5.13 IMAZETHAPYR (289)

TOXICOLOGY

Imazethapyr is the ISO-approved common name for 5-ethyl-2-[(*RS*)-4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl]nicotinic acid (IUPAC), with the CAS number 81335-77-5. It acts as a herbicide by inhibition of the plant enzyme acetolactate synthase.

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

This evaluation is based mainly on the study reports submitted by the sponsor. All critical studies contained statements of compliance with GLP, unless otherwise specified. Most toxicological studies were conducted according to internationally recognized guidelines, except where indicated otherwise.

A literature search was conducted, and the articles relevant to a toxicological or human health evaluation were included in the evaluation and are described in the appropriate sections.

Biochemical aspects

The absorption, excretion, tissue residues and metabolism of ^{14}C-labelled imazethapyr were investigated in rats. The administered ^{14}C-labelled imazethapyr in oral doses of 10 and 1000 mg/kg bw was readily excreted; greater than 94% of the dose was eliminated in the urine and faeces within 48 hours. Urinary elimination of administered radiocarbon after 7 days was essentially complete in both sexes. The elimination of administered radiocarbon in faeces after 7 days ranged from 2.5% to 4.2% in males and from 1.2% to 4.1% in females. Radiocarbon eliminated as $^{14}CO_2$ accounted for less than 1% of the dose for all treatments. When comparing the effects seen in groups receiving a single dose of radiolabelled test material (low-dose group) with groups receiving consecutive doses of non-radiolabelled test material (at the same daily dosage rate) followed by a single dose of radiolabelled test material, virtually no differences in elimination were evident. Total ^{14}C residues in major organs and tissues at 7 days after treatment were generally low. There were no indications for accumulation in tissues or organs.

Imazethapyr was metabolized to only a limited extent. The metabolite OH-imazethapyr (CL 288511, the 1-hydroxyethyl derivative of imazethapyr) was detected in faeces and urine, amounting to 0.8–2.2% of the administered dose.

Toxicological data

Imazethapyr was of low acute toxicity after oral, dermal and inhalation exposure. The oral LD_{50} in mice was greater than 5000 mg/kg bw, and the oral LD_{50} in rats and rabbits was greater than 2000 mg/kg bw. The dermal LD_{50} in rats and rabbits was greater than 2000 mg/kg bw, and the inhalation LC_{50} in rats was greater than 3.27 mg/L. In rabbits, imazethapyr was not irritating to the skin but induced slight transient eye irritation. In a guinea-pig Buehler test, no skin sensitization occurred.

Short-term toxicity studies with oral administration were conducted in the rat and dog. Imazethapyr was generally of low toxicity, and no common effect could be identified among species.

In a 13-week toxicity study, groups of rats received diets containing imazethapyr at a concentration of 0, 1000, 5000 or 10 000 ppm (equal to 0, 78, 393 and 779 mg/kg bw per day for males and 0, 86, 427 and 856 mg/kg bw per day for females, respectively). The NOAEL was 5000 ppm (equal to 393 mg/kg bw per day), based on hepatocellular necrosis at 10 000 ppm (equal to 779 mg/kg bw per day).

In a second 13-week toxicity study, groups of rats received diets containing imazethapyr at concentrations adjusted to maintain target dose levels of 0, 150, 400 and 1000 mg/kg bw per day (achieved dose levels were 0, 151, 408 and 1009 mg/kg bw per day for males and 0, 145, 405 and 997 mg/kg bw per day for females, respectively). The NOAEL was 997 mg/kg bw per day, based on the absence of adverse effects up to the highest dose tested.

In a 90-day toxicity study, groups of dogs received diets containing imazethapyr at a concentration of 0, 1000, 5000 or 10 000 ppm (equivalent to 0, 25, 125 and 250 mg/kg bw per day, respectively). The NOAEL was 10 000 ppm (equivalent to 250 mg/kg bw per day), based on the absence of adverse effects up to the highest dose tested.

In a 12-month toxicity study, groups of dogs received diets containing imazethapyr at a concentration of 0, 1000, 5000 or 10 000 ppm (equal to 0, 36.1, 177 and 358 mg/kg bw per day for males and 0, 37.7, 198 and 382 mg/kg bw per day for females, respectively). The NOAEL was 10 000 ppm (equal to 358 mg/kg bw per day), based on the absence of adverse effects up to the highest dose tested.

In an 18-month toxicity and carcinogenicity study, groups of mice received diets containing imazethapyr at a concentration of 0, 1000, 5000 or 10 000 ppm (equivalent to 0, 150, 750 and 1500 mg/kg bw per day, respectively). The NOAEL was 5000 ppm (equivalent to 750 mg/kg bw per day), based on lower body weights at 10 000 ppm (equivalent to 1500 mg/kg bw per day). The Meeting concluded that no treatment-related increases in tumour incidence were observed in this study.

In a 2-year toxicity and carcinogenicity study, groups of rats received diets containing imazethapyr at a concentration of 0, 1000, 5000 or 10 000 ppm (equal to 0, 44, 222 and 447 mg/kg bw per day for males and 0, 55, 276 and 562 mg/kg bw per day for females, respectively). The NOAEL was 1000 ppm (equal to 55 mg/kg bw per day), based on a significant decrease in body weight gain in females at 5000 ppm (equal to 276 mg/kg bw per day). The Meeting concluded that no treatment-related increases in tumour incidence were observed in this study.

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

Imazethapyr was tested for genotoxicity in a range of assays, both in vitro and in vivo. Imazethapyr was negative in Ames tests, an in vitro HPRT study with metabolic activation and an in vitro unscheduled DNA synthesis test in rat hepatocytes, but it resulted in increases in chromosomal aberrations in vitro and HPRT gene mutant frequency without metabolic activation. However, there was no genotoxic activity in follow-up in vivo studies on clastogenicity/aneugenicity. Although no follow-up in vivo study on the induction of gene mutations was submitted, the Meeting considered it likely that imazethapyr acted via a mechanism or mechanisms exhibiting a threshold rather than via DNA reactivity.

Overall, the Meeting considered that the available studies provided no evidence of genotoxic effects in vivo and concluded that imazethapyr was unlikely to be genotoxic to humans from exposure through the diet.

A two-generation reproductive toxicity study in rats was conducted with imazethapyr using dietary concentrations of 0, 1000, 5000 and 10 000 ppm (equivalent to 0, 67, 333 and 667 mg/kg bw per day, respectively). The NOAELs for adverse effects on parental animals and reproduction were 10 000 ppm (equivalent to 667 mg/kg bw per day), based on the absence of adverse effects up to the highest dose tested. The NOAEL for adverse effects on offspring was 5000 ppm (equivalent to 333 mg/kg bw per day), based on reduced offspring body weights at 10 000 ppm (equivalent to 667 mg/kg bw per day).

In a rat developmental toxicity study that tested imazethapyr at gavage doses of 0, 125, 375 and 1125 mg/kg bw per day, the NOAEL for maternal toxicity was 375 mg/kg bw per day, based on clinical signs of toxicity occurring after several doses at 1125 mg/kg bw per day. The NOAEL for

embryo and fetal effects was 375 mg/kg bw per day, based on increased resorptions and delayed development at 1125 mg/kg bw per day.

In a rabbit developmental toxicity study that tested imazethapyr at gavage doses of 0, 100, 300 and 1000 mg/kg bw per day, the NOAEL for maternal toxicity was 300 mg/kg bw per day, based on mortality observed between gestation days 17 and 22 at 1000 mg/kg bw per day. The NOAEL for embryo and fetal effects was 300 mg/kg bw per day, based on abortions observed between gestation days 16 and 20 and slight decreases in fetal weight of equivocal toxicological relevance at 1000 mg/kg bw per day.

The Meeting concluded that imazethapyr is not teratogenic.

Toxicological data on metabolites and/or degradates

Data were submitted on a soil metabolite of imazethapyr, an intermediate in the synthesis of imazethapyr, two phototransformation products of imazethapyr and a plant metabolite of imazethapyr.

The acute oral LD_{50} for CL 266858 (5-hydroxy-2-[4-methyl-5-oxo-4-(propan-2-yl)-4,5-dihydro-1*H*-imidazol-2-yl]pyridine-3-carboxylic acid, a soil metabolite of imazethapyr) in rats was greater than 5000 mg/kg bw.

The acute oral LD_{50} for CL 180032 (5-ethyl-2,3-pyridinedicarboxylic acid anhydride, an intermediate in the synthesis of imazethapyr) in male rats was 3299 mg/kg bw. The acute dermal LD_{50} for CL 180032 in male rabbits was greater than 2000 mg/kg bw. Regarding skin irritation, one rabbit exhibited well-defined erythema and eschar formation; both findings returned to normal by day 14 after administration, and no cutaneous irritation was observed in any of the other animals during the study. The test material was corrosive to the eyes of rabbits.

The acute oral LD_{50} values for the phototransformation products CL 290084 (5-ethyl-pyridine-3-carboxylic acid) and CL 271197 (5-ethylpyridine-2,3-dicarboxylic acid) in rats were greater than 5000 mg/kg bw.

The acute oral LD_{50} for OH-imazethapyr (CL 288511, 5-(1-hydroxyethyl)-2-[4-methyl-5-oxo-4-(propan-2-yl)-4,5-dihydro-1*H*-imidazol-2-yl]pyridine-3-carboxylic acid, a plant metabolite of imazethapyr) in rats was greater than 5000 mg/kg bw.

The Meeting anticipated that humans would hydrolyse Glu-OH-imazethapyr (glucoside of OH-imazethapyr, CL 182704) to OH-imazethapyr after dietary exposure. In considering their structures, based on expert judgement, the Meeting concluded that it would be unlikely that the metabolites Glu-OH-imazethapyr and OH-imazethapyr would be of greater toxicity than imazethapyr.

Human data

No adverse effects on the health of workers involved in the manufacture of imazethapyr were observed. No information on accidental or intentional poisoning in humans is available.

Imazethapyr was included in the epidemiological studies based on the cohort of the Agricultural Health Study (AHS). No associations between imazethapyr exposure and an increased likelihood of developing a wide variety of adverse non-cancer health effects were reported.

In other epidemiological studies based on the cohort of the AHS, there are reports of an association of imazethapyr exposure with increased risk of developing cancer of the proximal colon and of the bladder. Regarding the risk of developing prostate cancer, a negative association was observed. These associations need to be balanced against the fact that these were seen from evaluations of a single cohort. Although data were stratified for confounders, it needs to be kept in mind that participants were also exposed to additional compounds.

Based on the conclusion that imazethapyr was unlikely to be genotoxic to humans from exposure through the diet, the lack of carcinogenicity in mice and rats and considerations of

epidemiological data from occupational exposures, the Meeting concluded that imazethapyr is unlikely to pose a carcinogenic risk to humans from exposure through the diet.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.6 mg/kg bw on the basis of a NOAEL of 55 mg/kg bw per day for decreased body weight gain in females in a long-term study in rats, with application of a safety factor of 100.

Taking into account the close structural similarity of OH-imazethapyr and Glu-OH-imazethapyr with imazethapyr, the Meeting concluded that it would be unlikely that OH-imazethapyr and Glu-OH-imazethapyr would be of greater toxicity than imazethapyr and that these metabolites would be covered by the ADI for imazethapyr.

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

A toxicological monograph was prepared.

Levels relevant to risk assessment of imazethapyr

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	5 000 ppm, equivalent to 750 mg/kg bw per day	10 000 ppm, equivalent to 1 500 mg/kg bw per day
		Carcinogenicity	10 000 ppm, equivalent to 1 500 mg/kg bw per day[b]	–
Rat	Ninety-day toxicity study[a]	Toxicity	5 000 ppm, equal to 393 mg/kg bw per day	10 000 ppm, equal to 779 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	1 000 ppm, equal to 55 mg/kg bw per day	5 000 ppm, equal to 276 mg/kg bw per day
		Carcinogenicity	10 000 ppm, equal to 447 mg/kg bw per day[b]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	10 000 ppm, equivalent to 667 mg/kg bw per day[b]	–
		Parental toxicity	10 000 ppm, equivalent to 667 mg/kg bw per day[b]	–
		Offspring toxicity	5 000 ppm, equivalent to 333 mg/kg bw per day	10 000 ppm, equivalent to 667 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	375 mg/kg bw per day	1 125 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
		Embryo and fetal toxicity	375 mg/kg bw per day	1 125 mg/kg bw per day
Rabbit	Developmental toxicity study[c]	Maternal toxicity	300 mg/kg bw per day	1 000 mg/kg bw per day
		Embryo and fetal toxicity	300 mg/kg bw per day	1 000 mg/kg bw per day
Dog	One-year study of toxicity[a]	Toxicity	10 000 ppm, equal to 358 mg/kg bw per day[b]	–

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

Acceptable daily intake (ADI; applies to imazethapyr, OH-imazethapyr and Glu-OH-imazethapyr, expressed as imazethapyr)

0–0.6 mg/kg bw

Acute reference dose (ARfD)

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 imazethapyr

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, > 90% in the rat
Dermal absorption	No data
Distribution	Widely distributed
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	Rapidly excreted, mainly via urine and approximately 5% via faeces within 2 days
Metabolism in animals	Limited metabolism
Toxicologically significant compounds in animals and plants	Parent compound, OH-imazethapyr and Glu-OH-imazethapyr
Acute toxicity	
Rat, LD_{50}, oral	> 2 000 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	> 3.27 mg/L
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Slightly irritating (reversible)

Guinea-pig, dermal sensitization	Non-sensitizing (Buehler)
Short-term studies of toxicity	
Target/critical effect	Hepatocellular necrosis (rat)
Lowest relevant oral NOAEL	393 mg/kg bw per day (rat)
	358 mg/kg bw per day (dog), highest dose tested
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day, highest dose tested (rat, rabbit)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Body weight
Lowest relevant NOAEL	55 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity[a]	
	Weight of evidence indicates unlikely to be genotoxic from exposure through the diet
Reproductive toxicity	
Target/critical effect	No reproductive toxicity; reduced pup weight (rat)
Lowest relevant parental NOAEL	667 mg/kg bw per day, highest dose tested (rat)
Lowest relevant offspring NOAEL	333 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	667 mg/kg bw per day, highest dose tested (rat)
Developmental toxicity	
Target/critical effect	Resorptions and delayed development (rat); abortions, body weight (rabbit)
Lowest relevant maternal NOAEL	375 mg/kg bw per day (rat)
	300 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	375 mg/kg bw per day (rat)
	300 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data; no indication of neurotoxic effects in 90-day rat study
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity	No data
Studies on toxicologically relevant metabolites	
OH-Imazethapyr	Rat oral LD_{50}: > 5 000 mg/kg bw
Human data	
Occupational	No effects reported in manufacturing workers
Cancer	Association of imazethapyr exposure and risk of developing colon or bladder tumours observed in one cohort study[a]

Non-cancer health effects	No associations between imazethapyr exposure and increased likelihood of developing a wide variety of adverse non-cancer health effects reported

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

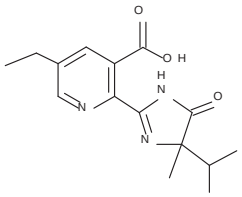
	Value	Study	Safety factor
ADI[a]	0–0.6 mg/kg bw	Long-term toxicity and carcinogenicity study (rat)	100
ARfD	Unnecessary	–	–

[a] Applies to imazethapyr, OH-imazethapyr and Glu-OH-imazethapyr, expressed as imazethapyr.

RESIDUE AND ANALYTICAL ASPECTS

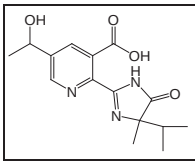
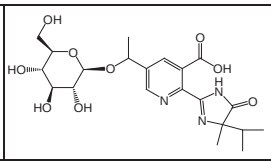
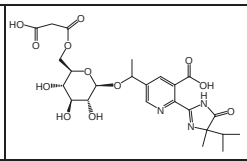
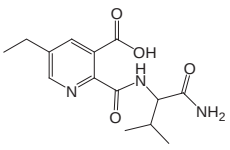
Imazethapyr is an imidazolinone herbicide developed for the control of grasses and broadleaf weeds in a variety of crops and is registered in many countries. The mode of action of imazethapyr, like other imidazolinone herbicides, is the inhibition of acetohydroxy acid synthase (AHAS) which catalyses the production of branched-chain amino acids.

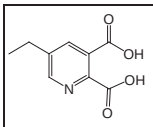
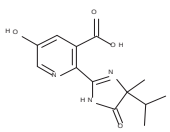
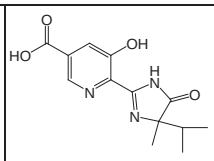
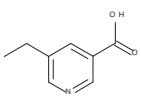
Imazethapyr was included in the Codex Priority List at the 46th Session of the CCPR in 2014 and is reviewed by JMPR for the first time.



The Meeting received information on physical and chemical properties, plant (including rotational crops) and animal metabolism, environmental fate in soil, analytical methods, storage stability, use patterns, supervised trials, processing, and farm animal feeding studies.

The following abbreviated names were used for the metabolites referred to in this Appraisal.

			
OH-Imazethapyr (CL 288511)	Glu-OH-Imazethapyr (CL 182704)	Malonyl-Glu-OH-Imazethapyr (MAE-CL 192705)	CL 290395

			
CL 271197	CL 266858	CL 354825	CL 290084

Plant metabolism

The Meeting received information on the fate of imazethapyr in pea, soya bean, maize, rape seed and alfalfa. For the studies, imazethapyr labelled with ^{14}C at position 6 of the pyridine ring ([pyridine-6-^{14}C]-imazethapyr; hereafter described as ^{14}C-imazethapyr) was used. In metabolism studies, total radioactive residues (TRR) are expressed in mg/kg imazethapyr equivalents unless otherwise stated.

Imidazolinone-tolerant varieties are commercially available for certain crops, such as maize and rape seed among others, and some were used in the metabolism studies. They have several variant AHAS genes which give imidazolinone tolerance and this would not affect the metabolism of imidazolinone in these plants.

When ^{14}C-imazethapyr was applied to the soil surface as a pre-plant incorporation treatment at a rate of 0.105 kg ai/ha (2 times the maximum US GAP rate) in a small outdoor plot, the TRR in the mature pea hay, pod and seed collected 110 days after treatment (DAT) were 0.19, 0.17 and 0.07 mg eq/kg, respectively.

When ^{14}C-imazethapyr was applied to pea plant at its 2–3 leaf stage (30 days after seeding) as post-emergence treatment at a rate 0.105 kg ai/ha in a small outdoor plot, the TRR in the mature pea hay, pod and seed collected 77 DAT were 0.19, 0.15 and 0.06 mg eq/kg, respectively. After either of the two treatments, the TRR in seeds were low (0.06 and 0.07 mg eq/kg).

Very high percentage (97–99% TRR) of the radioactive residues in the pea green vine samples collected at various timings and dry seed samples were extracted by aqueous acetone (50:50). In the aqueous acetone extracts, imazethapyr was the major residue on day 0 but decreased sharply to less than 3.3% of TRR (< 0.01 mg eq/kg) in the dry seed samples collected 53 days after post emergence treatment, and 110 days after pre-plant incorporation treatment. Imazethapyr was not detected in the green vine sample taken 75 days after pre-plant incorporation treatment.

In the green vine (75 DAT, pre-plant incorporation) and dry seed (110 DAT, pre-plant incorporation; and 53 DAT, post-emergence) samples, hydroxylated imazethapyr at position 1 of the ethyl side chain attached to position 5 of the pyridine ring (OH-Imazethapyr) and its glucoside (Glu-OH-Imazethapyr) were found at significant levels. The most abundant radioactive metabolite was Glu-OH-Imazethapyr ranging from 35 to 45% of TRR. However, the concentrations were quite low ranging between 0.01 and 0.03 mg eq/kg. The second most abundant metabolite was OH-Imazethapyr ranging from 16 to 34% of TRR (0.01–0.03 mg eq/kg). No other metabolites exceeded 10% TRR or 0.01 mg eq/kg.

When ^{14}C-imazethapyr was applied to the soil surface as a pre-plant incorporation treatment at a rate of 0.28 kg ai/ha (4 × US GAP rate) in a small outdoor plot, the TRR in the mature soya bean seed, hull and straw collected at maturity (4.5 months after treatment) were 0.02, 0.04 and 0.31 mg eq/kg, respectively.

When ^{14}C-imazethapyr was applied to soya bean plant at its 4 leaf stage as post-emergence treatment at a rate of 0.28 kg ai/ha in a small outdoor plot, the TRR in the mature soya bean seed, hull and straw collected at maturity (4 months after treatment) were 0.02, 0.04 and 0.34 mg eq/kg, respectively. TRR in green plant sharply declined after the post-emergence treatment, from 27 mg eq/kg at day 0 to 0.31 mg eq/kg 2 months after the treatment. After either of the two treatments, the TRR in seeds were low (0.02 mg eq/kg).

A mixture of methanol and water (80:20) extracted 88–96% of TRR from green plant samples taken 2 weeks and 1 month after both treatments and 66–71% of TRR from straw harvested at maturity. A mixture of methanol and water (50:50) further extracted 12% TRR from the straw sample from post-emergence treatment. The solution of methanol and water (80:20) extracted only around 30% TRR from the seed samples harvested at maturity with about 70% TRR unextracted.

In the aqueous methanol extracts of green plant samples, imazethapyr was found at very low proportion and concentrations, showing the tendency to decrease over time (e.g., 2 weeks after the post-emergence, 15% TRR at 0.78 mg eq/kg; and one month after 1.4% TRR at 0.009 eq mg/kg) and was not detected in straw samples harvested at maturity after both treatments.

The most abundant metabolite in green plants was Glu-OH-Imazethapyr showing the increasing tendency in proportion over time: in green plant samples taken one month after the treatments, 52% TRR (0.17 mg eq/kg) from pre-plant incorporation and 36% TRR (0.22 mg eq/kg) from post-emergence. However, this compound was not detected in straw.

OH-Imazethapyr was the second most abundant residue in green plant taken 2 weeks and 1 month after the treatment (22 and 13% of TRR corresponding to 0.06 and 0.04 mg eq/kg after pre-plant incorporation; and 4.6 and 8.0% TRR corresponding to 0.24 and 0.05 mg eq/kg) and the most abundant in straw at 37–42% TRR (0.075 and 0.10 mg eq/kg).

TRR in the seed samples were too low to characterize or identify metabolites.

^{14}C-imazethapyr was applied as pre-plant incorporation treatment to soil or post-emergence treatment to maize plants of two different imidazolinone-tolerant hybrids (Hybrid A and K) at their 4–5 leaf stage in a small outdoor plot, at a rate of 0.106 kg ai/ha (1.5 times the maximum US GAP rate). After post-emergence treatment, TRR in foliage declined sharply from 6.5–7.3 mg eq/kg at 0 DAT to less than 0.03 mg eq/kg 32 DAT (Hybrid K) or 90 DAT (Hybrid A). After pre-plant incorporation, TRR in foliage were below 0.03 mg eq/kg 32 DAT. TRR in cob or grain taken 90 DAT or later contained very low radioactivity (maximum at 0.014 mg eq/kg).

Aqueous acetone (50:50) extracted more than 90% of radioactivity in maize foliage taken up to 32 DAT for both treatments and decreased to 54–65% at maturity (109 or 117 DAT). From the grain samples collected at maturity, 65% or 75% or radioactivity was extracted with aqueous acetone.

Imazethapyr declined over time in foliage from post-emergence treatment: at 7 DAT the maximum of 25% of TRR (0.49 mg eq/kg); 15 DAT and later, less than 8.2% TRR and 109 DAT or 117 DAT, less than 1% TRR (< 0.003 mg eq/kg). In the grain samples collected 109 DAT (post-emergence) or 117 DAT (pre-plant) at maturity, imazethapyr accounted for 2.9% (< 0.003 mg eq/kg) (Hybrid K) or 15% (0.003 mg eq/kg) (Hybrid A) of TRR, respectively.

The predominant radioactive residue was OH-Imazethapyr in all maize samples analysed. It accounted for 24–48% TRR in the foliage samples of Hybrid K and 9.6–26% TRR in the foliage samples of Hybrid A. In grain samples harvested 109 DAT or 117 DAT, OH-Imazethapyr accounted for 32% TRR (0.004 mg eq/kg) (Hybrid K) or 27% TRR (0.005 mg eq/kg) (Hybrid A) respectively. Unlike pea or soya bean, Glu-OH-Imazethapyr was present in much less proportion and was never higher than 10% TRR.

In another study on maize grown in an outdoor small plot, ^{14}C-imazethapyr was applied to seedling of maize at the 4–5 leaf stage at a rate of 0.28 kg ai/ha (4 times the maximum US GAP rate). TRR in whole plant decreased from 15.4 mg eq/kg on the day of application to 0.28 mg eq/kg at 15 DAT and to 0.07 mg eq/kg at 60 DAT. TRR in grain harvested at maturity (97 DAT) was 0.02 mg eq/kg even at 4 times higher application rate.

Aqueous acetone extracted 78–106% TRR in whole plant samples taken at various times up to the harvest time and grain samples harvested at maturity. The proportion of unextracted radioactivity gradually increased over time to reach 28% TRR (0.02 mg eq/kg) in whole plant (excluding grain) 94 DAT. From the radioactivity remaining in the post-extraction solid of whole

plant taken 94 DAT, 3.3% of TRR was extracted using 2% HCl in methanol and 14% TRR using 6N NaOH, with 6.0% (0.005 mg eq/kg) still unextracted.

Imazethapyr accounted for 94% TRR in whole plant immediately after the treatment but decreased significantly over time, and at 30 DAT and later around 3% TRR or less and < 0.005 eq mg/kg. In grain sample, it was less than 1% TRR and < 0.005 mg eq/kg. OH-Imazethapyr increased in proportion over time and accounted for 51% TRR (0.14 mg eq/kg) 15 DAT, reached 62% TRR (0.04 mg eq/kg) 60 DAT and declined to 45% (0.03 mg eq/kg) 94 DAT. In the grain sample, OH-Imazethapyr accounted for 71% TRR at 0.014 mg eq/kg. Glu-OH-Imazethapyr was present at significantly lower proportion and concentrations but gradually increased to reach 8.3% of TRR at 94 DAT in whole plant (excluding grain). In the grain, Glu-OH-Imazethapyr accounted for 8.4% of TRR but less than 0.005 mg eq/kg. In the 6N NaOH extract, only one discernible peak was observed that was identified as Glu-OH-Imazethapyr and it accounted for 3.5% TRR.

A single foliar spray of ^{14}C-imazethapyr was applied to imidazolinone-tolerant rape seed grown in a small outdoor plot at a rate of 0.054 kg ai/ha (3.6 times the maximum GAP rate in Canada) when seedlings were at the 3–4 leaf stage.

TRR in plants immediately after the treatment were 1.6–2.6 mg eq/kg but TRR in rape seed harvested at the maturity was less than 0.01 mg eq/kg. Characterization and identification of metabolite was not conducted due to the low TRR.

Alfalfa (grown from the seeds and established) grown in a small outdoor plots were treated with ^{14}C-imazethapyr at a rate of 0.15 kg ai/ha (ca 1.4 times the maximum US GAP) (seedlings at the first trifoliate stage, dormant established alfalfa and late treatment of established alfalfa).

TRR in the alfalfa forage declined sharply after the treatment of seedlings of or established alfalfa (29 or 64 mg eq/kg at 0 DAT for treatment of seedlings, 19 mg eq/kg at 0 DAT for treatment of dormant established alfalfa, and 6.9 mg eq/kg at 0 DAT for late treatment of established alfalfa; declined to less than 0.7 mg eq/kg at 28 DAT in all samples). At mature harvest, TRR in hay was at the maximum 0.54 mg eq/kg.

Aqueous acetone extracted significant proportions of radioactive residue ranging between 70 and 88% of TRR. Acidic methanol extracted additional radioactivity.

In alfalfa forage and hay, the predominant metabolite in the aqueous acetone extracts was Glu-OH-Imazethapyr (14–45% TRR, up to 0.21 mg eq/kg) and the second most abundant metabolite was OH-Imazethapyr (7.7–21% TRR, up to 0.14 mg eq/kg).

Unlike other plants tested, from alfalfa forage and hay, an additional metabolite, malonic acid ester of Glu-OH-Imazethapyr (malonyl-Glu-OH-Imazethapyr), was detected in the aqueous acetone extracts up to 18% TRR but, in general, did not exceed the proportions of Glu-OH-Imazethapyr or OH-Imazethapyr. The sum of the two conjugates (Glu-OH-Imazethapyr and malonyl ester of Glu-OH-Imazethapyr) was in a range of 16–56% TRR.

In the acidic methanol extracts of post extraction solid, Glu-OH-Imazethapyr was the predominant metabolite (2.2–27% TRR) followed by OH-Imazethapyr (1.3–7.9% TRR). Imazethapyr was either not detected or 0.2–2.1% of TRR. These compounds were all < 0.01 mg eq/kg.

The metabolic profiles of pea, soya bean, alfalfa and maize were similar. Imazethapyr undergoes hydroxylation of the α-carbon of the ethyl side chain on the position 5 of the pyridine ring to produce α-hydroxyethyl metabolite OH-Imazethapyr. This compound combines with glucose to produce the glucose conjugate, Glu-OH-Imazethapyr, for further conjugation or other metabolism.

At the time of mature harvest of edible parts of food crops, no or little imazethapyr would be found. In feed crops such as alfalfa, imazethapyr may be found above the LOQ at short intervals after treatment. OH-Imazethapyr and Glu-OH-Imazethapyr may be found at levels above to the LOQ in food crops and feed crops.

Animal metabolism

The Meeting received information on the results of studies on lactating goats, lactating cows and laying hens which were fed ^{14}C-labelled imazethapyr or ^{14}C-labelled OH-Imazethapyr.

Metabolism of imazethapyr in the rat

Metabolism studies on laboratory animals including rats were reviewed in the framework of toxicological evaluation by the current JMPR.

Metabolism of imazethapyr in the lactating goat

Imazethapyr

^{14}C-Imazethapyr was orally dosed once daily in capsules to lactating goats at the mean daily dose of 0.25 ppm or 1.25 ppm in the diet, equivalent to 0.019 mg eq/kg body weight or 0.085 mg eq/kg body weight respectively, for 7 consecutive days. TRR of daily collected milk samples were all below the LOQ of 0.01 mg/kg for both dose levels. No radioactive residues above the LOQ (0.05 mg/kg) were found in muscle, liver, kidney or fat taken 18 hours after the final dose.

OH-Imazethapyr

The plant metabolism studies indicate that livestock would be exposed to OH-Imazethapyr and its conjugates in feed crops or by-products of food crops while it was unlikely that livestock would be exposed to the parent compound. Studies were conducted on metabolism of OH-Imazethapyr in lactating goat and cow as well as laying hens.

In a study on lactating goat with oral administration of ^{14}C- OH-Imazethapyr in capsule once daily at a dose equivalent to 42 ppm in feed (1.12 mg eq/kg body weight) for 7 consecutive days, radioactivity was eliminated mostly via faeces (70% AR) and in a lesser amount from urine (17% AR) at the end of the study.

The TRR of daily milk samples and muscle and fat samples obtained 20 hours after the last dose were below the LOQ of 0.01 mg/kg but one milk sample contained 0.01 mg eq/kg and kidney and liver contained 0.09 mg eq/kg and 0.02 mg eq/kg respectively.

About 77 and 72% of TRR in the kidney and liver was extracted with acetone with additional 21% TRR from kidney with aqueous methanol. Unchanged OH-Imazethapyr accounted for 98 and 92% of the extracted radioactivity from kidney or liver, respectively. OH-Imazethapyr was rapidly excreted in faeces and urine and was not metabolized in the lactating goat.

Metabolism of OH-Imazethapyr in the lactating cow

^{14}C-OH-Imazethapyr was administered orally in capsules twice daily to lactating cows for 7 consecutive days at a mean daily dose of 27 ppm in the diet (equivalent to 0.70 mg eq/kg body weight).

TRR in all milk samples collected twice daily was below the LOQ of 0.01 mg eq/kg. No radioactive residues above the LOQ of 0.05 mg/kg were found in muscle, liver, kidney or fat collected 15 hours after the final dose. The results confirm those obtained from the goat study.

Metabolism of imazethapyr in laying hens

Imazethapyr

^{14}C-imazethapyr was orally administered in capsule to laying hens twice daily at a dose of 0.5 (0.030 mg eq/kg bw) or 2.5 ppm (0.17 mg eq/kg bw) in feed for 7 consecutive days. The TRR in all egg yolk and white samples collected throughout the study and tissue samples (muscle, liver, kidney and skin with adhering fat)(no report on timing) were less than the LOQ of 0.05 mg/kg.

OH-Imazethapyr

^{14}C-OH-Imazethapyr was orally dosed to laying hens in capsules twice daily for 7 consecutive days at a rate of 10 ppm in the diet (0.83 mg eq/kg body weight). Over the 7 day dosing period, 93–94% of cumulative applied dose was excreted in the excreta and pan paper wash.

The TRR in eggs throughout the administration period were all below the LOQ of 0.01 eq mg/kg. The TRR in muscle, liver, kidney and skin with adhering fat taken 16 hours after the final dose were all below the LOQ of 0.01 mg eq/kg.

The animal metabolism studies indicate that when livestock was exposed to OH-Imazethapyr in feed, it is rapidly excreted without significant metabolism and it is unlikely to result in significant residues of OH-Imazethapyr in animal tissues, milk or eggs.

Rotational crops

A confined rotational crop study was conducted using winter wheat (Massey), maize (Pioneer 3704) and soya bean (William I) in which ^{14}C-imazethapyr was applied to bare soil in small isolated plots at an actual rate of 0.14 kg ai/ha and mixed in the upper soil layer (5–8 cm from the surface) 30 minutes later by hand rake before seeding of soya beans, or to soya bean seedlings at the 4 leaf stage at an actual rate of 0.14 kg ai/ha, equivalent to ca. 2 times the maximum US GAP rate for soya beans or maize. Four months after treatment, soya bean crops were harvested. The straw was chopped into small pieces, evenly spread on each plot surface and dug into the top 5–8 cm of soil and then wheat was sown in one subplot. Maize was sown 9.8 months after the treatment in the other subplot.

No residues above 0.01 mg eq/kg was found in follow-up maize planted 9.8 months after the treatment.

In a separate study, ^{14}C-imazethapyr was applied to bare soil in small isolated plots at an actual rate of 0.14 kg ai/ha and mixed in the upper soil layer (5–8 cm from the surface) 30 minutes later by hand rake before seeding of soya beans or to soya bean seedlings at the 4 leaf stage at an actual rate of 0.14 kg ai/ha. Four months after treatment, soya bean crops were harvested and the straw was chopped into small pieces, evenly spread on each plot surface and dug into the top 5–8 cm of soil. Maize was sown 9.6 months after the treatment.

TRR in the follow-up maize were 0.02–0.06 mg eq/kg, 0.01–0.02 mg eq/kg and 0.02–0.04 mg eq/kg in harvested grain, cob and stalk, respectively. In forage collected 1.6 months after planting (11.2 months after treatment), TRR was 0.01–0.02 mg eq/kg.

Although imazethapyr was quite persistent in soil under aerobic conditions, maize used in metabolism studies did not seem to incorporate imazethapyr from soil significantly. The results of confined rotational crop studies with maize and plant metabolism studies using pre-plant incorporation treatment indicate that low residue may be found in follow-up crops. No information was available on leafy crops or root crops which may be used for crop rotation.

Environmental fate

The Meeting received information on aerobic soil metabolism, fate in succeeding crop, hydrolysis and photolysis of imazethapyr on soil surface.

Aerobic soil metabolism

A number of studies were conducted on aerobic soil metabolism with diverse results. Some minor degradates were found, such as OH-Imazethapyr, common metabolite in plants and animals, CL 354825, CL 290395 were detected but each accounted for less than 5% AR. CL 266858 (ethyl side chain was replaced with hydroxyl group) was found up to 12% AR. Imazethapyr was eventually mineralized to become CO_2.

Imazethapyr was found to be quite persistent in sandy loam soils under aerobic conditions with a half-life in a range of 158–210 days in sandy loam soils.

Hydrolysis

Imazethapyr was stable in pond water or in buffers at pH 5, 7 and 9 at 25 °C for at least 30 days. After incubating at pH 9 for 6 months, an average of 63% of imazethapyr remained with CL 290395 (with imidazole ring cleaved) detected at an amount equivalent to 36% of the applied imazethapyr. The calculated half-life at pH 9 was 257 days.

Imazethapyr was slowly hydrolysed but hydrolysis was not a major degradation route of imazethapyr at the environmental conditions.

Photodegradation

Imazethapyr is slowly degraded at 25 °C on soil surface under photolytic conditions with the formation of CL 263601 (less than 7% of the applied dose). The half-life of imazethapyr was calculated to be 126 days. Photolysis is unlikely to contribute to the degradation of imazethapyr.

Methods of analysis

Analytical methods for determination of residues of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr were developed for a wide range of matrices of plant and animal origin. Descriptions and validation results of the analytical methods were provided to the Meeting to cover plants on which supervised trials were conducted and animal commodities.

In general, the methods employ extraction by homogenization with a mixture of methanol/water/1M HCl (60:39:1, v/v), clean-up with solvent partitioning and/or solid phase extraction, and determination of analytes using LC-MS/MS, LC-MS, GC-NPD or capillary electrophoresis-UV (240 nm). The analytical methods do not involve acid hydrolysis except in specific methods for the determination of Glu-OH-Imazethapyr which employ hydrolysis by boiling in 2N HCl for 30 minutes.

A number of methods for plant matrices were found suitable for analysis of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr with LOQ ranging 0.01–0.1 mg/kg for these analytes.

One method for animal matrices was found suitable for analysis of imazethapyr and OH-Imazethapyr with LOQ of 0.01 mg/kg for bovine muscle, fat, kidney, liver and milk and poultry egg.

Stability of pesticide residues in stored analytical samples

The stability of imazethapyr residues during frozen storage at -29 to -10 ºC was investigated in a range of plant and animal matrices for which supervised residue trials were submitted.

Compounds tested were imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr. Each compound was spiked to matrices at 0.1, 0.2 or 1.0 mg/kg. In one study, samples with incurred residues were used.

All of the three compounds tested were found to be stable (>70% remaining) during the storage periods tested: 2 years in soya beans (only imazethapyr was tested), maize, rice (imazethapyr and OH-Imazethapyr), peanut and alfalfa.

For animal matrices, no storage stability study was conducted as all samples were analysed within 30 days of collection of samples in the feeding study except milk. Milk samples were tested for OH-Imazethapyr. OH-Imazethapyr was stable for at least 91 days.

These storage periods are longer than the longest storage conditions in trials on respective crops and animal commodities.

Definition of the residue

The plant metabolism studies indicate that no or little residues of imazethapyr or its metabolites are expected to be found in edible parts of food crops harvested at maturity because low TRR were observed even at exaggerated application rates. In most of supervised trials on various crops, parent imazethapyr was not detected at the time of mature harvest. In metabolism studies, where TRR was sufficiently high to allow identification of metabolites, the predominant metabolite at maturity was Glu-OH-Imazethapyr in pea, soya bean (except straw) and alfalfa while it was OH-Imazethapyr in maize (plant and seed). In soya bean straw samples, Glu-OH-Imazethapyr was not detected.

The metabolism studies and residue trials, in which all of these three compounds were analysed, indicate that even when imazethapyr was not found above LOQ in a sample, quantifiable Glu-OH-Imazethapyr and/or OH-Imazethapyr may be found.

In feed crops such as alfalfa and clover and by-products of food crops, imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr may be found above the LOQ (in the residue trials) at short intervals after treatment.

According to the confined rotational crop studies with maize and the plant metabolism studies using pre-plant incorporation treatment, it was unlikely to find imazethapyr or its degradates in follow-up crops which falls in the same classification as those crops for which residue trials were conducted.

Suitable analytical methods are available to analyse these three compounds. However, the Meeting noted that analytical standards of conjugated compounds are generally not readily available for analytical laboratories.

The Meeting considered that imazethapyr and OH-Imazethapyr were suitable markers for enforcement of MRLs for plant commodities.

In animal metabolism, orally administered parent imazethapyr or OH-Imazethapyr was excreted efficiently and rapidly. OH-Imazethapyr was also detected in a small amount in rat. Virtually no or little residue of imazethapyr or OH-Imazethapyr was expected to occur in milk, egg, or edible tissues of goats, cows and hens.

The Meeting considered that imazethapyr and OH-Imazethapyr were suitable markers for enforcement of MRLs and for dietary risk assessment for animal commodities.

With the logPow lower than 2 and absence of significant residues in animal tissues in the animal metabolism studies and animal feeding study, the Meeting considered imazethapyr residue not fat soluble.

Imazethapyr was evaluated toxicologically by the present Meeting. The ADI covers OH-Imazethapyr and Glu-OH-Imazethapyr in addition to imazethapyr, and these metabolites were evaluated to be of no greater toxicity than the parent. As Glu-OH-Imazethapyr was the major

metabolite in crops used in the plant metabolism studies and residue trials when analysed, the Meeting agreed to include Glu-OH-Imazethapyr in the residue definition for dietary risk assessment for plant commodities, in addition to the parent and OH-Imazethapyr.

Based on the above, the Meeting recommended the following residue definitions.

Definition of the residue for plant commodities (for enforcement of MRLs) and for animal commodities (for enforcement of MRLs and for dietary risk assessment): *Sum of imazethapyr, 5-hydroxyethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid (OH-Imazethapyr), expressed as imazethapyr.*

Definition of the residue for plant commodities (for dietary risk assessment): *Sum of imazethapyr, and 5-hydroxyethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid (OH-Imazethapyr), and 5-[1-(beta-D-glucopyranozyloxyethyl)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid (Glu-OH-Imazethapyr), expressed as imazethapyr.*

The residue is not fat soluble.

Results of supervised residue trials on crops

The Meeting received supervised trial data for imazethapyr on various beans and peas, soya beans, maize, rice, peanut, rape seed, sunflower, alfalfa and clover.

For summing up residues of imazethapyr and OH-Imazethapyr, or imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr, the Meeting used the following calculation methods. For calculating total residues for dietary risk assessment, the Meeting took into consideration the far less contribution of the parent in the resulting residues. Concentrations of the compounds in the residue definitions from residue trials are expressed as imazethapyr equivalents hereafter.

For summing up residues of imazethapyr and OH-Imazethapyr for the estimation of maximum residue levels:

Imazethapyr	OH-Imazethapyr	Total
Value a	Value b	Value a + Value b
< LOQ (a)	Value b	LOQ value (a) + Value b
< LOQ (a)	< LOQ (b)	LOQ value (a) + LOQ value (b)

For summing up residue of imazethapyr, OH-imazethapyr and Glu-OH-Imazethapyr for dietary risk assessment for plant commodities and for calculating animal dietary burden

Imazethapyr	OH-Imazethapyr	Glu-OH-Imazethapyr	Total
Value a	Value b	Value c	Value a + Value b + Value c
< LOQ (a)	Value b	Value c	Value b + Value c
< LOQ (a)	< LOQ (b)	Value c	LOQ value (b) + Value c
<LOQ (a)	<LOQ (b)	< LOQ (c)	LOQ value (b) + LOQ value (c)

Common bean (Phaseolus sp) ((pods and/or immature seeds) and (dry))

Six supervised trials were conducted on beans belonging to the genus Phaseolus: four trials on snap bean in the USA, one trial on French bean in France and one trial on white bean in Canada.

As only imazethapyr was analysed in these trials, the Meeting concluded that the data were insufficient to estimate maximum residue levels STMR or HR for beans.

Vicia beans (dry)

Two supervised trials were conducted on beans belonging to the genus Vicia: one trial on spring horse bean in France and one trial on winter bean in the UK.

As only imazethapyr was analysed in these trials, the Meeting concluded that the data were insufficient to estimate maximum residue levels STMR or HR for Vicia beans.

Lentil (dry)

Six supervised trials were conducted in Canada on imidazolinone-tolerant lentil with application rate of 0.015 kg ai/ha at the 3–6 node stage. In these trials, imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr were analysed and reported.

GAP in the USA for Navy, great northern, red kidney, black turtle, cranberry, pinto, lima, and small white type dry beans, adzuki, lentils, white lupines, chickpeas and dry edible peas, English and southern peas allows one application of imazethapyr at 0.053 kg ai/ha (pre-plant, pre-emergence and post-emergence) with a PHI of 60 days. However, no trials matched this GAP. As residues were all below the respective LOQ, it was not appropriate to scale up the residues using the proportionality principle.

GAP in Canada for lentil allows one application at 1-9 node stage at 0.015 kg ai/ha with a PHI of 60 days.

The sum of imazethapyr and OH-Imazethapyr in lentil seed from trials matching the GAP in Canada was (n = 4): < 0.097 (4) mg/kg including the trials in which samples were taken at shorter interval than the PHI (48 and 55 DALA). In two other trials using the application rate of 0.020 kg ai/kg, the sum of these two compounds was < 0.097 mg/kg (2).

The sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr in trials matching the GAP in Canada were: < 0.078 mg eq/kg (4) including the trials in which samples were taken at shorter interval than the PHI (48 and 55 DALA). In two other trials at the application rate of 0.020 kg ai/ha, total residues was < 0.078 mg/kg (2).

The Meeting estimated a maximum residue level of 0.1 * mg/kg and STMR of 0.078 mg/kg for lentils.

Peas ((pods and succulent = immature seeds) and (dry))

Nineteen supervised trials were conducted on peas: six trials in the United Kingdom, six trials in Argentina, five trials in the USA and two trials in Canada. In the two Canadaian trials, imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr were analysed. In all other trials, only imazethapyr was analysed.

The Meeting concluded that two trials were insufficient for estimating maximum residue levels, STMRs or HRs for peas.

Soya bean (dry)

A total of 12 independent supervised trials were conducted on soya beans: four in Brazil (conventional soya bean) and eight in the USA (glyphosate-tolerant soya bean).

In the trials in Brazil, only imazethapyr was analysed and these trials were not considered.

In the trials in the USA, imazethapyr was applied at a rate of 0.10 or 0.30 kg ai/ha and mature seeds were collected 64–72 DALA. In these trials, imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr were analysed. These trials did not match GAP in the USA. Seed samples were collected before the PHI prescribed in the GAP.

Critical GAP in Brazil for soya bean allows one application of early post emergence application at the maximum rate of 0.10 kg ai/ha with a PHI of 66 days.

The Meeting evaluated the trials in the USA against the GAP in Brazil.

The sum of imazethapyr and OH-Imazethapyr in trials matching the GAP in Brazil was (n = 8): < 0.0195 (7) and 0.022 mg/kg.

The Meeting estimated a maximum residue level of 0.03 mg/kg.

The sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr from trials matching GAP in Brazil was (n = 8): 0.019, 0.026, 0.033, 0.047, 0.048, 0.077, 0.23, and 0.46 mg/kg.

The Meeting estimated an STMR of 0.0475 mg/kg for soya bean (dry).

Maize

A total of 17 trials were conducted on imidazolinone-tolerant maize in the USA and one in Canada. In the US trials, imazethapyr was applied once as post-emergence treatment at a rate of 0.070 or 0.14 kg ai/ha (except one trial in which the rate of 0.28 or 0.56 kg ai/ha was used) and maize grain samples were collected 95–138 DALA. In the trial in Canada, imazethapyr was applied once at 0.075 or 0.15 mg/kg and maize grain samples were collected 127 DALA.

Imazethapyr is approved for use only on imidazolinone-tolerant maize. GAP in the USA allows one application up to post-emergence at a rate of 0.071 kg ai/ha with a PHI of 45 days. However, no grain samples were harvested before 100 days after the treatment. GAP for maize in Argentina allows one application at a rate of 0.1 kg ai/ha before the 2 true leaf stage without specific PHI. However, in many trials the application rates were higher than the maximum rate approved in Argentina and application was made at later growth stages.

Despite that no trials matched the critical GAP in Argentina, residues from 18 trials (USA and Canada) at higher application rates (0.14, 0.15, 0.28 and 0.56 kg ai/ha) and later application timing than the GAP were all below the LOQ of respective components: the sum of imazethapyr and OH-Imazethapyr in all the trials was < 0.097 mg/kg.

Sum of imazethapyr, OH-Imazethapyr and Glu-OH-imazethapyr in corresponding trials was < 0.078 mg/kg.

The Meeting estimated a maximum residue level of 0.1 * mg/kg and STMR of 0 mg/kg for maize.

Rice

A total of 19 trials were conducted on imidazolinone-tolerant rice in the USA. In these trials, imazethapyr was applied twice, each at a rate of 0.105 kg ai/ha or 0.14 kg ai/ha; once at 0.14 kg ai/ha; or twice at exaggerated rates. The last application was made at the 2–6 leaf stage. In these trials, imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr were analysed and reported.

GAP in the USA for imidazolinone-tolerant rice allows a total of two applications with the second application before flooding at a maximum rate of 0.14 kg ai/ha and the maximum annual rate of 0.21 kg ai/ha with a PHI of 85 days for the annual rate above 0.14 kg ai/ha.

The sum of imazethapyr and OH-Imazethapyr from US trials matching GAP in the USA was (n = 8): < 0.097 (8) mg/kg.

The sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr from trials matching the GAP in the USA were: < 0.078 (7) and 0.090 mg/kg. In one trial where only one application was made at the 6 leaf stage at a rate of 0.14 kg ai/ha, the total residues of the three components were 0.085 mg/kg while in other trials using two applications at a rate of 0.14 kg ai/ha, no residues above the LOQ.

The Meeting estimated a maximum residue level of 0.1 * mg/kg and an STMR of 0.078 mg/kg for rice.

Peanut

A total of five trials were conducted on peanut: one in Argentina and four in the USA. In the trial in Argentina, imazethapyr was applied at 0.10 or 0.20 kg ai/ha 14 days after planting and peanut samples were collected 138 DALA. Only imazethapyr was analysed.

In the trials in the USA, imazethapyr was applied at a rate of 0.14 kg ai/ha at the pegging stage and peanut samples were collected 78–107 DALA. Three components included in the residue definition for dietary risk assessment from plant commodities were analysed.

The critical GAP for peanut in Argentina allows one application at a maximum rate of 0.10 kg ai/ha with a PHI of 90 days.

The sum of imazethapyr and OH-imazethapyr in trials in the USA using 1.4 times the maximum application rate of the GAP of Argentina was < 0.097 mg/kg in all trials including one trial in which seed samples were taken earlier (78 DALA) than the prescribed PHI of 90 days.

The sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr in trials in the USA using 1.4 times the maximum application rate of the GAP in Argentina was: < 0.<u>078</u> (3) and 0.078 mg/kg. Scaling to the GAP rate, residues are < 0.056 (3) and 0.056 mg/kg.

The Meeting estimated a maximum residue level of 0.1* mg/kg and an STMR of 0.056 mg/kg for peanut.

Rape seed

A total of 13 trials were conducted on imidazolinone-tolerant rape seed in Canada. In ten trials, imazethapyr and OH-Imazethapyr were analysed and in three others, only imazethapyr was analysed.

The registered use on imidazolinone-tolerant rape seed in Canada allows one application at a maximum application rate of 0.015 kg ai/ha at 2–6 true leaf stage with a PHI of 60 days.

No information was available on the level of Glu-OH-Imazethapyr in rape seed in residue trials or in the metabolism study. However, its level could be regarded as below the LOQ since the TRR in the mature seeds (103 DAT) in the metabolism study was less than 0.01 mg/kg after post-emergence treatment at the 3–4 leaf stage at the application rate which is 3.6 times the maximum rate in GAP in Canada.

No trials matched the GAP in Canada. However, in all the trials using exaggerated application rates, up to 0.20 kg ai/ha (13 times the maximum rate in GAP in Canada), imazethapyr and OH imazethapyr in seeds harvested at maturity were below the LOQ of 0.05 mg/kg.

Sum of imazethapyr and OH-Imazethapyr was in these four trials was < 0.097 mg/kg.

Sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr these trials was < <u>0.078</u> mg/kg.

The Meeting estimated a maximum residue level of 0.1* mg/kg and an STMR of 0 mg/kg for rape seed.

Sunflower seed

A total of five trials were conducted on imidazolinone-tolerant sunflower in Canada and the USA: two in Canada and three in the USA. In each of these trials one application was made at BBCH 55–69 at a rate of 0.015 kg ai/ha. In these trials only imazethapyr was analysed.

GAP in Argentina for imidazolinone-tolerant sunflower allows one application at 0.075 kg ai/ha at the growth stage before 6th leaf was fully unfolded without specific PHI. No trials matched the GAP in Argentina.

GAP in Canada for imidazolinone-tolerant sunflower allows one application at 0.015 kg ai/ha at the 2–8 leaf stage with a PHI of 60 days.

While the application was made later than specified in GAP in Canada, in most of trials imazethapyr was < 0.05 mg/kg. However, in one trial, imazethapyr was found at 0.07 mg/kg. It was not possible to calculate total residues as no information was available on the ratio between the parent and OH-Imazethapyr or Glu-OH-Imazethapyr.

The Meeting concluded that it was not possible to estimate a maximum residue level for sunflower seed.

Animal feeds

Alfalfa fodder and forage (green)

According to an approved label in the USA for alfalfa and clover, they are tolerant to post-emergence applications after the second trifoliate leaf has expanded.

A total of 23 trials were conducted in the USA and Australia: 21 in the USA and two in Australia. In these trials, imazethapyr was applied once as a post-emergence treatment at a rate of 0.14 kg ai/ha in the trials in the USA, or 0.075 or 0.144 kg ai/ha in the trials in Australia.

GAP in the USA allows one application of post-emergence treatment at a rate of 0.105 kg ai/ha: to seedlings at the 2 trifoliate leaf stage or larger but before reaching 7.6 cm; to dormant established alfalfa when the height was less than 7.6 cm of re-growth, or to actively growing alfalfa after cutting. For 30 days following the treatment, alfalfa must not be fed, grazed or harvested. No trials matched this GAP and it was not possible to apply the proportionality principle (difference in application rate and sampling interval).

GAP in Australia allows one application of imazethapyr at an application rate of 0.098 kg ai/ha with a PHI of 14 days for alfalfa grown from seeds (not to graze or cut for stock food). For established alfalfa, application can be made after cutting or grazing. No trials matched GAP in Australia. The Meeting decided to use the proportionality principle to estimate a maximum residue level, median residues and highest residues for alfalfa on a basis of residues in alfalfa samples collected at 14 DALA in the trials in the USA and Australia.

In forage collected at 14 DALA from the trials in the USA with 0.14 kg ai/ha of imazethapyr applied to seedlings, the sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr was (n = 10): 0.38, 0.63, 0.65, 0.67, 0.76, 0.77, 0.98,1.30, 1.56, and 1.78 mg/kg. From the trials in Australia with 0.072 kg ai/ha, the sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr was (n = 2): 0.40 and 0.43 mg/kg.

Scaling to the GAP rate of 0.098 kg ai/ha, the residues were (n = 12): 0.27, 0.44, 0.46, 0.47, 0.53, 0.54, 0.54, 0.58, 0.69, 0.91, 1.09, 1.25 mg/kg

The Meeting estimated a median residue of 0.54 mg/kg and highest residue of 1.25 mg/kg (on an as received basis).

As for hay, no trials matched the GAP in Australia. The Meeting concluded that it was not possible to estimate a maximum residue level, median residue or highest residue for alfalfa hay.

Clover hay or fodder

Twelve trials were conducted in the USA. GAP in the USA allows one application of post-emergence treatment at a rate of 0.105 kg ai/ha: to seedlings at the 2 trifoliate leaf stage or larger but before reaching 7.6 cm; to dormant established clover when the height was less than 7.6 cm of re-growth, or to actively growing clover after cutting. For 30 days following the treatment, clover must not be fed, grazed or harvested.

Sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr in the trials matching GAP in the USA was (n = 12): < 0.78 (9), 0.84, 0.84 and 1.15 mg/kg.

The Meeting estimated a median residue of 0.78 mg/kg (as received) and highest residue of 1.15 mg/kg (as received).

A part of forage sample taken at each interval was left in the field to day and collected days after. Sum of imazethapyr and OH-Imazethapyr in clover hay from trials matching the GAP in the USA was (n = 12): < 0.97 (11) and 0.97 mg/kg.

Sum of imazethapyr, OH-imazethapyr and Glu-OH-Imazethapyr in clover hay from the trials matching GAP in the USA were (n = 12): < 0.78(5), 0.79, 0.81, 0.96, 1.00, 1.17, 1.19 and 2.81 mg/kg.

The Meeting estimated a maximum residue level of 1.5 mg/kg (dry weight basis) for clover hay or fodder. The Meeting also estimated a median residue of 0.80 mg/kg and highest residue of 2.81 mg/kg for clover hay or fodder (as received).

Pea vine, hay and straw

There were two trials in which vine, hay or straw were analysed. The Meeting concluded that the data were insufficient to estimate a maximum residue level, mean residue or highest residue for these commodities.

Maize fodder and forage

Five trials were conducted in the USA on imidazolinone-tolerant maize.

According to GAP in the USA, grazing and feeding forage and silage, fodder or grain is allowed 45 days after treatment (GAP rate, 0.071 kg ai/ha).

Total residues in maize forage from trials with 0.14 kg ai/ha and DALA of 45 days were: < 0.078 (4) and 0.35 mg/kg. Scaling to GAP rate, total residues were:< 0.040 (4) and 0.176 mg/kg. In one trial in Canada using the application rate of 0.075 kg ai/ha, residue was < 0.078 mg/kg.

The Meeting estimated a median residue of 0.040 mg/kg and highest residue of 0.176 mg/kg for maize forage (as received).

In fodder, the sum of imazethapyr and OH-Imazethapyr from trials with 0.14 kg ai/ha and DALA of 45 days were: < 0.097 (5) mg/kg. In one trial in Canada using either 0.075 or 0.15 kg ai/ha, the residues were all below the respective LOQ of 0.05 mg/kg. At the GAP rate, the sum of imazethapyr and OH-Imazethapyr would be well below the LOQ (the sum of LOQ = 0.097 mg/kg).

Sum of imazethapyr, OH-imazethapyr and Glu-OH-Imazethapyr in maize fodder from trials with 0.14 kg ai/ha were: < 0.078(5) mg/kg.

The Meeting estimated a maximum residue level of 0.1 *mg/kg (dry weight basis). It also estimated a median residue/highest residue of 0.04 mg/kg (as received).

Rice straw

Sum of imazethapyr and OH-Imazethapyr in rice straw from trials matching GAP in the USA was: < 0.097 (8) mg/kg.

Sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr in rice straw in from the trials matching GAP in the USA were: < 0.078 (7) and 0.084 mg/kg.

The Meeting estimated a maximum residue level of 0.15 *mg/kg (dry weight basis) for rice straw. A median residue of 0.078 mg/kg and highest residue of 0.084 mg/kg were estimated for rice straw (as received).

Fate of residues during processing

High temperature hydrolysis

The hydrolysis studies on three imidazolinone pesticides were previously evaluated by the JMPR. All of them were stable under conditions simulating commercial processing practices: pasteurization; brewing, baking and boiling; and sterilization. However, as no or little imazethapyr was found in commodities, this information is not relevant to the residues derived from use of imazethapyr. No information was available on hydrolysis of OH-Imazethapyr or Glu-OH-Imazethapyr.

Processing

The Meeting received information on processing of oil seeds. The processing factor could not be calculated for imazethapyr because no imazethapyr was detected above the LOQ in raw agricultural commodities. In the maize processing study, only imazethapyr and OH-

Imazethapyr were analysed. However, as the maize metabolism studies indicate, OH-Imazethapyr was the predominant residue, the Meeting agreed to use the results of the processing study.

RAC	Processed commodity	Processing factor (best estimate)	STMR-P
Soya bean			0.0475
	Oil	0.26 [a]	0.012
	Meal	0.69 [a]	0.033
Maize grain			0
	Oil	< 0.85 [b]	0
	Meal	0.93 [b]	0
Alfalfa			0. 54
	Meal	2.6	1.4

[a] For the sum of imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr, expressed as imazethapyr equivalents

[b] For the sum of imazethapyr and OH-imazethapyr

Using the best estimates of processing factor, the STMR-P were calculated to be: 0.012 mg/kg and 0.033 mg/kg, respectively for soya bean oil and meal; 0 mg/kg for maize oil and meal, and 1.4 mg/kg for alfalfa meal.

Residues in animal commodities

Estimation of dietary burdens

The maximum and mean dietary burdens were calculated using the highest residues or median residues/STMRs (imazethapyr, OH-Imazethapyr and Glu-OH-Imazethapyr, expressed as imazethapyr) estimated at the current Meeting on a basis of the OECD Animal Feeding Table.

Summary of livestock dietary burdens (ppm of dry matter diet)

	US-Canada		EU		Australia		Japan	
	Max	mean	max	Mean	max	Mean	Max	mean
Beef cattle	0.56	0.17	2.71	1.43	3.83 [A]	2.60 [B]	0.22	0.22
Dairy cattle	1.14	0.74	2.25	1.69	2.93 [C]	2.18 [D]	0.62	0.45
Broilers	0.11	0.11	0.10	0.10	0.22	0.22	0.19	0.09
Layers	0.11	0.11	0.60 [E]	0.44 [F]	0.22	0.22	0.16	0.16

[A] Suitable for estimating maximum residue levels for meat, fat and edible offal of cattle.

[B] Suitable for estimating STMRs for meat, fat and edible offal of cattle

[C] Suitable for estimating maximum residue level for milk.

[D] Suitable for estimating STMR for milk

[E] Suitable for estimating maximum residue levels for meat, fat and edible offal of poultry and eggs.

[F] Suitable for estimating STMRs for meat, fat and edible offal of poultry and eggs.

Residues in milk and cattle tissues

Four groups of lactating Holstein cows were orally dosed daily with OH-Imazethapyr for 28 days at levels equivalent to 0, 11, 32, and 116 ppm in feed. Milk samples were collected twice daily. Within 24 hours after the last dose, cows were sacrificed. After sacrifice, loin, flank or hind leg and diaphragm muscle, subcutaneous, mesenteric and renal fat, liver and kidney were collected and analysed. Metabolism study on goat and rat showed that imazethapyr was not expected to occur in milk and tissues.

In all the milk samples, and skim milk and cream separated from day 24 milk, residues above the LOQ of 0.01 were not detected in the treatment groups except for in 32 ppm group at day 14 (0.016 mg/kg) and in 116 ppm group at day 10 (0.014 mg/kg) and day 14 (0.056 mg/kg). No plateau can be determined due to very low concentrations in milk.

At the maximum dietary burden of 2.93 ppm and mean of 2.18 ppm, OH-Imazethapyr in milk was expected to be well below the LOQ of 0.01 mg/kg.

No residues above the LOQ were found in muscle and liver in any of dose groups. In fat, only one single value of 0.016 mg/kg was observed in the 116 ppm group. In kidney, one single value at the LOQ (0.0095 mg/kg parent equivalent) was observed in the 11 ppm group. In higher dose groups, finite residues were observed in kidney.

At the maximum and mean dietary burden of 3.83 and 2.60 ppm, residues of OH-Imazethapyr in tissues were estimated to be below the LOQ.

The Meeting estimated a maximum residue level of 0.01* mg/kg for milk, muscle, edible offal and fat of mammals other than marine mammals; STMR of 0 mg/kg for milk and muscle and liver, 0.001 mg/kg (0.014 mg/kg × 2.60/32) for kidney.

Residues in egg and poultry tissues

No feeding study was conducted on laying hens. However, the metabolism study on laying hens at the dose of 10 ppm of OH-Imazethapyr or 2.5 ppm of imazethapyr in the diet resulted in no residues in eggs or tissues above the LOQ. At the maximum and mean dietary burden of 0.60 and 0.44 ppm, no residue above the LOQ was expected in eggs or tissues.

The Meeting estimated a maximum residue levels of 0.01* mg/kg for eggs and muscle, fat and edible offal of poultry; STMR of 0 mg/kg for these commodities.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI assessment.

Definition of the residue (for compliance) for plant commodities and (for compliance and and for dietary risk assessment) for animal commodities: *Sum of imazethapyr, 5-hydroxyethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid, expressed as imazethapyr.*

Definition of the residue (for dietary risk assessment) for plant commodities: *Sum of imazethapyr, and 5-hydroxyethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid and*

5-[1-(beta-D-glucopyranozyloxyethyl)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid, expressed as imazethapyr.

The residue is not fat soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The current Meeting established an ADI of 0–0.6 mg/kg bw.

The International Estimated Dietary Intakes (IEDIs) of imazethapyr were calculated for the 17 GEMS/Food cluster diets using STMRs estimated by the current Meeting (Annex 3). The calculated IEDIs were 0.0–0.1% of the maximum ADI (0.6 mg/kg bw). The Meeting concluded that the long-term dietary exposure to residues of imazethapyr, from the uses considered by the current JMPR, is unlikely to present a public health concern.

Short-term dietary exposure

The 2016 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term dietary exposure of residues of imazethapyr is unlikely to present a public health concern.