5.14 ISOFETAMID (290)

TOXICOLOGY

Isofetamid is the ISO-approved common name for *N*-[1,1-dimethyl-2-(4-isopropoxy-*o*-tolyl)-2-oxoethyl]-3-methylthiophene-2-carboxamide (IUPAC), with the CAS number 875915-78-9. Isofetamid is a systemic, broad-spectrum thiophene fungicide. It acts as a succinate dehydrogenase inhibitor, adversely affecting respiration in plants and fungi.

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

All critical studies were performed by laboratories that were certified for GLP and complied with relevant national or international test guidelines, unless otherwise indicated. A search of the open literature did not reveal any relevant publications.

Biochemical aspects

Following gavage dosing of rats, isofetamid was rapidly and almost completely absorbed. At the low dose (5 mg/kg bw), absorption calculated from the radioactivity recovered in bile, urine and carcass was greater than 93% of the administered dose. Absorption was incomplete at the high dose (200 mg/kg bw); a 40-fold increase in dose resulted in an approximately 25-fold increase in the maximum concentration in plasma (C_{max}) and the area under the plasma concentration–time curve (AUC). At the low dose, biliary excretion was a major route of elimination (83–88%), with evidence of reabsorption of biliary excreted metabolites and subsequent excretion in urine. Excretion of radioactivity was rapid, with the majority eliminated within 48 hours. Urinary excretion of radioactivity (phenyl label) was approximately 11% in males and 47% in females at the low dose (5 mg/kg bw) and approximately 8% in males and 23% in females at the high dose (200 mg/kg bw). Maximum plasma concentrations were achieved between 2 and 6 hours at the low dose and at about 8 hours at the high dose. The plasma elimination half-life of radiolabelled material was approximately 38 hours, regardless of sex, dose or radiolabel position.

Overall, isofetamid was metabolized in rats by two main routes, *O*-dealkylation and hydroxylation, which was followed by glucuronidation. Minor metabolic routes included methylation, sulfation and cleavage between the benzene and thiophene ring structures. There were no qualitative differences in the metabolites between sexes.

Toxicological data

In rats, the acute oral LD_{50} was greater than 2000 mg/kg bw, the acute dermal LD_{50} was greater than 2000 mg/kg bw and the acute inhalation LC_{50} was greater than 4.82 mg/L. Isofetamid was non-irritating to the skin of rabbits and mildly irritating to the eyes of rabbits. It was not a skin sensitizer in mice, as determined by the local lymph node assay.

In repeated-dose toxicity studies, liver was the common target organ in rats and dogs. Thyroid was also a target organ in rats.

In a 13-week toxicity study in mice using dietary concentrations of isofetamid of 0, 100, 1000 and 8000 ppm (equal to 0, 13, 129 and 1067 mg/kg bw per day for males and 0, 16, 161 and 1306 mg/kg bw per day for females, respectively), the NOAEL was 1000 ppm (equal to 161 mg/kg bw per day), based on decreased weight gain in female mice at 8000 ppm (equal to 1306 mg/kg bw per day).

In a 28-day range-finding toxicity study in rats using dietary concentrations of isofetamid of 0, 100, 500, 2500 and 15 000 ppm (equal to 0, 8.4, 42, 210 and 1271 mg/kg bw per day for males and 0, 9.3, 45, 215 and 1322 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm

(equal to 42 mg/kg bw per day), based on elevated relative liver weight and changes in clinical chemistry at 2500 ppm (equal to 210 mg/kg bw per day).

In a 90-day toxicity study in rats using dietary concentrations of isofetamid of 0, 100, 1000 and 10 000 ppm (equal to 0, 6.65, 68.9 and 637 mg/kg bw per day for males and 0, 7.83, 78.0 and 741 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 6.65 mg/kg bw per day), based on increased absolute and relative (to body weight) liver weights in both sexes, diffuse hepatocellular hypertrophy in both sexes, thyroid follicular cell hypertrophy in males, increased absolute and relative (to body weight) adrenal weights in females, increased gamma-glutamyltransferase (GGT) activity in males and prolongation of activated partial thromboplastin time in females at 1000 ppm (equal to 68.9 mg/kg bw per day).

In a 28-day range-finding toxicity study in dogs using dietary concentrations of isofetamid of 0, 1000, 3000, 10 000 and 30 000 ppm (equal to 0, 30.3, 89.8, 299 and 987 mg/kg bw per day for males and 0, 34.8, 90.9, 315 and 933 mg/kg bw per day for females, respectively), changes in alkaline phosphatase activity, triglyceride level and body weight, increased absolute and relative liver weights, enlarged livers and centrilobular hepatocellular hypertrophy were observed at and above 3000 ppm (equal to 89.8 mg/kg bw per day).

In a 90-day oral toxicity study in dogs using dietary isofetamid concentrations of 0, 100, 1000 and 10 000 ppm (equal to 0, 2.95, 29.3 and 301 mg/kg bw per day for males and 0, 3.07, 32.7 and 314 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 2.95 mg/kg bw per day), based on liver toxicity (increased liver weight, changes in clinical chemistry, hepatic centrilobular hypertrophy) at 1000 ppm (equal to 29.3 mg/kg bw per day).

In a 1-year oral toxicity study in dogs using dietary concentrations of isofetamid of 0, 60, 200 and 6000 ppm (equal to 0, 1.61, 5.34 and 166 mg/kg bw per day for males and 0, 1.57, 5.58 and 178 mg/kg bw per day for females, respectively), the NOAEL was 200 ppm (equal to 5.34 mg/kg bw per day), based on liver toxicity (increased liver weight, centrilobular hepatocellular hypertrophy), changes in blood chemistry (increased alkaline phosphatase and GGT activities, increased triglyceride levels and decreased albumin levels) and slight decreases in body weight gains at 6000 ppm (equal to 166 mg/kg bw per day).

The overall NOAEL in the 90-day and 1-year dog studies was 200 ppm (equal to 5.34 mg/kg bw per day), with an overall LOAEL of 1000 ppm (equal to 29.3 mg/kg bw per day).

In a 78-week carcinogenicity study in mice using dietary concentrations of isofetamid of 0, 100, 800, 3000 (females only) and 4000 (males only) ppm (equal to 0, 12, 92 and 502 mg/kg bw per day for males and 0, 14, 118 and 431 mg/kg bw per day for females, respectively), the NOAEL was 800 ppm (equal to 92 mg/kg bw per day), based on reduced body weight gains starting from week 9 at 3000 ppm (equal to 431 mg/kg bw per day). There were no neoplastic findings that were related to treatment.

In a 1-year toxicity study in rats using dietary concentrations of isofetamid of 0, 30, 100, 500 and 5000 ppm (equal to 0, 1.39, 4.68, 22.7 and 237 mg/kg bw per day for males and 0, 1.82, 5.92, 30.0 and 311 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm (equal to 22.7 mg/kg bw per day), based on changes in clinical chemistry (increased GGT activity and decreased bilirubin level in both sexes, increased cholesterol level in males), blood coagulation changes in females, haematological changes in both sexes and histopathological findings in the liver (cytoplasmic hepatocyte eosinophilic inclusion body and fatty change in males) and thyroid (follicular cell hypertrophy in both sexes) at 5000 ppm (equal to 237 mg/kg bw per day).

In a 2-year carcinogenicity study in rats using dietary concentrations of isofetamid of 0, 30, 100, 500 and 5000 ppm (equal to 0, 1.21, 4.07, 20.3 and 210 mg/kg bw per day for males and 0, 1.55, 5.02, 26.1 and 263 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm (equal to 20.3 mg/kg bw per day), based on microscopic changes in the liver (diffuse hepatocyte hypertrophy and hepatocellular cytoplasmic eosinophilic inclusion bodies in males and hepatocyte brown pigment [lipofuscin] in females) and in the thyroid (follicular cell hypertrophy in both sexes and follicular

cysts in males) at 5000 ppm (equal to 210 mg/kg bw per day). There were no neoplastic findings that were related to treatment.

In order to evaluate the mechanism of the effects of isofetamid in rats on the liver and thyroid, isofetamid was administered in feed to male rats at a concentration of 0, 5000 or 15 000 ppm (equal to 0, 432 and 1303 mg/kg bw per day, respectively) for a period of 28 days. Effects observed at both doses included a decrease in the plasma thyroxine (T_4) level and an increasing trend in thyroid stimulating hormone (TSH) level, as well as statistically significant increases in hepatic microsomal protein content of the liver, cytochrome P450 content and uridine diphosphate-glucuronosyl-transferase activities towards 4-nitrophenol and 4-hydroxybiphenyl. These data suggest that the effects observed in the liver and thyroid are secondary to hepatic enzyme induction, with adaptive hypertrophy and increased clearance of thyroid hormones, respectively.

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

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

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

In a two-generation reproductive toxicity study in rats using dietary concentrations of isofetamid of 0, 100, 1000 and 10 000 ppm (equal to 0, 6.58, 65.8 and 679 mg/kg bw per day for males and 0, 7.49, 76.6 and 775 mg/kg bw per day for females, respectively), the NOAEL for parental toxicity was 1000 ppm (equal to 65.8 mg/kg bw per day), based on decreased body weights, hepatocellular hypertrophy and follicular cell hypertrophy in the thyroid in both sexes and generations and decreased spleen weights and cytoplasmic eosinophilic inclusion bodies in the liver of F_1 males observed at 10 000 ppm (equal to 679 mg/kg bw per day). The NOAEL for offspring toxicity was 1000 ppm (equal to 76.6 mg/kg bw per day), based on decreased pup body weight in both sexes and generations observed at 10 000 ppm (equal to 775 mg/kg bw per day). The NOAEL for reproductive toxicity was 10 000 ppm (equal to 679 mg/kg bw per day), the highest dose tested.

In a developmental toxicity study in rats using oral gavage doses of isofetamid 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 increases in liver weights at 1000 mg/kg bw per day in the absence of clinical chemistry and histopathological assessments for effects that have been observed in other studies. The NOAEL for embryo and fetal toxicity was 300 mg/kg bw per day, based on more progressive ossification of equivocal toxicological significance seen at 1000 mg/kg bw per day.

In a developmental toxicity study in rabbits using oral gavage doses of isofetamid 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 decreased body weights and feed consumption during gestation days 6–9 seen at 1000 mg/kg bw per day. The embryo and fetal toxicity NOAEL was 300 mg/kg bw per day, based on skeletal anomalies observed at the maternally toxic dose of 1000 mg/kg bw per day.

The Meeting concluded that isofetamid is not teratogenic.

In an acute neurotoxicity study in rats administered a single oral gavage dose of isofetamid of 0, 500, 1000 or 2000 mg/kg bw, the NOAEL for systemic toxicity and neurotoxicity was 2000 mg/kg bw, the highest dose tested.

In a 90-day study of neurotoxicity in rats given diets containing isofetamid at a concentration of 0, 500, 3000 or 15 000 ppm (equal to 0, 34, 207 and 1049 mg/kg bw per day for males and 0, 40, 245 and 1213 mg/kg bw per day for females, respectively), the NOAEL for neurotoxicity and systemic toxicity was 15 000 ppm (equal to 1049 mg/kg bw per day), the highest dose tested.

The Meeting concluded that isofetamid is not neurotoxic.

No evidence of immunotoxicity was observed in an immunotoxicity study in female mice administered isofetamid in the diet at a dose level of 0, 1000, 3000 or 7000 ppm (equal to 0, 197, 644 and 1380 mg/kg bw per day, respectively) for 28 days.

The Meeting concluded that isofetamid is not immunotoxic.

Toxicological data on metabolites and/or degradates

The acute oral LD_{50} value for *N*-(1,1-dimethyl-2-[4-(β-D-glucopyranosyl)oxy-2-methylphenyl]-2-oxoethyl)-3-methylthiophene-2-carboxamide (GPTC; a plant metabolite of isofetamid) in female rats was greater than 2000 mg/kg bw. GPTC was negative for mutagenicity in a bacterial reverse mutation assay.

The Meeting concluded that GPTC is of no greater toxicity than the parent compound.

The metabolites 2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido)propanoyl]-phenoxy]propanoic acid (PPA) and *N*-[1,1-dimethyl-2-(4-hydroxy-2-methylphenyl)-2-oxoethyl]-3-methylthiophene-3-carboxamide (4HP) are major rat metabolites, and the Meeting considered that they would be covered by the ADI and ARfD established for isofetamid.

Human data

No adverse health effects in manufacturing plant personnel were reported. Also, there were no reports of poisonings with isofetamid.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.05 mg/kg bw on the basis of an overall NOAEL of 5.34 mg/kg bw per day in 90-day and 1-year dog studies, based on liver toxicity observed at 29.3 mg/kg bw per day. A safety factor of 100 was applied.

The Meeting established an ARfD of 3 mg/kg bw, based on the maternal and embryo and fetal toxicity NOAELs of 300 mg/kg bw per day for decreased body weights and feed consumption in dams during gestation days 6–9 and skeletal anomalies seen at 1000 mg/kg bw per day in the developmental toxicity study in rabbits, using a safety factor of 100.

The ADI and the ARfD are applicable to the metabolites GPTC, PPA and 4HP.

A toxicological monograph was prepared.

Levels relevant to risk assessment of isofetamid

Species	Study	Effect	NOAEL	LOAEL
Mouse	Seventy-eight-week study of toxicity and carcinogenicity[a]	Toxicity	800 ppm, equal to 92 mg/kg bw per day	3 000 ppm, equal to 431 mg/kg bw per day
		Carcinogenicity	3 000 ppm, equal to 431 mg/kg bw per day[b]	–
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	500 ppm, equal to 20.3 mg/kg bw per day	5 000 ppm, equal to 210 mg/kg bw per day
		Carcinogenicity	5 000 ppm, equal to 210 mg/kg bw per day[b]	–
	Two-generation study of reproductive	Reproductive toxicity	10 000 ppm, equal to 679 mg/kg bw per day[b]	–

Species	Study	Effect	NOAEL	LOAEL
	toxicity[a]	Parental toxicity	1 000 ppm, equal to 65.8 mg/kg bw per day	10 000 ppm, equal to 679 mg/kg bw per day
		Offspring toxicity	1 000 ppm, equal to 76.6 mg/kg bw per day	10 000 ppm, equal to 775 mg/kg bw per day
	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
	Acute neurotoxicity study[c]	Neurotoxicity	2 000 mg/kg bw[b]	–
	Ninety-day neurotoxicity study[a]	Neurotoxicity	15 000 ppm, equal to 1 049 mg/kg bw per day[b]	–
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	Ninety-day and 1-year studies of toxicity[a,d]	Toxicity	200 ppm, equal to 5.34 mg/kg bw per day	1 000 ppm, equal to 29.3 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Acceptable daily intake (ADI; applies to isofetamid and the metabolites GPTC, PPA and 4HP, expressed as isofetamid)

0–0.05 mg/kg bw

Acute reference dose (ARfD; applies to isofetamid and the metabolites GPTC, PPA and 4HP, expressed as isofetamid)

3 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapidly and extensively absorbed from gastrointestinal tract (≥ 93% in 48 h at the low dose)
Dermal absorption	About 10% in vivo (rat)

Distribution	Widely distributed; highest concentrations in gastrointestinal tract/contents and liver
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid and complete within 48 h, mainly in bile
Metabolism in animals	Extensive; O-dealkylation, oxidation, phenyl and thiophene ring hydroxylation, glucuronidation, sulfation
Toxicologically significant compounds in animals and plants	Isofetamid, GPTC, 4HP and PPA
Acute toxicity	
Rat, LD_{50}, oral	> 2 000 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.82 mg/L (4 h; nose only)
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Mildly irritating
Mouse, dermal sensitization	Non-sensitizing (local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Liver (dog and rat) and thyroid (rat)
Lowest relevant oral NOAEL	5.34 mg/kg bw per day (overall NOAEL; dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day, highest dose tested (rat)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver and thyroid (rat), decreased body weight gain (mouse)
Lowest relevant NOAEL	20.3 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity	
	No evidence of genotoxicity[a]
Reproductive toxicity	
Target/critical effect	Liver and thyroid, decreased body weights in adults and pups
Lowest relevant parental NOAEL	65.8 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	76.6 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	679 mg/kg bw per day (rat), highest dose tested
Developmental toxicity	
Target/critical effect	Skeletal anomalies (rabbit) and progressed ossification (rat)
Lowest relevant maternal NOAEL	300 mg/kg bw per day (rat, rabbit)
Lowest relevant embryo/fetal NOAEL	300 mg/kg bw per day (rat, rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested (rat)
Subchronic neurotoxicity NOAEL	1 049 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity NOAEL	No data

Other toxicological studies	
Immunotoxicity	1 380 mg/kg bw per day, highest dose tested (mouse)
Mechanistic study	28-day study establishing thyroid effects secondary to induction in liver
Studies on toxicologically relevant metabolites	
GPTC	Oral LD_{50}: > 2 000 mg/kg in rats
	Ames test: negative
Human data	
	No adverse effects reported in workers at manufacturing plants and agricultural workers

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

Summary

	Value	Study	Safety factor
ADI[a]	0–0.05 mg/kg bw	Ninety-day and 1-year toxicity studies (dog)	100
ARfD[a]	3 mg/kg bw	Developmental toxicity study (rabbit)	100

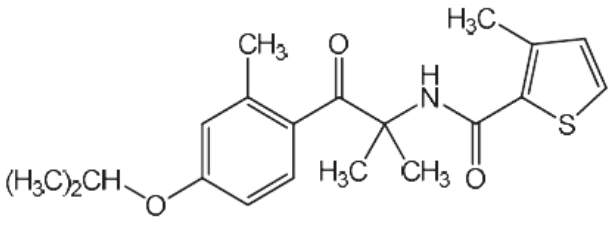
[a] Applies to isofetamid and the metabolites GPTC, PPA and 4HP, expressed as isofetamid.

RESIDUE AND ANALYTICAL ASPECTS

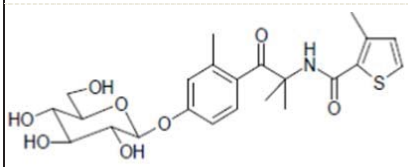
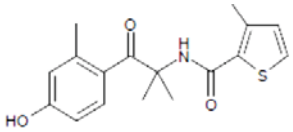
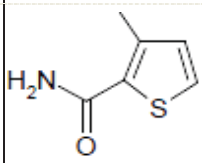
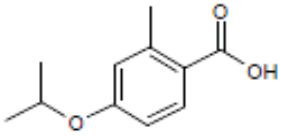
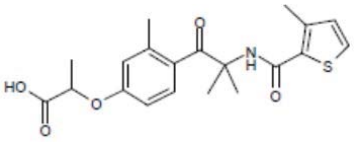
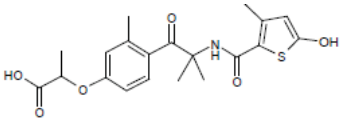
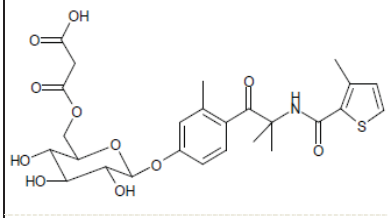
Isofetamid is a broad-spectrum fungicide belonging to the SDHI (Succinate Dehydrogenase Inhibitors) group. It inhibits succinate dehydrogenase in complex II of fungal mitochondrial respiration. Isofetamid is a locally systemic fungicide, which can control fungal pathogens belonging to *Ascomycetes* and *Deuteromycetes* groups. At the 47th Session of the CCPR (2015), the compound was scheduled for evaluation as a new compound by the 2016 JMPR.

The Meeting received information on identity, animal and plant metabolism, environment fate in water, rotational crops, analytical methods, storage stability, use pattern, supervised trials, and fate of residues in processing.

N-[1,1-dimethyl-2-(4-isopropoxy-*o*-tolyl)-2-oxoethyl]-3-methylthiophene-2-carboxamide



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

Glucoside of 4HP  Synonym: GPTC *N*-(1,1-dimethyl-2-[4-(β-D-glucopyranosyl)oxy-2-methylphenyl]-2-oxoethyl)- 3-methylthiophene-2-carboxamide	4HP  *N*-[1,1-dimethyl-2-(4-hydroxy-2-methylphenyl)-2-oxoethyl]-3-methylthiophene-2-carboxamide	3-MTCAM  3-methyl-2-thiophene carboxamide
IBA  2-methyl-4-(2-propyloxy) benzoic acid	PPA  2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido) propanoyl]phenoxy]propanoic acid	5-HPPA  2-[3-methyl-4-[2-methyl-2-(5-hydroxy-3-methylthiophene- 2-carboxamido)propanoyl] phenoxy] propanoic acid
Malonyl glucoside of 4HP  Synonym: Malonyl-GPTC Malonyl conjugate of *N*-(1,1-dimethyl-2-[4-(β-D- glucopyranosyl)oxy- 2-methylphenyl]-2-oxoethyl)-3-methylthiophene-2- carboxamide		

Plant metabolism

The Meeting received plant metabolism studies on grape, lettuce and French bean with isofetamid labeled with ^{14}C in two different rings ([phenyl-^{14}C] and [thiophene-^{14}C]).

In a grape metabolism study, [^{14}C]-isofetamid was applied to grapevines at a rate of 0.75 kg ai/ha. The TRR in foliage (16–17 mg equiv/kg) was higher than in grape berries (0.64–0.72 mg equiv/kg) at 43 DALA (mature harvest sample). Radioactive residues extracted with acetonitrile and acetonitrile:water were 88–93% of the TRR for grape berries and 83–86% TRR for grape foliage at 43 DALA.

Isofetamid was the main component in both grapes (46–60% TRR, 0.33–0.39 mg/kg) and foliage (38–61% TRR, 6.5–9.8 mg/kg). Two metabolites, the glucoside of 4HP (max 10% TRR) and 3-MTCAM (max 4% TRR) were also identified. Several unidentified conjugated metabolites were present in grapes and foliage and maximum levels of individual compounds were 8.0% and 5.5% TRR respectively. A polar fraction produced during work-up contained mixtures of metabolites and the maximum level of any single compound in this fraction of foliage was less than 4% TRR.

In a lettuce metabolism study, [^{14}C]-isofetamid were applied to lettuce at a rate of 0.75 kg ai/ha. TRRs in lettuce leaves were in the range of 1.7–2.6 mg equiv/kg (wrapper leaves) and 0.07–

0.09 mg equiv/kg (lettuce heads) at mature harvest (18 DALA). Radioactive residues extracted with acetonitrile and acetonitrile:water were 91–96% of the TRR for wrapper leaves and 93–95% TRR for lettuce heads at 18 DALA.

Isofetamid was the main component in lettuce heads (57–66% TRR, 0.04–0.05 mg/kg) and wrapper leaves (62–73% TRR, 1.0–1.9 mg/kg). Three metabolites, 4HP (max 3% TRR), the glucoside of 4HP (max 10% TRR) and 3-MTCAM (max 2% TRR), were also identified. There were no individual unidentified metabolites over 10% TRR.

In a French bean metabolism study, [^{14}C]-isofetamid was applied to French bean plants at a rate of 0.75 kg ai/ha. TRR in forage at 14 DALA (11–12 mg equiv/kg) and straw at 68 DALA (3.3–4.9 mg equiv/kg) were higher than those in immature (14 DALA) and mature (68 DALA) pods (0.21–0.41 mg equiv/kg) or immature and mature seeds (0.03–0.40 mg equiv/kg). Radioactive residues extracted with acetonitrile and acetonitrile:water were 96–98% TRR from forage, 97–99% TRR from immature pods and 96–99% TRR from immature seeds, and 93–94% TRR from straw, 93–95% TRR from mature pods and 32–57% TRR from mature seeds.

Isofetamid was the main individual component in forage (77% TRR, 8.1–8.9 mg/kg), straw (53–62% TRR, 1.7–3.1 mg/kg), immature pods (69–81% TRR, 0.21–0.28 mg/kg), and immature seeds (28–50% TRR, 0.07–0.11 mg/kg). Isofetamid was observed as the major single component in mature pods (18–36% TRR, 0.07–0.08 mg/kg) and mature seeds (0.5–1.1% TRR, < 0.01 mg/kg). Four metabolites, 4HP (max 1% TRR), the glucoside of 4HP (max 7% TRR), 3-MTCAM (max 7% TRR) and IBA (max 0.5% TRR), were also identified in forage, straw and pods. With the exception of the group of metabolites referred to as polar metabolites, no individual metabolites were present at levels >10% TRR. Polar metabolites were further characterised in pods and the maximum single component accounted for 11–12% TRR.

In summary, isofetamid was the major component of the residues found in grape, lettuce and French beans. The glucoside of 4HP was formed by O-dealkylation and glucose conjugation but it was not present as a significant residue in plants.

Animal metabolism

The Meeting received animal metabolism studies with isofetamid on lactating goat and laying hens. The metabolism and distribution of isofetamid in animals were investigated using the [^{14}C-phenyl] and [^{14}C-thiophene]-isofetamid.

Lactating goats were orally dosed with either of two radiolabeled isofetamids daily for 7 consecutive days at a dose level of 10 ppm in the diet. The majority of the administered dose, 51–53%, was eliminated in faeces. Urinary excretion accounted for 33–35% of the dose.

Following the administration of [^{14}C]-isofetamid, TRRs were 0.36–0.44 mg eq/kg in liver, 0.072–0.11 mg equiv/kg in kidney, 0.004–0.007 mg equiv/kg in muscle and 0.012–0.054 mg equiv/kg in fat. TRRs in the aqueous fraction of milk reached a maximum of 0.007–0.011 mg equiv/L and in the fat fraction of milk, reached a maximum of 0.048–0.16 mg eq/kg. Radioactive residues extracted with organic and aqueous solvent were 36–53% TRR from liver, 61–72% TRR from kidney, 71–88% TRR from fat, 91–99% TRR from the fat fraction of milk and 63% TRR from the aqueous fraction of milk. The remaining residues were released following protease digestion and acidic and basic hydrolysis (47–57% TRR from liver and 19–26% TRR from kidney).

Isofetamid accounted for 0.012–0.099 mg/kg (26–76% TRR) in milk fat fraction, 0.006–0.033 mg/kg (44–62% TRR) in fat and 0.0004–0.010 mg/kg (0.6–2% TRR) in liver and kidney. The metabolite PPA accounted for 0.029–0.062 mg equiv/kg (7–17% TRR) in liver, 0.005–0.021 mg equiv/kg (6–20% TRR) in kidney and 0.0002–0.003 mg equiv/kg (1–6% TRR) in aqueous and fat fraction of milk and fat. No other known residues were present in any matrix at a level greater than 0.033 mg equiv/kg.

Laying hens were orally dosed with either of the two radiolabeled isofetamid daily for 14 days at a dose level of 10 ppm in the diet. The majority of the dose was rapidly eliminated in the excreta.

In animals dosed with [^{14}C]-isofetamid, TRRs were 0.18–0.21 mg equiv/kg in liver, 0.023–0.025 mg equiv/kg in muscle, 0.030–0.035 mg equiv/kg in skin and 0.036–0.070 mg equiv/kg in fat. Maximum radioactivity in daily egg yolk samples was 0.18–0.22 mg equiv/kg and in egg white were 0.006–0.007 mg equiv/kg. Radioactive residues extracted with organic and aqueous solvent were 44–46% TRR from liver, 27–33% TRR from muscle, 69–79% TRR from fat, 59–62% TRR from skin and 47–52% TRR from egg yolk. The remaining residues were released following protease digestion and acidic and basic hydrolysis (39–41% TRR from liver, 33–35% TRR from skin and 46% TRR from egg yolk). The unextracted residues in muscle and fat were not further treated due to low TRRs.

3-MTCAM was only detected at low levels in egg yolk following acid reflux. None of the metabolites in individual matrices accounted for greater than 0.013 mg equiv/kg.

In summary, isofetamid was the major component in milk fat fraction and fat. PPA was the major component in liver and kidney of lactating goat. However, in tissues and eggs of laying hens no significant component was identified.

Rotational crop studies

The Meeting received confined rotational crop studies with ^{14}C-labeled isofetamid ([phenyl-^{14}C] and [thiophene-^{14}C]) and field rotational crop studies.

In a confined rotational crop study, rotational crops (lettuce, carrot and wheat) were sown at 30, 120 and 365 days after treatment (DAT). The SC formulated test substance ([phenyl-^{14}C] or [thiophene-^{14}C]-isofetamid) was applied to bare soil at a rate of 2.3 kg ai/ha (3 ×seasonal rate of the US GAP).

Isofetamid was present in the immature and mature lettuce extracts at < 0.1–6% TRR (< 0.001–0.005 mg/kg). The glucoside of 4HP accounted for >10% TRR in the immature and mature lettuce extracts at 19–55% TRR (0.002–0.14 mg equiv/kg). The malonyl glucoside of 4HP accounted for up to 20% TRR and 0.018 mg equiv/kg.

Carrot root extracts contained isofetamid (3–40% TRR, 0.001–0.036 mg/kg), malonyl glucoside of 4HP (11–31% TRR, 0.006–0.018 mg equiv/kg) and the glucoside of 4HP (1–18% TRR, 0.001–0.023 mg equiv/kg).

The main component in wheat forage, hay and the straw was generally the malonyl glucoside of 4HP (4–39% TRR, 0.025–0.51 mg equiv/kg). Isofetamid, glucoside of 4HP, PPA, IBA and 4HP were generally detected up to 12% TRR and 0.081 mg equiv/kg, with the exception of the glucoside of 4HP in wheat hay at 120 DAT (10% TRR and 0.24 mg equiv/kg), 4HP in wheat hay at 120 DAT (6% TRR and 0.13 mg equiv/kg) and PPA in wheat straw at 30 DAT (9–15% TRR and 0.13 mg equiv/kg). Wheat grain generally contained isofetamid, the malonyl glucoside of 4HP and PPA but each at less than 6% TRR and 0.004 mg equiv/kg. No other known metabolites were present.

The residue in succeeding crops is likely to be comprised of several compounds including isofetamid, the glucoside of 4HP, the malonyl glucoside of 4HP, 4HP, IBA and PPA depending on the crop type. The concentration of these compounds is likely to be lower at longer plantback intervals.

In a field rotational crop study in Europe, two foliar applications of isofetamid SC formulation were made to lettuce at a rate of 0.40 kg ai/ha and with a spray interval of 8–13 days (US GAP rate).

Residues of isofetamid and glucoside of 4HP in succeeding crops (spinach, radish and winter barley) at all PBIs (30, 120 and 365-day) were all below the LOQ, with the exception of radish tops

at the 30-day PBI. In the sample of radish tops, isofetamid was found at 0.023–0.029 mg/kg and the malonyl glucoside of 4HP 0.011–0.013 mg/kg.

In another field rotational crop study in the USA, three applications of isofetamid SC formulation were made at approximately 14-day intervals to the vegetation on the treated plot with a target application of 0.75 kg ai/ha each time (3 ×seasonal rate of the US GAP). Thirty, 120 and 365-day PBIs were tested with representative root crops, leafy crops and small grain crops.

For all PBIs no residues of isofetamid, the glucoside of 4HP or malonyl glucoside of 4HP were found in rotational crops (turnip, wheat, soya bean lettuce and kale), with the exception of turnip root (0.01 mg/kg) at the 30-day PBI.

In rotational crops, the Meeting concluded that no significant residues are expected.

Environmental fate in water

The Meeting received information on hydrolysis.

In the hydrolytic degradation study, isofetamid was hydrolytically stable at pH 4, 7 and 9 after incubation at 50 °C for 5 days (> 94% of applied radioactivity was recovered as unchanged isofetamid). Hydrolysis is not considered a significant degradation route of isofetamid.

In the photolysis study, the DT_{50} of isofetamid was 1–3 days in water. Photolysis may be a potential route of degradation of isofetamid.

Methods of analysis

The Meeting received descriptive and validation data of analytical methods for residues of isofetamid and the glucoside of 4HP in plant commodities and for residues of isofetamid, 4HP, PPA and 5-HPPA in animal commodities.

In the methods for determination of isofetamid and the glucoside of 4HP in plant, homogenized samples were extracted with acetonitrile:water (80:20 v/v), with or without clean up with a solid phase extraction, residues were determined by HPLC with MS/MS detection. The methods of analysis were validated at various fortification levels with an LOQ of 0.01 mg/kg for isofetamid and 0.01 mg/kg for the glucoside of 4HP.

In the methods for determination of isofetamid, 4HP, PPA and 5-HPPA in animal commodities, samples were homogenized with acetonitrile:water (15:2 v/v), and DisQuE extraction mixture (used developed QuEChERS method) was added and mixed. An aliquot was diluted in formate buffer. Residues were determined by HPLC with MS/MS detection. The method of analysis was validated with LOQs of the 0.01 mg/kg for isofetamid, 4HP, PPA and 5-HPPA.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the freezer storage stability of isofetamid and the glucoside of 4HP in plant (almonds, rape seeds, grapes, lettuce, potatoes and dry beans).

Storage stability results indicate that isofetamid residue was stable at -20 °C for at least 12 months in almonds, rape seeds, grapes, lettuce, potatoes and dry beans. The glucoside of 4HP residue was stable at -20 °C for at least 12 months in almonds, grapes, lettuce, potatoes and dry beans and at least 1 month in rape seeds.

The periods of storage stability studies generally cover the sample storage intervals of residue trials, except oilseed rape.

Definition of the residue

In plant metabolism studies, parent isofetamid was the major component (28–81% TRR) in grape, lettuce and French bean. The glucoside of 4HP was found at 0.01–0.07 mg equiv/kg (10% TRR) in grapes and lettuce heads. No other individual metabolite was present in the edible plant parts at a level greater than 10% TRR.

No significant residues are likely to be found in rotational crops.

The Meeting decided that the suitable analyte for enforcement purposes and for dietary risk assessment is isofetamid in plant commodities.

In the lactating goat study, PPA is the major component of the residue in liver (7–17% TRR, 0.029–0.062 mg equiv/kg) and kidney (6–20% TRR, 0.005–0.021 mg equiv/kg). On the other hand, isofetamid was the major component in milk fat (26–76% TRR, 0.012–0.099 mg equiv/kg) and fat (44–62% TRR, 0.006–0.033 mg equiv/kg). In the laying hen study, the concentration of each of identified components in the tissues and egg yolk were below 0.01 mg equiv/kg.

An analytical method to determine residues of isofetamid and PPA in animal commodities is available.

The Meeting decided that isofetamid and PPA are suitable analytes for enforcement purposes and dietary risk assessment in animal commodities.

The octanol/water coefficient (log P_{ow}) of isofetamid is 2.5. However, the sum of isofetamid and PPA in fat is 5 times higher than in muscle, and, in milk fat, 45 times higher than in the aqueous fraction of milk. The Meeting considered the residue of isofetamid is fat soluble.

Definition of the residue (for compliance with MRLs and for dietary risk assessment) for plant commodities: *Isofetamid*

Definition of the residue (for compliance with MRLs and for dietary risk assessment) for animal commodities: *Sum of isofetamid and 2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido) propanoyl] phenoxy] propanoic acid (PPA), expressed as isofetamid*

The residue is fat soluble.

Results of supervised residue trials on crops

The Meeting received supervised trial data for foliar application of isofetamid on cherries, plum, apricot, peach, grapes, strawberry, lettuce, almonds and oilseed rape. Residue trials were conducted in Belgium, Germany, Hungary, the Netherlands, the UK, France, Greece, Italy, Spain, Canada and the USA.

Labels from Canada and the USA were available.

Stone fruits

Data were available from supervised trials on cherries, plums, apricots and peaches in Europe. However, no GAP information was provided.

As there was no GAP information available to support the trials, the Meeting could not estimate a maximum residue level for stone fruits.

Small fruit vine climbing

Grapes

Data were available from supervised trials on grapes in Canada, the USA and European countries.

The GAP for grapes of Canada allows three foliar applications at a maximum rate of 0.64 kg ai/ha with a PHI of 14 days. The GAP of the USA for small fruits vine climbing (US Crop Subgroup 13-07D), except fuzzy kiwifruit allows foliar applications of 0.58–0.64 kg ai/ha at a maximum annual rate of 1.9 kg ai/ha with a PHI of 14 days.

Isofetamid residues in grapes from independent trials in Canada and the USA matching GAP were (n = 15): 0.12, 0.17 (2), 0.49, 0.51, 0.54, 0.67, 0.73, 0.82, 0.83, 0.84, 0.87, 1.1, 1.5 and 1.9 mg/kg.

Based on the trials on grapes in Canada and the USA, the Meeting estimated a maximum residue level of 3 mg/kg, an STMR value of 0.73 mg/kg and an HR value of 2.6 mg/kg (based on the highest residue of replicate samples) for isofetamid in small fruit vine climbing.

Low growing berries

Strawberry

Data were available from supervised trials on strawberry in Canada, the USA and European countries.

The GAP for low growing berry of Canada is five foliar applications at a maximum rate of 0.50 kg ai/ha with a PHI of 0 day; and the GAP for the low growing berry subgroup of the USA is for foliar applications of 0.39–0.45 kg ai/ha at a maximum annual rate of 1.6 kg ai/ha with a PHI of 0 day.

Isofetamid residues in strawberries from independent trials in Canada and the USA, matching the Canadian GAP, were (n = 10): 0.16, 0.31, 0.32, 0.47, 0.48, 0.50, 0.54, 1.0, 1.2 and 2.7 mg/kg.

Based on the trials on strawberries in Canada and the USA, the Meeting estimated a maximum residue level of 4 mg/kg, an STMR value of 0.49 mg/kg and an HR value of 3.1 mg/kg (based on a highest residue of replicate samples) for isofetamid in low growing berries.

Lettuce

Data were available from supervised trials on head and leaf lettuce in Canada, the USA and a number of European countries.

The GAP in Canada for lettuce (head and leaf) is two foliar applications at a rate of 0.36 kg ai/ha with a PHI of 14 days; the GAP in the USA for lettuce (head and leaf) is for foliar applications at 0.36 kg ai/ha at a maximum annual rate of 0.72 kg ai/ha with a PHI of 14 days. No GAP was received for Europe.

Isofetamid residues in head lettuce with wrapper leaves from independent trials in Canada and the USA matching GAP were (n = 11): < 0.01 (2), 0.01, 0.17, 0.21, 0.29, 0.34 (2), 0.35, 1.4 and 3.4 mg/kg.

Based on the trials on head lettuce in Canada and the USA, the Meeting estimated a maximum residue level of 5 mg/kg, an STMR value of 0.29 mg/kg and an HR value of 4.7 mg/kg (based on a highest residue of replicate samples) for isofetamid in head lettuce.

Isofetamid residues in leaf lettuce from independent trials in Canada and the USA matching GAP were (n = 12): < 0.01, 0.01 (3), 0.05, 0.08, 0.15, 0.39, 0.76, 0.88, 1.4 and 4.9 mg/kg.

Based on the trials on leaf lettuce in Canada and the USA, the Meeting estimated a maximum residue level of 7 mg/kg, an STMR value of 0.115 mg/kg and an HR value of 5.2 mg/kg (based on a highest residue of replicate samples) for isofetamid in leaf lettuce.

Almonds

Data were available from supervised trials on almonds in the USA.

The GAP of the USA for almond is foliar applications of 0.39–0.50 kg ai/ha at a maximum annual rate of 2.0 kg ai/ha with the application timing from pink bud to petal fall.

Isofetamid residues in almond nutmeats from independent trials in the USA matching GAP were (n = 5): < 0.01 (5) mg/kg.

Based on the trials on almonds in the USA, the Meeting estimated a maximum residue level of 0.01 * mg/kg, an STMR value of 0.01 mg/kg and an HR value of 0.01 mg/kg for isofetamid in almonds.

Rape seed

Data were available from supervised trials on rape seed in Canada, the USA and European countries.

The GAP of Canada for the rapeseed subgroup is two foliar applications at a maximum rate of 0.35 kg ai/ha with the application timing at 20–40% flowering (BBCH 62–64) and near the end of flowering (BBCH 67–69); the GAP on the rapeseed subgroup of the USA is for foliar applications of 0.30–0.35 kg ai/ha at a maximum annual rate of 0.71 kg ai/ha with the application timing of 20–40% flowering (BBCH 62–64) and near the end of flowering (BBCH 67–69).

Isofetamid residues in rape seed from independent trials in Canada and the USA matching GAP were (n = 17): < 0.01 (14) and 0.01 (3) mg/kg.

Based on the trials on oilseed rape in Canada and the USA, the Meeting estimated a maximum residue level of 0.015 mg/kg and an STMR value of 0.01 mg/kg for isofetamid in rape seed.

Animal feedstuffs

Almond hulls

Data were available from supervised trials on almonds in the USA.

The GAP of the USA for almond is foliar applications of 0.39–0.50 kg ai/ha at a maximum annual rate of 2.0 kg ai/ha with the application timing from pink bud to petal fall.

Isofetamid residues in almond hulls (dry weight basis) from independent trials in the USA matching GAP were (n = 5): < 0.01 (4) and 0.41 mg/kg.

Based on the trials for almonds in the USA, the Meeting estimated a maximum residue level of 0.8 mg/kg and a median residue value of 0.01 mg/kg for isofetamid in almond hulls on a dry weight basis.

Fate of residues during processing

High temperature hydrolysis

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

Residues in processed commodities

The fate of isofetamid residues has been examined in grape and rape seed processing studies. 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)
		Isofetamid	Isofetamid		
Grape	Must	1.0, 1.1	1.05	0.73	0.77
	Juice	0.11, 0.11, 0.12, 0.13, 0.17, 0.45, 0.75	0.13		0.095
	Wet pomace	2.1, 2.9, 3.7, 4.4, 4.5	3.7		2.7
	Red wine	0.20, 0.20, 0.22, 0.26	0.21		0.15
	White wine	0.26, 0.39, 0.48	0.39		0.28
	Dried grapes	1.1, 1.5, 2.2, 2.3, 2.4, 2.7	2.3		1.7
Rape seed	Meal	0.17	0.17	0.01	0.0017
	Refined oil	2.0	2.0		0.02

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

The Meeting estimated maximum residue levels of 7 mg/kg (3 × 2.3 = 6.9 mg/kg) and an HR value of 5.98 (2.6 × 2.3 = 5.98 mg/kg) for dried grapes and 0.03 mg/kg (0.015 × 2.0 = 0.03 mg/kg) for rape seed oil.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of isofetamid in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual third edition, 2016. Calculations from the highest residue, STMR (some bulk commodities) and STMR-P values provide levels in feed suitable for estimating MRLs, while calculations using STMR and STMR-P values for feed are 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 on a dry weight basis.

Estimated maximum and mean dietary burdens of farm animals

The calculations were made according to the animal rations from US-Canada, EU, Australia and Japan in the Table (Appendix IX of the FAO manual).

Potential feed items include: almond hulls, grape wet pomace and rape seed meal.

Livestock dietary burden, isofetamid, ppm of dry matter diet								
	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	0	0	0.00039	0.00039	**3.60**[A]	**3.60**[B]	0.00029	0.00029
Dairy cattle	0.001	0.001	0.00019	0.00019	**3.60**[C]	**3.60**[D]	0.00048	0.00048
Poultry – broiler	0	0	0	0	0.00010	0.00010	0.00010	0.00010
Poultry – layer	0	0	0.00019	0.00019	0.00010	0.00010	**0.00029**[E]	**0.00029**[F]

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

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

[C] Highest maximum dairy cattle dietary burden suitable for MRL estimates for milk

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

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

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

Farm animal feeding studies

Farm animal feeding studies were not submitted.

Animal commodities maximum residue levels

For MRL estimation, the residue definition in the animal commodities is isofetamid and PPA, expressed as isofetamid.

The maximum dietary burden for beef and dairy cattle is 3.6 ppm which is lower than the dose level in the lactating goat metabolism study (10 ppm). In the study, in which isofetamid equivalent to 10 ppm in the diet was dosed to lactating goats for 7 consecutive days, maximum residues of isofetamid were detected at 0.10 mg/kg in liver, 0.033 mg/kg in fat and < 0.01 mg/kg in kidney, muscle and aqueous fraction of milk. For milk fat isofetamid residues were 0.12 mg/kg (TRR reached a maximum of 0.16 mg equiv/kg and isofetamid residues were 76.1% TRR in [^{14}C-phenyl] study). PPA residues were detected at 0.062 mg equiv/kg in liver, 0.021 mg equiv/kg in kidney and < 0.01 mg equiv/kg in milk (aqueous and fat), muscle and fat. The maximum dietary burden for beef and dairy cattle is 36% of the dose rate in the metabolism study.

The highest estimated total residues (isofetamid and PPA) were 0.043 mg/kg ((0.12+< 0.01)×0.36) in milk fat, 0.058 mg/kg ((0.10 + 0.062) × 0.36) in liver, 0.0076 mg/kg ((< 0.01+0.021) × 0.36) in kidney, 0.012 mg/kg ((0.033+< 0.01) × 0.36) in fat and < 0.01 mg/kg in muscle.

The ratio of milk fat in whole milk was average 6% in the lactating goat metabolism study. The highest estimated total residue in whole milk was 0.003 mg/kg.

The Meeting estimated a maximum residue level of 0.01* mg/kg and an STMR value of 0.003 mg/kg in milk.

The Meeting estimated a maximum residue level of 0.02 mg/kg in mammalian fat and meat (fat).

The Meeting estimated an STMR value of 0.012 mg/kg and an HR value of 0.012 mg/kg in mammalian fat.

The Meeting estimated an STMR value of 0.01 mg/kg and an HR value of 0.01 mg/kg in mammalian muscle.

The Meeting estimated a maximum residue level of 0.07 mg/kg, an STMR value of 0.058 mg/kg and an HR value of 0.058 mg/kg in mammalian edible offal.

The maximum dietary burden for broiler and layer poultry is 0.0003 ppm and is considerably lower than the dose level in the laying hen metabolism study of 12.7–13.5 ppm. In the metabolism study, in which isofetamid equivalent to 13.5 ppm in the diet was dosed to laying hens for 7 consecutive days, the maximum TRR was 0.21 mg/kg in liver. There would be no significant residues in poultry meat, fat, edible offal and eggs at the maximum dietary burden for broiler and layer poultry.

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 in Annex 1 are suitable for estimating maximum residue limits and for IEDI and IESTI assessment.

Definition of the residue (for compliance with MRLs and for dietary risk assessment) for plant commodities: *Isofetamid*

Definition of the residue (for compliance with MRLs and for dietary risk assessment) for animal commodities: *Sum of isofetamid and 2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido) propanoyl] phenoxy] propanoic acid (PPA), expressed as isofetamid*

The residue is fat soluble

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The International Estimated Daily Intakes (IEDIs) of isofetamid were calculated for the 17 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.05 mg/kg bw and the calculated IEDIs were 0–1% of the maximum ADI (0.05 mg/kg bw). The Meeting concluded that the long-term exposure to residues of isofetamid, resulting from the uses considered by current JMPR, is unlikely to present a public health concern.

Short-term dietary exposure

The International Estimated Short-Term Intakes (IESTI) of isofetamid were calculated for food commodities and their processed commodities using HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting (Annex 4). The ARfD is 3 mg/kg bw and the calculated IESTIs were a maximum of 3% of the ARfD for the general population and 10% of the ARfD for children. The Meeting concluded that the short-term dietary exposure to residues of isofetamid, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.