0.05 (3) mg/kg as received basis. Imazapyr residues in wheat straw from data in Australia at exaggerated rate of 0.014 kg ai/ha (2 × GAP rate) were < 0.05 (5) mg/kg and 0.028 kg ai/ha (4 × GAP rate) were < 0.05 (5) mg/kg.

Based on the residues in wheat straw from trials in Australia, the Meeting estimated a maximum residue level, a median residue value and a highest residue value for imazapyr in wheat straw and fodder of 0.05 (*), 0 and 0 mg/kg respectively.

Wheat forage

Imazapyr residues in wheat forage from trials in Australia matching GAP were (n=3): < 0.05 (3) mg/kg as received basis. Imazapyr residues in wheat forage from data in Australia at exaggerated rates of 0.014 kg ai/ha (2 × GAP rate) were < 0.05 (5) and 0.087 mg/kg, and 0.028 kg ai/ha (4 × GAP rate) were < 0.05 (5) and 0.11 mg/kg as received basis.

Based on the residues in wheat forage from trials in Australia, the Meeting estimated a median residue value and a highest residue value for imazapyr in wheat forage both at 0.05 mg/kg.

Rape forage

Data were available from supervised residue trials on imidazolinone-tolerant rape in Australia.

Trials from Australia on rape were reported for the foliar application of a WG formulation (GAP: a foliar application of a rate of 0.005–0.012 kg ai/ha, do not graze or cut for 5 weeks).

Imazapyr residues in rape forage from trials in Australia matching GAP were (n=1): < 0.05 mg/kg. Imazapyr residues in rape forage from data in Australia at an exaggerated rate of 0.028 kg ai/ha (2.3 × GAP rate) or at DALA 25–29 days were < 0.05 (4) mg/kg.

Based on the residues in rape forage from trials in Australia, the Meeting estimated a median residue value and a highest residue value for imazapyr in rape forage both at 0 mg/kg.

Fate of residues during processing

High temperature hydrolysis

The degradation of [^{14}C] imazapyr was studied under hydrolytic conditions at high temperatures in sterile aqueous buffers at pH 4, 5 and 6 for periods of up to 60 minutes to simulate common processing practice (pasteurization, baking/brewing/boiling, and sterilization). No degradates were detected at any of the investigated pH and temperature ranges. Imazapyr is stable under hydrolytic conditions at high temperatures.

Residues in processed commodities

The fate of imazapyr residues were examined in maize grains, rape seeds and sunflower seed processing studies. Based on the results of processing studies conducted in Canada and the USA in combination with the residues from supervised trials, the Meeting concluded that no residues are expected in processed rape and sunflower commodities. Estimated processing factors and the derived STMR-Ps are summarized in the Table below.

Processing factors, STMR-P and HR-P for food and feed

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors*	PF (Mean or best estimate)	RAC STMR (mg/kg)	STMR-P (mg/kg)
Maize grain	Meal	1.2	1.2	0.05	0.06
	Crude oil	< 0.50	< 0.50		0.025

* Each value represents a separate study. The factor is the ratio of the residue in processed commodity divided by the residue in the RAC.

Residue in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of imazapyr in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual 2009. Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed in a dry weight basis.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Appendix IX of the FAO manual. The calculations were made according to the animal diets from US-Canada, EU, Australia and Japan in the Table (Appendix IX of the FAO manual).

Livestock dietary burden, imazapyr, ppm of dry matter diet

	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	0.063	0.063	0.085	0.085	0.20 [a]	0.20 [b]	0.061	0.061
Dairy cattle	0.083	0.083	0.057	0.057	0.15	0.15 [c]	0.045	0.045
Poultry—broiler	0.056d	0.056e	0.040	0.040	0.014	0.014	0.040	0.040
Poultry—layer	0.056	0.056	0.073 [d]	0.073 [e]	0.014	0.014	0.045	0.045

[a] Highest maximum beef cattle dietary burden suitable for MRL estimates for mammalian meat, fat, edible offal and milk

[b] Highest mean beef cattle dietary burden suitable for STMR estimates for mammalian meat, fat and edible offal

[c] Highest mean dairy cattle dietary burden suitable for STMR estimates for milk

[d] Highest maximum broiler poultry dietary burden suitable for MRL estimates for poultry meat, fat, edible offal and eggs

[e] Highest mean broiler poultry dietary burden suitable for STMR estimates for poultry meat, fat, edible offal and eggs

Farm animal feeding studies

The Meeting received a lactating dairy cow feeding study using imazapyr, which provided information on likely residues resulting in animal commodities and milk from imazapyr residues in the animals' diet.

A poultry feeding study was not submitted as the expected residues of imazapyr in poultry feed were extremely low. A poultry metabolism study at a dose rate of 9.7 ppm imazapyr in the feed

demonstrated that there was very low transfer to eggs and tissues with all residues of imazapyr less than 0.01 mg/kg.

Lactating dairy cows

Lactating dairy cows were dosed with imazapyr for 28–29 days at the dose equivalent to 58, 157, 607 and 1680 ppm in the diet. Residues of imazapyr were at or less than the LOQ (0.01 mg/kg) in whole milk at 58 ppm of feeding level. In the three higher dose groups (157, 607 and 1680 ppm feed), imazapyr residues in milk reached a plateau after 2–3 days. In kidney, imazapyr was detected as the highest concentrations among all tissues and milk in all treated groups.

Animal commodities maximum residue levels

For MRL estimation, the residue in the animal commodities is imazapyr.

The maximum dietary burden for beef and dairy cattle is 0.20 and is lower than the dose level in the lactating goat metabolism study of 18 ppm and the lactating cow feeding study of 58 ppm. In the metabolism study, in which imazapyr equivalent to 18 ppm in the diet was dosed to lactating goats for 7 consecutive days, residues of imazapyr were detected at 0.01 mg/kg in milk and 0.08 mg/kg in kidney. The maximum dietary burden for beef and dairy cattle is 1% of the dose rate in feed of the metabolism study.

The Meeting estimated a maximum residue level of 0.01 (*) mg/kg and an STMR value of 0 mg/kg in milk.

The Meeting estimated a maximum residue level of 0.05 (*) mg/kg, an STMR value of 0 mg/kg and an HR value of 0 mg/kg in mammalian meat and fat.

The Meeting estimated a maximum residue level of 0.05 (*) mg/kg, an STMR value and an HR value of 0.0008 in mammalian edible offal.

The maximum dietary burden for broiler and layer poultry is 0.073 and is lower than the dose level in the laying hen metabolism study of 9.7 ppm. In the metabolism study, in which imazapyr equivalent to 9.7 ppm in the diet was dosed to laying hens for 7 consecutive days, no residues of imazapyr exceed 0.01 mg/kg were detected in tissues and eggs.

The Meeting estimated a maximum residue level of 0.01 (*) mg/kg, an STMR value of 0 mg/kg and an HR value of 0 mg/kg in poultry meat, fat, edible offal and eggs.

RECOMMENDATIONS

On the basis of the data from supervised trials, the Meeting concluded that the residue levels listed below are suitable for estimating maximum residue limits and for IEDI and IESTI assessment.

Plant and animal commodities:

Definition of the residue for plant commodities (for compliance with the MRL and for estimation of dietary intake): *Imazapyr*.

The residue is not fat soluble.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of imazapyr were calculated for the 13 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–3 mg/kg bw and the calculated IEDIs were 0% of the maximum ADI (3 mg/kg bw). The Meeting concluded that the long-term intakes of residues of imazapyr, resulting from the uses considered by current JMPR, are unlikely to present a public health concern.

Short-term intake

The 2013 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of residues of imazapyr is unlikely to present a public health concern.