ISOFETAMID (290)

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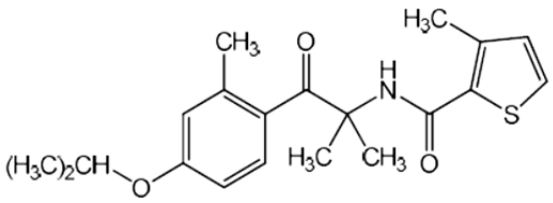
EXPLANATION

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 and is used to control fungal pathogens belonging to *Ascomycetes* and *Deuteromycetes* groups.. It was scheduled for evaluation as a new compound at the 47th Session of the CCPR (2015) by the 2016 JMPR. An ADI of 0–0.05 mg/kg bw and an ARfD of 3 mg/kg bw were established.

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.

IDENTITY

Common name	Isofetamid
Chemical name	
IUPAC:	*N*-[1,1-dimethyl-2-(4-isopropoxy-*o*-tolyl)-2-oxoethyl]-3-methylthiophene-2-carboxamide
CAS:	*N*-[1,1-dimethyl-2-[2-methyl-4-(1-methylethoxy)phenyl]-2-oxoethyl]-3-methyl-2-thiophenecarboxamide
CAS Registry No:	875915-78-9
CIPAC No:	972
Synonyms:	IKF-5411
Structural formula:	
	
Molecular formula:	$C_{20}H_{25}NO_3S$
Molecular weight:	359.48

Physical and chemical properties

Pure active ingredient

Property	Results	Reference
Appearance (colour, physical state, door)	White / crystalline powder / no discernible door (99.9% purity)	Turner, 2011 JSM0171
Vapour pressure	4.2×10^{-7} Pa at 25 °C (99.9% purity)	Turner, 2011 JSM0169
Melting point	103.5 – 105.0 °C (99.9% purity)	Turner, 2011 JSM0171
Boiling point	Isofetamid started to decompose at temperatures above approximately 176°C without boiling (99.9% purity)	
Octanol/water partition coefficient	log Pow = 2.5 (99.9% purity)	Turner, 2011 JSM0183

Property	Results		Reference
Solubility in water	5.33 mg/L at 20 °C (99.9% purity)		Turner, 2011 JSM0139
Solubility in organic solvent (99.9% purity)	n-Heptane	1.2 g/L at 20 °C	Turner, 2011 JSM0175
	Xylene	61.4 g/L at 20 °C	
	n-Octanol	31.7 g/L at 20 °C	
	1,2-dichlorethane	>250 g/L at 20 °C	
	Acetone	>250 g/L at 20 °C	
	Methanol	>250 g/L at 20 °C	
	Ethyl acetate	>250 g/L at 20 °C	
Relative density	1.23 g/cm^3 at 20 °C (99.9% purity)		Turner, 2011 JSM0171
Hydrolysis	Hydrolytically stable at pH 4, 7 and 9 at 50 °C over 5 days corresponds to a DT_{50} of more than a year (99.61% purity)		Fletcher, 2010 2244/073
Photolysis	DT_{50} = 2.7 days in distilled water DT_{50} = 2.7 days at pH 5 DT_{50} = 1.3 days at pH 9		
Dissociation constant	Not possess a dissociation constant at pH 4 – 10 (99.9% purity)		Turner, 2011 JSM0170

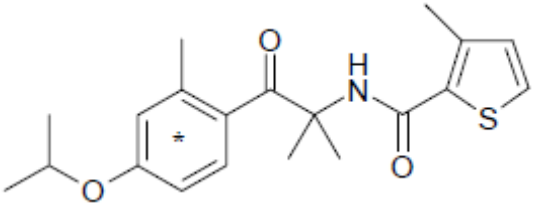
Technical material

Property	Results		Reference
Appearance (colour, physical state, door)	Pale brown / powder with various sized agglomerates / no discernible door		Turner, 2011 JSM0173
Solubility in organic solvents (96.68% purity)	n-Heptane	1.0 g/L at 20 °C	Turner, 2011 JSM0167
	Xylene	71.4 g/L at 20 °C	
	n-Octanol	34.9 g/L at 20 °C	
	1,2-dichloroethane	>250 g/L at 20 °C	
	Acetone	>250 g/L at 20 °C	
	Methanol	>250 g/L at 20 °C	
	Ethyl acetate	>250 g/L at 20 °C	

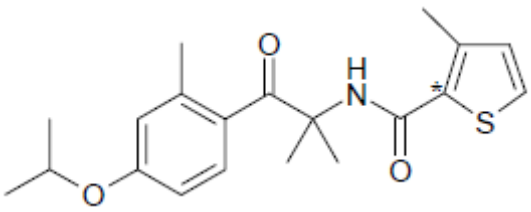
Formulations: Suspension concentrate (SC)

METABOLISM AND ENVIRONMENTAL FATE

The metabolism and distribution of isofetamid has been investigated in animals and plants. The fate and behaviour of isofetamid in animals, plants and the environment was investigated using the [^{14}C] labelled test materials shown in Figure 1.



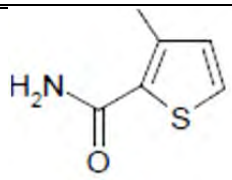
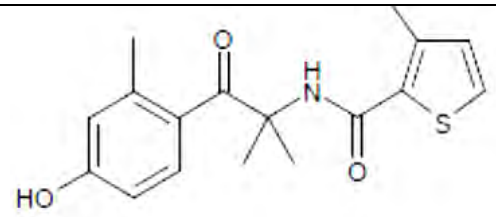
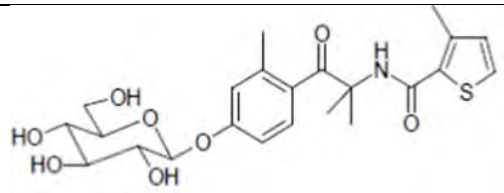
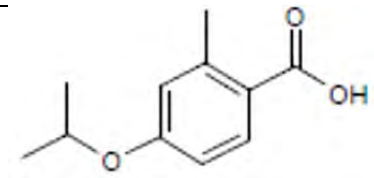
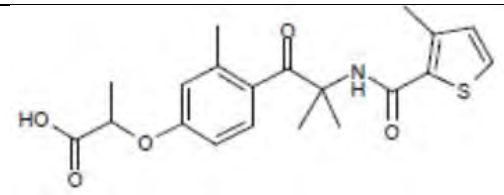
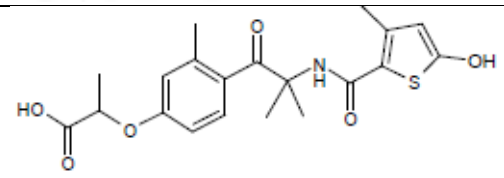
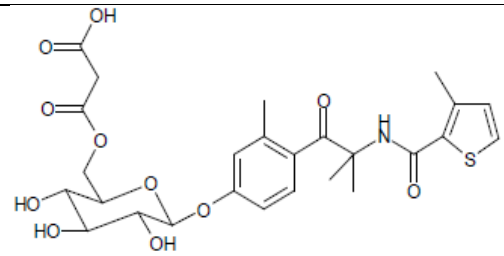
[Phenyl-U-^{14}C]-isofetamid



[Thiophene-2-^{14}C]-isofetamid

Figure 1 [^{14}C]-Labelled test materials used in animals, plants metabolism studies, and the environmental fate studies

The chemical structures of the major degradation compounds from the metabolism of isofetamid are provided below.

Compound name		Structure	Found in metabolism studies
3-MTCAM	3-methyl-2-thiophene carboxamide		Plants
4HP	N-[1,1-dimethyl-2-(4- hydroxy-2-methylphenyl)-2-oxoethyl]-3-methyl thiophene-2-carboxamide		Plants, Livestock
Glucoside of 4HP (GPTC)	*N*-(1,1-dimethyl-2-[4-(β-D-glucopyranosyl)oxy-2-methylphenyl]-2-oxoethyl)-3-methylthiophene-2- carboxamide		Plants
IBA	2-methyl-4-(2-propyloxy) benzoic acid		Plants, Livestock
PPA	2-[3-methyl-4-[2-methyl-2- (3-methylthiophene-2-carboxamido)propanoyl] phenoxy]propanoic acid		Plants, Livestock
5-HPPA	2-[3-methyl-4-[2-methyl-2- (5-hydroxy-3-methyl thiophene-2-carboxamido) propanoyl]phenoxy] propanoic acid		Livestock
Malonyl glucoside of 4HP (Malonyl-GPTC)	Malonyl conjugate of *N*-(1,1-dimethyl-2-[4-(β-D-glucopyranosyl)oxy-2-methylphenyl]-2-oxoethyl)-3-methylthiophene-2- carboxamide		Plants

Plant metabolism

Plant metabolism studies were performed on grapevine, lettuce and French bean with isofetamid ^{14}C-labeled at phenyl or thiophene to track metabolites. Metabolites were identified using multiple chromatographic systems and authentic standards.

Grapes

The metabolism of isofetamid was investigated in grapes and foliage from grapevines (variety Müller Thurgau) following three foliar applications of [^{14}C]-isofetamid at a rate of 0.75 kg ai/ha in an application volume of 400 L/ha (Lewis, 2012: 2244/069).

A commercial variety (Müller Thurgau) of grapevines was grown outdoors. Established grapevine plants were treated with [^{14}C]-isofetamid on three occasions at the end of flowering (BBCH 67–69), when pea sized berries were present (BBCH 71–75) and the beginning of ripening (BBCH 77–79). A 50% SC formulation was used. The two radiolabeled forms of isofetamid were radiolabeled in either the phenyl ring or the thiophene ring systems. There were three harvesting occasions, immature harvest 14 days after last application (DALA), when the majority of berries were touching (BBCH 79), mature harvest one month later (43 DALA), between softening of berries and berries ripe for harvest (BBCH 85–89) and 10 days later (53 DALA) when surplus leaves at the beginning of leaf discolouration (BBCH 91–92) were collected. The immature harvest samples were only taken to provide additional foliage and grapes in case they were needed for metabolite identification.

Samples were surface-washed by immersing each sample in acetonitrile. The mature harvest samples were homogenised to a powder in dry-ice. Homogenised sample (5 replicates) were taken for initial overall residue determination by sample oxidation and liquid scintillation counting (LSC). Homogenised sample were extracted sequentially with acetonitrile, acetonitrile:water (1:1, v/v) and water. Foliage samples were additionally extracted with 0.1M hydrochloric acid and 0.1M sodium hydroxide and all samples were then extracted with acetone. All extracts and acetonitrile surface washes were analysed by LSC. After extraction, the remaining residue was analysed by oxidation and LSC. Additional extractions were performed where residual radioactivity was present more than 10% TRR. Concentrated surface washes and combined acetonitrile and acetonitrile:water extracts, cleaned-up via solid phase extraction and concentrated, were analysed by HPLC.

After three foliar applications of [^{14}C]-isofetamid, the TRR in foliage (16.0–16.9 mg equiv/kg) were higher than in grapes (0.64–0.72 mg equiv/kg). Most (>83%) of the residue in grapes and foliage was recovered in the sum of the acetonitrile rinses and acetonitrile or acetonitrile:water extracts and was characterised by HPLC and/or by TLC. Surface rinses contained mainly isofetamid and extracts contained isofetamid with its metabolites. Isofetamid was the main component of the TRR in both grapes (46.0–60.1%) and foliage (38.2–61.1%).

Table 1 Radioactivity in surface washes, extracts and residues from the mature harvest of grapes and foliage

	Grapes (fruit)				Foliage (leaves)			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Surface wash	0.23	31.6	0.30	46.9	5.76	34.0	8.54	53.5
Extracts*	0.41	56.8	0.30	46.2	8.37	49.5	5.24	32.8
Others	0.02	2.5	0.01	0.8	1.86	10.9	0.74	4.7
Unextracted	0.07	9.0	0.04	6.1	0.93	5.5	1.44	9.0
Total	0.72	99.9	0.64	100	16.93	99.9	15.96	100

* acetonitrile + acetonitrile:water extracts

Two metabolites were identified by co-chromatography with authentic reference compounds, glucoside of 4HP (max 10.0% TRR) and 3-MTCAM (max 4.0% TRR). 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 of metabolites produced during work-up contained mixtures of metabolites, maximum levels of any single compound in this fraction of foliage were less than 4% TRR. It was not possible to obtain good chromatography of the corresponding fraction from grapes as the amounts of residue involved were low (<10% TRR and 0.04–0.06 mg equiv/kg). It is considered that several metabolites would have been present in the polar fraction from grapes.

Table 2 Nature of the radioactive residues (sum of surface washes and analysed plant extracts) in grapes and foliage

Components	Grapes (fruit)				Foliage (leaves)			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Extract	0.64	88.4	0.60	93.2	14.1	83.4	13.8	86.3
Isofetamid	*0.33*	*46.0*	*0.39*	*60.1*	*6.48*	*38.2*	*9.75*	*61.1*
3-MTCAM	*NA*	*NA*	*0.01*	*1.7*	*NA*	*NA*	*0.65*	*4.0*
Glucoside of 4HP	*0.07*	*10.0*	*0.02*	*3.4*	*0.81*	*4.8*	*0.50*	*3.1*
Polar	*0.01*	*1.6*	*0.04*	*6.0*	*1.71*	*10.1*	*0.62*	*3.9*
Unknowns	*0.17*	*23.1*	*0.07*	*11.1*	*4.71*	*27.8*	*0.86*	*5.4*
Maximum single unknown	*0.06*	*8.0*	*0.01*	*2.0*	*0.93*	*5.5*	*0.27*	*1.7*

NA: Not applicable

Lettuce

The metabolism of [^{14}C]-isofetamid was investigated in lettuce (variety Saladin) following three applications of [phenyl-^{14}C]-isofetamid or [thiophene-^{14}C]-isofetamid at a rate of 0.75 kg ai/ha (Lewis, 2012: 2244/070). Lettuces were treated on three occasions with either one or the other of two radiolabelled forms of isofetamid, as SC formulation. The application interval between treatments was 14 days and the final application was conducted 18 days prior to the harvest of mature lettuces. Plants were maintained in an outdoor enclosure and were grown to maturity. Lettuces (the leafy part above ground) from the [^{14}C]-isofetamid treated crops were harvested on two occasions corresponding to immature and mature harvest. One lettuce per treatment was taken for the immature harvest (7 DALA) and three lettuces were left for the mature harvest (18 DALA). Control lettuces were taken at mature harvest only. At each sampling occasion, dead and withered leaves were removed.

The surface of the treated and control samples harvested at maturity was washed with acetonitrile and portions of the wrapper leaves and heads were homogenised prior to extraction. Sub-samples of the homogenates were extracted sequentially with acetonitrile, acetonitrile:water (1:1 v/v) and water. Samples were further extracted with 0.1 M hydrochloric acid, 0.1 M sodium hydroxide solution and acetone. Radioactivity in the extracts was determined by LSC. The amount of radioactivity remaining unextracted in the solid residue was determined by combustion analysis. TRR values were determined by summation of extracted and unextracted radioactivity and were compared to direct combustions of unextracted samples to check recovery. Sub-samples of the acetonitrile and acetonitrile:water extracts were combined and cleaned-up by solid phase extraction prior to concentration and analysis by HPLC. Metabolites were confirmed by TLC with authentic reference standards.

Polar compounds, defined as those with little to no retention in the HPLC method used, were further characterised by TLC. The maximum level of a single metabolite in the polar fraction following treatment of plants with the thiophene label was 6% TRR. There were no unidentified compounds present in lettuce plants at >10% TRR.

TRRs in lettuce leaves after three foliar applications of isofetamid at a rate of 0.75 kg ai/ha were in the range 1.7–2.6 mg equiv/kg (wrapper leaves) and 0.07–0.09 mg equiv/kg (lettuce heads) at mature harvest. Most (> 90% TRR) of this residue was recovered in surface rinses with acetonitrile or was extracted from the plants in acetonitrile or acetonitrile:water. More than 90% TRR of each commodity (wrapper leaves or heads) was characterised by HPLC and/or by TLC.

Table 3 Radioactivity in surface washes, extracts and residues from lettuce

	Wrapper leaves				Lettuce heads			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Surface wash	1.67	65.1	0.83	49.1	0.03	40.5	0.04	42.4
Extracts*	0.80	31.3	0.70	41.7	0.03	52.2	0.05	52.3

	Wrapper leaves				Lettuce heads			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Others	0.05	1.9	0.06	3.8	0.001	1.2	0.003	2.6
Unextracted	0.04	1.7	0.09	5.6	0.004	6.0	0.003	2.8
Total	2.56	100	1.69	100	0.07	99.9	0.09	100

* acetonitrile + acetonitrile:water extracts

Surface rinses contained mainly parent compound and plant extracts contained parent compound with metabolites. Parent compound was the main component of the TRR (57–73% TRR). Three metabolites were identified by co-chromatography with authentic reference compounds, 4HP (max 3% TRR), glucoside of 4HP (max 10% TRR) and 3-MTCAM (max 2% TRR). Polar compounds, defined as those with little to no retention in the HPLC method used, were further characterised by TLC. The maximum level of a single metabolite in the polar fraction following treatment of plants with the thiophene label was 6% TRR. There were no unidentified compounds present in lettuce plants at >10% TRR.

Table 4 Nature of the radioactive residues (sum of surface washes and analysed extracts) in lettuce

Components	Wrapper leaves				Lettuce heads			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Extract	2.47	96.4	1.53	90.8	0.06	92.7	0.08	94.7
Isofetamid	*1.87*	*72.9*	*1.04*	*61.8*	*0.04*	*66.4*	*0.05*	*56.7*
4HP	*0.02*	*1.0*	*0.03*	*1.5*	*< 0.01*	*3.1*	*< 0.01*	*3.3*
3-MTCAM	*NA*	*NA*	*0.04*	*2.4*	*NA*	*NA*	*< 0.01*	*1.1*
Glucoside of 4HP	*0.14*	*5.3*	*0.11*	*6.6*	*0.01*	*10.1*	*0.01*	*9.4*
Polar	*0.07*	*2.8*	*0.12*	*7.2*	*< 0.01*	*6.2*	*0.01*	*11.1*
Unknowns	*0.36*	*14.0*	*0.18*	*10.9*	*< 0.01*	*5.7*	*0.01*	*10.0*
Maximum single unknown	*0.11*	*4.5*	*0.05*	*3.0*	*< 0.01*	*1.2*	*< 0.01*	*1.6*

NA: Not applicable

French beans

The metabolism of [^{14}C]-isofetamid was investigated in French bean (variety Algarve) following three foliar applications of [phenyl-^{14}C]-isofetamid or [thiophene-^{14}C]-isofetamid at a rate of 0.75 kg ai/ha (Lewis, 2012: 2244/071).

French bean plants were treated on three occasions with either one or the other of two radiolabeled forms of isofetamid, as SC formulation. The first application was at the beginning of flowering (BBCH 60–61) and the application interval between treatments was 8 days. The plants were maintained in an outdoor enclosure. There were three harvests from the [^{14}C]-isofetamid treated crops. The first harvest was immediately after the final application and the whole plant (leafy above ground parts) was taken as one sample. The second harvest was 14 DALA and the plants were separated into forage and green beans. The green beans were further separated into pods and seeds. The third harvest was 68 DALA when the plants had died back, had lost most of their leaves and appeared like bean straw. The plants were separated into bean straw, pods and seeds. Control plants were harvested once, 12 days before the final harvest of treated plants (because they matured earlier). They were separated into bean straw, pods and seeds.

The surface of the treated and control samples were washed with acetonitrile prior to freezing and the surface wash kept for analysis. Sub-samples of homogenised sample (5 replicates) were taken for initial overall residue determination by sample oxidation and LSC. A sub-sample (50 g) of each homogenate was extracted by maceration three times with acetonitrile, followed by three times with acetonitrile:water (1:1 v/v) and three times with water. Samples were further extracted by maceration twice with 0.1M hydrochloric acid, followed by twice with 0.1M sodium hydroxide solution and once

with acetone. Each solvent extract was kept separate and analysed by LSC. Sub-samples of the acetonitrile and acetonitrile:water extracts were combined, cleaned-up by passing through an C_{18} SPE column and concentrated on a rotary evaporator prior to analysis by HPLC. The amount of radioactivity remaining unextracted in the solid residue was determined by combustion analysis. TRR values were determined by LSC of appropriate extracts and combusted residues. The TRR in each sample was calculated from the sum of the radioactivity in the extracts and the radioactivity remaining unextracted.

TRR in forage (10.5–11.6 mg equiv/kg) and straw (3.3–4.9 mg equiv/kg) were higher than in pods (0.21–0.41 mg equiv/kg) or seeds (0.03–0.40 mg equiv/kg) after three foliar applications of isofetamid at a rate of 0.75 kg ai/ha. Most (> 90% TRR) of the residue in forage, straw, pods and second harvest seeds was recovered in surface wash with acetonitrile or was extracted from the plants in acetonitrile or acetonitrile:water extracts. Seeds at the third harvest had very low residues (0.03–0.06 mg equiv/kg) which were less readily extracted. More than 90% TRR of each commodity (except for third harvest seeds) was characterised by HPLC and/or by TLC.

Table 5 Radioactivity in surface washes, extracts and residues from the first harvest of French beans

	Whole plant			
	Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR
Surface wash	13.7	61.5	18.2	71.4
Extracts*	8.45	37.8	7.08	27.8
Others	0.02	0.1	0.04	0.1
Unextracted	0.12	0.5	0.18	0.7
Total	22.3	99.9	25.5	99.9

* acetonitrile + acetonitrile:water extracts

Table 6 Radioactivity in surface washes, extracts and residues from the second harvest of French beans

	Bean forage				Immature pods				Immature seeds			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Surface wash	6.39	60.6	5.23	45.1	0.12	46.0	0.13	31.7	0.08	53.9	0.11	27.6
Extracts*	3.88	36.9	5.87	50.6	0.14	52.6	0.27	65.0	0.06	44.6	0.28	68.8
Others	0.13	1.3	0.21	1.8	ND	ND	0.01	2.0	ND	ND	0.01	3.0
Unextracted	0.14	1.4	0.29	2.5	< 0.01	1.4	0.01	1.4	< 0.01	1.5	< 0.01	0.7
Total	10.5	100	11.6	100	0.26	100	0.41	100	0.14	100	0.40	100

* acetonitrile + acetonitrile:water extracts

Table 7 Radioactivity in surface washes, extracts and residues from the third harvest of French beans

	Bean straw				Mature pods				Mature seeds			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Surface wash	1.59	48.6	2.89	58.5	0.05	22.3	0.06	15.8	ND	ND	ND	ND
Extracts*	1.48	45.4	1.70	34.4	0.15	72.6	0.29	76.9	0.01	32.2	0.04	57.3
Others	0.09	2.8	0.17	3.5	< 0.01	1.5	0.02	4.8	0.01	47.3	0.02	26.1
Unextracted	0.11	3.2	0.18	3.6	0.01	3.6	0.01	2.5	0.01	20.6	0.01	16.6
Total	3.27	100	4.94	100	0.21	100	0.37	100	0.03	100	0.06	100

* acetonitrile + acetonitrile:water extracts

Surface washes contained mainly parent compound and plant extracts contained parent compound with metabolites. Parent compound was the main individual component in forage (76.8–77.1% TRR), straw (52.6–62.0% TRR), second harvest pods (68.7–80.8% TRR), and second harvest

seeds (28.0–49.7% TRR). In third harvest pods parent compound was the major single component (18.2–36.4% TRR) but polar radioactivity was a major component (26.0–49.1% TRR). In third harvest seeds, parent compound was only a minor component (0.5–1.1% TRR) and polar radioactivity was the major component (22.4–50.5% TRR), but with a very low associated radioactive residue (0.01–0.03 mg equiv/kg).

Four metabolites were identified by co-chromatography with authentic reference compounds, 4HP (max 1.1% TRR), glucoside of 4HP (max 7.4% TRR), 3-MTCAM (max 6.6% TRR) and IBA (max 0.5% TRR). 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 was 12% TRR after treatment with the thiophene label and 11% TRR after treatment with the phenyl label. Enzyme hydrolysis tests showed that there was at least one conjugate present after treatment with the thiophene label and at least two or three after treatment with the phenyl label. The polar metabolites are therefore likely to be mixtures of conjugated compounds.

Table 8 Nature of the radioactive residues (sum of surface washes and analysed extracts) from the first harvest of French beans

Components	Whole plant			
	Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR
Extract	22.2	99.3	25.2	99.2
Isofetamid	*20.7*	*92.6*	*23.2*	*91.0*
4HP	*ND*	*ND*	*0.07*	*0.3*
3-MTCAM	*NA*	*NA*	*0.84*	*3.3*
IBA	*0.11*	*0.5*	*NA*	*NA*
Maximum single unknown	*0.24*	*1.1*	*0.11*	*0.5*

NA: Not applicable

Table 9 Nature of the radioactive residues (sum of surface washes and analysed extracts) from the second harvest of French beans

Components	Forage				Immature pods				Immature seeds			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Extract	10.3	97.5	11.1	95.7	0.26	98.6	0.40	96.7	0.14	98.5	0.39	96.4
Isofetamid	*8.12*	*77.1*	*8.90*	*76.8*	*0.21*	*80.8*	*0.28*	*68.7*	*0.07*	*49.7*	*0.11*	*28.0*
4HP	*ND*	*ND*	*0.02*	*0.2*	*ND*	*ND*	*ND*	*ND*	-	-	-	-
3-MTCAM	*NA*	*NA*	*0.76*	*6.6*	*NA*	*NA*	*< 0.01*	*0.6*	*NA*	*NA*	*< 0.01*	*0.9*
3-MTCA	*NA*	*NA*	*0.01*	*0.1*	-	-	-	-	-	-	-	-
IBA	*0.06*	*0.5*	*NA*	*NA*	*ND*	*ND*	*NA*	*NA*	-	-	-	-
Glucoside of 4HP	*0.17*	*1.7*	*0.20*	*1.7*	*0.01*	*4.7*	-	-	-	-	-	-
Polar	*0.11*	*1.1*	*0.25*	*2.2*	*0.01*	*2.8*	*0.10*	*23.9*	*0.03*	*17.1*	*0.11*	*28.1*
Maximum single unknown	*0.42*	*4.0*	*0.18*	*1.6*	*0.01*	*2.9*	*0.01*	*1.8*	*0.01*	*3.6*	*0.03*	*7.4*

NA: Not applicable

Table 10 Nature of the radioactive residues (sum of surface washes and analysed extracts) from the third harvest of French beans

Components	Straw				Mature pods				Mature seeds			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Extract	3.08	94.0	4.60	92.9	0.20	94.9	0.35	92.7	0.01	32.2	0.04	57.3
Isofetamid	*1.72*	*52.6*	*3.07*	*62.0*	*0.08*	*36.4*	*0.07*	*18.2*	*< 0.01*	*1.1*	*< 0.01*	*0.5*
4HP	*ND*	*ND*	*0.05*	*1.1*	-	-	-	-	-	-	-	-

Components	Straw				Mature pods				Mature seeds			
	Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C		Phenyl-^{14}C		Thiophene-^{14}C	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
3-MTCAM	*NA*	*NA*	*0.23*	*4.6*	-	-	-	-	-	-	-	-
Glucoside of 4HP	*0.16*	*5.0*	*0.24*	*4.8*	*0.02*	*7.4*	-	-	-	-	-	-
Polar	*0.24*	*7.2*	*0.22*	*4.5*	*0.06*	*26.0*	*0.18*	*49.1*	*0.01*	*22.4*	*0.03*	*50.5*
Maximum single unknown	*0.14*	*4.4*	*0.14*	*2.9*	*0.01*	*6.7*	*0.01*	*3.4*	*< 0.01*	*1.3*	*< 0.01*	*1.5*

NA: Not applicable

Summary of plant metabolism

Metabolism of ^{14}C labelled isofetamid has been studied in grapes, lettuce and French beans, which are suitable to cover the crop groups of fruits, leafy crops and pulses. Isofetamid is the major component of the residues found in grapes, lettuce, and French beans. Isofetamid is primarily metabolized in plants by O-dealkylation to 4HP and subsequent conjugation to form glucoside of 4HP. One other degradation pathway includes cleavage of the ring systems to form 3-MTCAM and IBA. The following metabolic pathway was derived from the plant metabolism studies available.

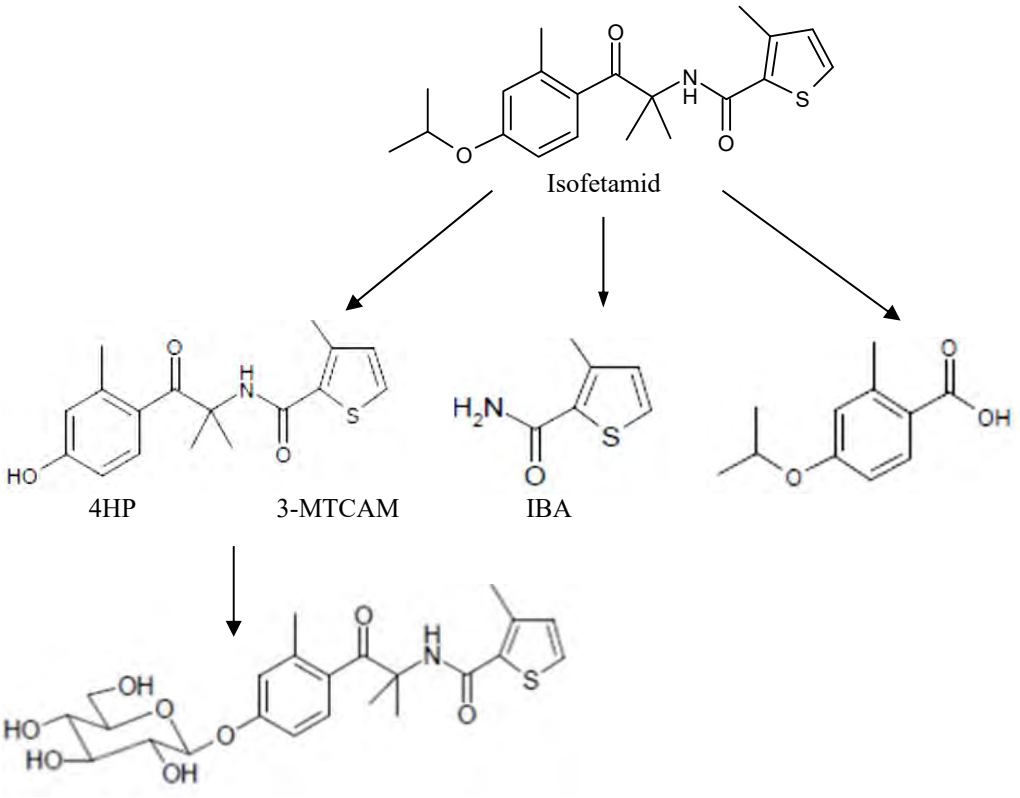


Figure 2: Metabolic Pathway of Isofetamid in Plants (grape, lettuce and French beans)

Farm Animal metabolism

The Meeting received studies on the metabolism of isofetamid in lactating goat and laying hens.

Lactating goat

The absorption, distribution and excretion of [^{14}C]-isofetamid were investigated following repeated oral administration of phenyl or thiophene radiolabelled isofetamid to the lactating goat (Hardwick, 2012: 2244/083). Each radiolabelled form of [^{14}C]-isofetamid was orally administered daily for 7 consecutive days to lactating goats at a dose level of 10 ppm in the diet. Urine and faeces were collected daily and milk collected twice daily. Approximately 23 hours following the final dose administration the goats were sacrificed by anaesthetic overdose. Liver, kidney, muscle and fat were either excised or sampled as appropriate. Milk was split into the fat and aqueous fractions. Radioactivity was determined in all samples by direct LSC or following solubilisation. Tissue and milk samples were extracted by various methods and subjected to metabolite profiling and identification.

The mean dose in animals dosed with [^{14}C-phenyl]-isofetamid was 10.0 ppm in the diet and, in animals dosed with [^{14}C-thiophene]-isofetamid was 9.8 ppm in the diet. Recovery of radioactivity was *ca* 90% of the administered dose. The majority of the administered dose, *ca* 52%, was eliminated in faeces. Urinary excretion accounted for *ca* 32 to 35% of the dose. Low levels of radioactivity were detected in both the aqueous and fat fractions of milk. Steady state conditions were achieved within three days in both aqueous and fat fractions of milk for both radiolabels. Radioactivity was detected in all tissues and milk fractions *ca* 23 hours after the last dose administration.

Following administration of [^{14}C-phenyl]-isofetamid, concentrations were 0.436 mg equiv/kg in liver, 0.072 mg equiv/kg in kidneys, 0.007 mg equiv/kg in flank muscle, 0.005 mg equiv/kg in loin muscle, 0.052 mg equiv/kg in omental fat, 0.054 mg equiv/kg in renal fat and 0.040 mg equiv/kg in subcutaneous fat. Concentrations of radioactivity were 0.044 mg equiv/kg in blood and plasma. Concentrations of radioactivity in the aqueous fraction of milk reached a maximum of 0.011 mg equiv/L on day 4 *pm* and, in the fat fraction of milk, reached a maximum of 0.16 mg equiv/kg on day 1 *pm*.

Following administration of [^{14}C-thiophene]-isofetamid, concentrations were 0.357 mg equiv/kg in liver, 0.105 mg equiv/kg in kidneys, 0.006 mg equiv/kg in flank muscle, 0.004 mg equiv/kg in loin muscle, 0.014 mg equiv/kg in omental fat, 0.012 mg equiv/kg in renal fat and 0.012 mg equiv/kg in subcutaneous fat. Concentrations of radioactivity were 0.034 mg equiv/kg in blood and 0.037 mg equiv/kg in plasma. Concentrations of radioactivity in the aqueous fraction of milk reached a maximum of 0.007 mg equiv/L on day 4 *pm*; in the fat fraction of milk, a maximum of 0.048 mg equiv/kg was reached on day 3 *pm.*

Table 11 Recovery of radioactivity in lactating goats following oral administration of [^{14}C]-isofetamid at a nominal dose level of 10 ppm in the diet

Sample	% of administered dose	
	[^{14}C-phenyl]	[^{14}C-thiophene]
Urine	32.8	35.1
Faeces	53.3	50.7
Cage wash	5.26	3.33
Milk fat fraction	0.017	0.009
Milk aqueous fraction	0.026	0.029
Tissues	0.402	0.416
Total	91.8	89.5

Table 12 Recovery of radioactivity in milk of lactating goats following oral administration of [^{14}C]-isofetamid at a nominal dose level of 10 ppm in the diet

Sampling time		[^{14}C-phenyl]				[^{14}C-thiophene]			
		Aqueous fraction		Fat fraction		Aqueous fraction		Fat fraction	
		mg/L eq	%AR	mg/kg eq	%AR	mg/L eq	%AR	mg/kg eq	%AR
Day 1	am	NA	NA	NA	NA	NA	NA	NA	NA
	pm	0.011	0.002	0.16	0.002	0.005	0.003	0.036	0.001
Day 2	am	0.003	0.002	0.016	< 0.001	0.003	0.002	0.009	< 0.001

Sampling time		[^{14}C-phenyl]				[^{14}C-thiophene]			
		Aqueous fraction		Fat fraction		Aqueous fraction		Fat fraction	
		mg/L eq	%AR	mg/kg eq	%AR	mg/L eq	%AR	mg/kg eq	%AR
	pm	0.007	0.001	0.088	0.002	0.007	0.003	0.037	0.001
Day 3	am	0.003	0.002	0.018	0.001	0.003	0.001	0.009	< 0.001
	pm	0.005	0.001	0.074	0.001	0.007	0.002	0.048	0.001
Day 4	am	0.004	0.002	0.022	0.001	0.003	0.002	0.010	< 0.001
	pm	0.011	0.002	0.092	0.001	0.007	0.004	0.041	0.001
Day 5	am	0.004	0.002	0.031	0.001	0.003	0.002	0.010	< 0.001
	pm	0.009	0.002	0.13	0.002	0.006	0.003	0.041	0.001
Day 6	am	0.003	0.002	0.027	0.001	0.003	0.001	0.012	< 0.001
	pm	0.007	0.001	0.097	0.003	0.006	0.003	0.039	0.001
Day 7	am	0.004	0.002	0.027	0.001	0.004	0.002	0.011	< 0.001
	pm	0.007	0.001	0.11	0.002	0.004	0.002	0.018	0.001
Day 8	am	0.004	0.002	0.028	0.001	0.004	0.001	0.015	0.001
	pm	NA	NA	NA	NA	NA	NA	NA	NA
Total			0.026		0.017		0.029		0.009

Table 13 Recovery of radioactivity in tissues of lactating goats following oral administration of [^{14}C]-isofetamid at a nominal dose level of 10 ppm in the diet

Sample	[^{14}C-phenyl]		[^{14}C-thiophene]	
	mg/kg eq	% of administered dose	mg/kg eq	% of administered dose
Kidney	0.072	0.008	0.105	0.013
Liver	0.436	0.323	0.357	0.384
Muscle (flank)	0.007	0.003	0.006	0.001
Muscle (loin)	0.005	0.001	0.004	< 0.001
Omental fat	0.052	0.031	0.014	0.012
Renal fat	0.054	0.035	0.012	0.005
Subcutaneous fat	0.040	0.001	0.012	< 0.001
Total	0.666	0.402	0.510	0.415

Table 14a Characterization and identification of radioactive residues in tissues of lactating goat following oral administration of [^{14}C]-isofetamid at a nominal dose level of 10 ppm in the diet

Compound	TRR, mg/kg ([^{14}C-phenyl])									
	Milk aqueous fraction		Milk fat fraction		Liver		Kidney		Fat	
	mg/L eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
TRR	0.011	100	0.130	100	0.436	100	0.072	100	0.053	100
Extract	0.007	62.9	0.129	99.0	0.156	35.7	0.044	61.0	0.046	88.0
Identified	0.002	19.1	0.101	77.1	0.063	14.5	0.008	11.0	0.033	62.2
Isofetamid	*0.002*	*17.3*	*0.099*	*76.1*	*0.010*	*2.3*	*0.0004*	*0.6*	*0.033*	*62.2*
5-HPPA	*NA*	-	*NA*	-	*0.008*	*1.9*	*NA*	-	*NA*	-
4HP	*NA*	-	*NA*	-	*0.011*	*2.5*	*0.003*	*4.0*	*NA*	-
IBA	*NA*	-	*NA*	-	*0.006*	*1.3*	*NA*	-	*NA*	-
PPA	*0.0002*	*1.8*	*0.001*	*1.0*	*0.029*	*6.6*	*0.005*	*6.4*	*NA*	-
Protease digest + hydrolysis	NA	-	NA	-	0.247	56.6	0.018	25.6	NA	-
Unextracted	0.004	37.1	0.001	1.0	0.034	7.7	0.010	13.4	0.006	12.0

Table 14b Characterization and identification of radioactive residues in tissues of lactating goat following oral administration of [^{14}C]-isofetamid at a nominal dose level of 10 ppm in the diet

Compound	TRR, [^{14}C-thiophene]							
	Milk fat fraction		Liver		Kidney		Fat	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
TRR	0.048	100	0.357	100	0.105	100	0.013	100
Extract	0.044	90.5	0.187	52.5	0.075	71.6	0.010	71.3
Identified	0.015	30.8	0.103	29.0	0.026	24.4	0.007	53.4

Compound	TRR, [^{14}C-thiophene]							
	Milk fat fraction		Liver		Kidney		Fat	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
Isofetamid	*0.012*	*25.6*	*0.007*	*2.0*	*NA*	-	*0.006*	*44.4*
3-MTCAM	*NA*	-	*0.004*	*1.1*	*NA*	-	*NA*	-
5-HPPA	*NA*	-	*0.020*	*5.6*	*NA*	-	*NA*	-
4HP	*NA*	-	*0.011*	*2.9*	*0.005*	*4.9*	*0.0004*	*3.0*
PPA	*0.003*	*5.2*	*0.062*	*17.3*	*0.021*	*19.5*	*0.0008*	*6.0*
Protease digest + hydrolysis	NA	-	0.166	46.6	0.020	18.6	NA	-
Unextracted	0.005	9.5	0.003	0.9	0.010	9.8	0.004	28.7

NA= not analysed

Residues in the tissues were not totally extractable with organic solvents or polar solvents most noticeably following administration of [^{14}C-phenyl]-isofetamid. Following administration of [^{14}C-phenyl]-isofetamid, 36% TRR (0.156 mg equiv/kg) of liver residues and 61% TRR (0.044 mg equiv/kg) of kidney residues were extracted with organic and aqueous solvents. Following administration of [^{14}C-thiophene]-isofetamid, 53% TRR (0.187 mg equiv/kg) of liver residues and 72% TRR (0.075 equiv/kg) of kidney residues were extracted with organic and aqueous solvents. The remaining residues were released only following protease digestion or vigorous acidic hydrolysis. The more aggressive extraction methods may have converted the residues to different components which may or may not have been present in the original sample. The metabolism of [^{14}C]-isofetamid was extensive, with individual extracts from tissues containing up to 22 peaks or diffuse region of interest, many of which were considered to be multi-component. A number of radioactive residues, following both more and less aggressive extraction techniques, shared chromatogramphic properties with parent compound and supplied metabolite standards.

Following administration of [^{14}C-phenyl]-isofetamid, less than 0.10 mg/kg (76.1% TRR) of the residues from individual tissues showed similar chromatographic properties to isofetamid. Following administration of [^{14}C-thiophene]-isofetamid, less than 0.012 mg/kg (25.6% TRR) of the residues from individual tissues showed similar chromatographic properties to isofetamid. Identified residues, from animals dosed with [^{14}C-phenyl]-isofetamid, were 4HP, PPA, IBA, 5-HPPA and isofetamid. Identified residues, from animals dosed with [^{14}C-thiophene]-isofetamid, were 3-MTCAM, 4HP, PPA, 5-HPPA and isofetamid. Only isofetamid and PPA accounted for greater than 0.050 mg/kg.

No other individual residue was present in an individual matrix at a level greater than 0.033 mg/kg. From the identification of the residues, the parent compound was the major component in milk with PPA being a minor component. Although difficulty was experienced extracting residues, the TRR in any sample accounted for <0.5% of the administered dose.

Laying hens

The absorption, distribution, metabolism and excretion of [^{14}C]-isofetamid were investigated following repeated oral administration of phenyl or thiophene radiolabelled isofetamid to the laying hen (Hardwick, 2012: 2244/082). Each radiolabelled form of [^{14}C]-isofetamid was orally administered daily for 14 days to groups of laying hens at a dose level of 10 ppm in the diet. Excreta were collected daily and eggs collected twice daily. Approximately 23 hours following the final dose administration the hens were sacrificed by cervical dislocation. Liver, skin, muscle and fat were either excised or sampled as appropriate. Radioactivity was determined in all samples by direct liquid scintillation counting (LSC) or following solubilisation. Tissue and egg samples were extracted by various methods and subjected to metabolite profiling and identification.

The mean dose in animals dosed with [^{14}C-phenyl]-isofetamid was 13.5 ppm in the diet and, in animals dosed with [^{14}C-thiophene]-isofetamid was 12.7 ppm in the diet. Recovery of radioactivity was essentially quantitative. Steady state conditions were achieved within 8 days in egg yolk and 4

days in egg white. Radioactivity was detected in all tissues and eggs *ca* 23 hours after the last dose administration.

In animals dosed with [^{14}C-phenyl]-isofetamid, concentrations were 0.207 mg equiv/kg in liver, 0.025 mg equiv/kg in pooled muscle, 0.035 mg equiv/kg in skin and 0.070 mg equiv/kg in pooled fat. Maximum concentrations of radioactivity in egg yolk were 0.22 mg equiv/kg on day 14 and were 0.006 mg equiv/kg in egg white on day 4.

In animals dosed with [^{14}C-thiophene]-isofetamid, concentrations were 0.180 mg equiv/kg in liver, 0.023 mg equiv/kg in pooled muscle, 0.030 mg equiv/kg in skin and 0.036 mg equiv/kg in pooled fat. Maximum concentrations of radioactivity in egg yolk were 0.18 mg equiv/kg on day 15 and were 0.007 mg equiv/kg in egg white on day 6.

Table 15 Mean recovery of radioactivity in group of laying hens following oral administration of [^{14}C]-isofetamid at a nominal dose level of 10 ppm in the diet

Sample	% of administered dose	
	[^{14}C-phenyl]	[^{14}C-thiophene]
Excreta	116	103
Egg white	0.008	0.009
Egg yolk	0.158	0.120
Tissues	0.051	0.045
Cage wash	1.33	1.09
Total	117	104

Table 16 Recovery of radioactivity in egg of laying hens following oral administration of [^{14}C]-isofetamid at a nominal dose level of 13 ppm in the diet

Sampling time	[^{14}C-phenyl]				[^{14}C-thiophene]			
	Egg white		Egg yolk		Egg white		Egg yolk	
	mg/kg eq	%AR	mg/kg eq	%AR	mg/kg eq	%AR	mg/kg eq	%AR
Day 2	0.001	< 0.001	< 0.001	< 0.001	0.003	< 0.001	0.001	< 0.001
Day 3	0.005	0.001	0.019	0.001	0.003	< 0.001	0.012	< 0.001
Day 4	0.006	0.001	0.066	0.005	0.006	0.001	0.034	0.002
Day 5	0.005	0.001	0.10	0.007	0.004	0.001	0.087	0.011
Day 6	0.005	0.001	0.15	0.011	0.007	0.001	0.15	0.006
Day 7	0.003	< 0.001	0.18	0.013	0.005	0.001	0.15	0.012
Day 8	0.005	0.001	0.19	0.017	0.005	< 0.001	0.16	0.008
Day 9	0.003	< 0.001	0.20	0.014	0.005	0.001	0.16	0.012
Day 10	0.004	0.001	0.20	0.014	0.005	0.001	0.17	0.010
Day 11	0.005	0.001	0.20	0.014	0.004	< 0.001	0.17	0.008
Day 12	0.006	0.001	0.19	0.014	0.006	0.001	0.16	0.013
Day 13	0.004	0.001	0.21	0.015	0.006	0.001	0.17	0.010
Day 14	0.004	0.001	0.22	0.016	0.005	0.001	0.18	0.014
Day 15	0.003	< 0.001	0.22	0.016	0.005	0.001	0.18	0.014
Total		0.008		0.158		0.009		0.120

Table 17 Mean recovery of radioactivity in tissues of laying hens following oral administration of [^{14}C]-isofetamid at a nominal dose level of 13 ppm in the diet

Sample	[^{14}C-phenyl]		[^{14}C-thiophene]	
	mg/kg	% of administered dose	mg/kg	% of administered dose
Fat (peritoneal)	0.014	0.002	0.009	0.002
Fat (perirenal)	0.051	< 0.001	0.027	< 0.001
Muscle (breast)	0.010	0.004	0.009	0.003
Muscle (thigh)	0.015	0.002	0.014	0.001
Liver	0.207	0.041	0.180	0.038
Skin	0.035	0.002	0.030	0.001
Total	0.333	0.051	0.269	0.045

Table 18 Characterization and identification of radioactive residues in tissues of laying hen following oral administration of [^{14}C]-isofetamid at a nominal dose level of 13 ppm in the diet

Compound	TRR, mg/kg ([^{14}C-phenyl])									
	Egg yolk		Liver		Muscle		Fat		Skin	
	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR	mg/kg eq	%TRR
TRR	0.216	100	0.207	100	0.011	100	0.015	100	0.035	100
Extract	0.102	47.0	0.095	45.9	0.004	33.4	0.012	79.2	0.021	59.1
Identified	0.018	8.2	0.030	14.6	0.000	0.9	0.001	9.6	0.001	1.7
Isofetamid	*0.002*	*0.9*	*0.001*	*0.4*	*NA*	-	*0.001*	*6.2*	*NA*	-
Mw180 & 209	*NA*	-	*0.012*	*5.9*	*NA*	-	*NA*	-	*NA*	-
4HP	*0.009*	*4.1*	*0.004*	*1.9*	*0.000*	*0.9*	*0.001*	*3.4*	*NA*	-
PPA	*0.006*	*2.8*	*0.009*	*4.1*	*NA*	-	*NA*	-	*0.001*	*1.7*
IBA	*0.001*	*0.5*	*0.005*	*2.3*	*NA*	-	*NA*	-	*NA*	-
Protease digest + hydrolysis	0.099	45.6	0.085	40.9	NA	-	NA	-	0.011	32.6
Unextracted	0.016	7.4	0.028	13.2	0.007	66.6	0.003	20.8	0.003	8.3
Compound	TRR, mg/kg ([^{14}C-thiophene])									
	Egg yolk		Liver		Muscle		Fat		Skin	
	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR
TRR	0.176	100	0.180	100	0.011	100	0.010	100	0.030	100
Extract	0.091	51.5	0.080	44.3	0.003	27.0	0.007	68.5	0.019	62.0
Identified	0.009	4.8	0.008	4.4	NA	-	0.002	15.5	0.001	2.0
Isofetamid	*0.002*	*1.1*	*NA*	-	*NA*	-	*0.001*	*11.3*	*NA*	-
3-MTCAM	*0.002*	*1.1*	*NA*	-	*NA*	-	*NA*	-	*NA*	-
4HP	*0.003*	*1.8*	*0.005*	*2.8*	*NA*	-	*0.000*	*4.1*	*0.001*	*2.0*
PPA	*0.001*	*0.8*	*0.003*	*1.6*	*NA*	-	*NA*	-	*NA*	-
Protease digest + hydrolysis	0.081	45.9	0.071	39.4	NA	-	NA	-	0.011	35.4
Unextracted	0.004	2.6	0.030	16.3	0.008	73.0	0.003	31.5	0.001	2.6

NA= not analysed -: not provided

Residues in the tissues and egg yolk were not readily extractable with organic solvents or polar solvents; up to 79% of the TRR was extracted from each tissue. The residues were released only following protease digestion or vigorous acidic hydrolysis. The more aggressive extraction methods may have converted the residues to different components which may or may not have been present in the original sample. The metabolism of [^{14}C]-isofetamid was extensive, with individual extracts from tissues containing up to 21 peaks or diffuse regions of interest, many of which were considered to be multi-component. A number of radioactive residues, following both more and less aggressive extraction techniques, shared chromatogramphic properties with parent compound and supplied metabolite standards but at levels below 0.01 mg/kg in each extraction matrix.

Less than 0.004 mg equiv/kg of the residues from all tissues showed similar chromatographic properties to parent compound, isofetamid. Identified residues, from animals dosed with [^{14}C-phenyl]-isofetamid, were 4HP, PPA, IBA and isofetamid plus two minor residues identified by HPLC/MS with molecular weights of 180 and 209. Identified residues, from animals dosed with [^{14}C-thiophene]-isofetamid, were 3-MTCAM, 4HP, PPA, and isofetamid. 3-MTCAM was only detected at low levels in egg yolk following acid reflux.

None of the residues in individual matrices accounted for greater than 0.013 mg equiv/kg. From the identification of the residues, the parent compound was not a significant component in the tissues or eggs. Although difficulty was experienced extracting residues, the TRR in any sample accounted for < 0.2% of the administered dose. Only the livers, from both groups, and perirenal fat, from animals dosed with [^{14}C-phenyl]-isofetamid, contained total radioactive residues above 0.050 mg equiv/kg.

Summary of animal metabolism

The metabolism of ^{14}C labelled isofetamid has been studied in lactating goat and laying hens. In both studies, isofetamid was shown to undergo extensive metabolism the major routes being O-dealkylation, carboxylation and subsequent hydroxylation and cleavage between the phenyl and thiophene ring structures. There were only minor quantitative and qualitative differences in metabolism due to the position of the radiolabel in the metabolism of isofetamid. The following metabolic pathways were proposed based upon the animal metabolism studies available.

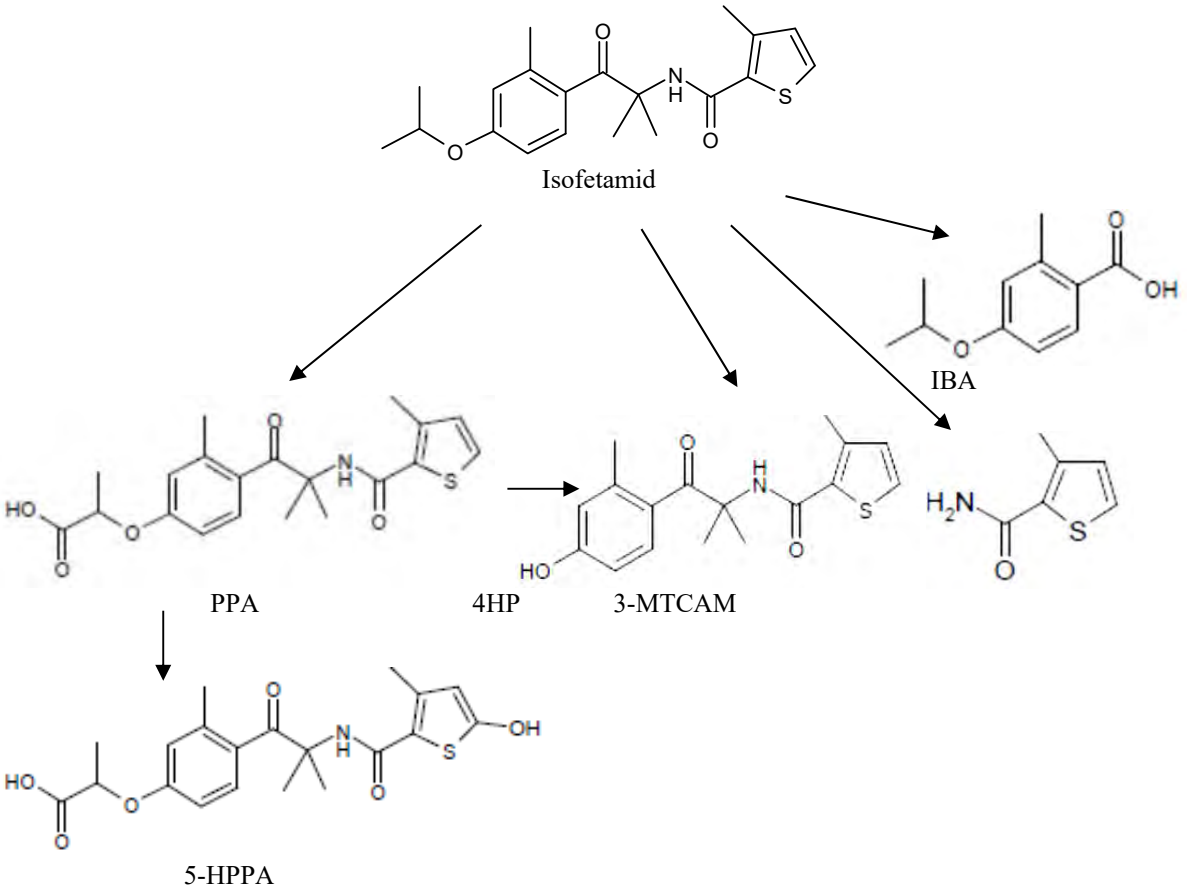


Figure 4: Metabolic Pathway of Isofetamid in Animals (lactating goat and laying hen)

Rotational crop studies

Confined rotational crop studies

Study 1

The residues of [^{14}C-phenyl]-isofetamid in rotational crops were investigated following one treatment of test substance SC formulation, simulating the maximum anticipated seasonal treatment rate according to agricultural practice (Graham, 2012: 8211603). The formulated test substance was applied to bare soil at rates close to the intended value of 2.25 kg ai/ha. The spray volumes were in the intended range of 400–1000 L/ha. The succeeding crops (lettuce, carrots and wheat) were sown 30, 120 and 365 DAT (plant back interval: PBI) to bare soil in glasshouse.

Crops were harvested as close as possible to their appropriate growth stages and TRR values were determined for each crop fraction by combustion with LSC. Soil cores were also taken at regular intervals but were not processed further. Crop samples were sequentially extracted with acetonitrile, acetonitrile:water (1:1 v/v) and water (neutral extracts). Selected samples were further extracted by maceration with 0.1 M hydrochloric acid and with 0.1 M sodium hydroxide, which was followed by

extraction with acetone. The unextracted radioactivity was quantified by combustion with LSC. Where the unextracted residues, following dilute acid or base extraction, accounted for ≥10% TRR or ≥ 0.05 mg/kg, whichever was the greater, harsh extractions were performed. The post-extracted solids were refluxed overnight with 6 M hydrochloric acid followed by 10 M sodium hydroxide. The neutral extracts containing notable levels of radioactivity were combined and prepared for analysis by SPE, partition with dichloromethane or direct concentration. The concentrated extracts were analysed by TLC and representative extracts were analysed by HPLC. Enzyme hydrolysis was performed on selected samples in an attempt to deconjugate polar material into known metabolites. Aqueous and organic fractions before and after hydrolysis were analysed by TLC. Polar material was isolated from concentrated extracts of the 30 PBI wheat hay sample by TLC with plate scraping and extraction of the silica. The isolated polar material was further isolated by HPLC with fraction collection. Fractions containing a large peak were combined and concentrated for LC-MS analysis.

Each of the TRR values at 365 PBI were lower than those observed at 30 and 120 PBIs. TRRs were generally highest at 30 PBI, with the exception of wheat forage and hay which had highest residues at 120 PBI. The neutral extractions removed up to 94% TRR, depending on the crop type and fraction. Dilute acid extracted up to 6% TRR and dilute base and the following acetone extraction combined removed up to a further 11% TRR from the crop fractions. Unextracted radioactivity ranged from 2–59% TRR.

Table 19 Total radioactive residues (TRRs) found in crops for confined rotational crop study

Sample			TRR (mg/kg eq)		
			30 PBI	120 PBI	365 PBI
Lettuce	Immature		0.328	0.123	0.030
	Mature		0.077	0.089	0.035
Carrot	Immature	Foliage	0.397	0.327	0.072
		Root	0.194	0.097	0.022
	Mature	Foliage	0.227	0.213	0.192
		Root	0.092	0.058	0.043
Wheat	Forage		0.323	0.882	0.168
	Hay		1.20	2.29	0.889
	Straw		1.43	1.41	0.905
	Grain		0.073	0.068	0.051

TLC analysis was used to analyse all samples but HPLC analysis allowed separation of polar material into several components and allowed identification of malonyl glucoside of 4HP. HPLC analysis confirmed the presence and proportions of isofetamid and its metabolites determined by TLC.

Isofetamid was present in the immature and mature lettuce extracts at 0.3–6.4% TRR (0.001–0.005 mg equiv/kg). Glucoside of 4HP accounted for >10% TRR in the immature and mature lettuce extracts at 27–54% TRR (0.008–0.137 mg equiv/kg). In addition to the metabolites detected by TLC for mature lettuce, HPLC analysis demonstrated that malonyl glucoside of 4HP accounted for up to 20% TRR and 0.018 mg equiv/kg. HPLC and TLC analysis showed that isofetamid accounted for a small proportion of the TRR, with glucoside of 4HP and malonyl glucoside of 4HP accounting for a total of 74% TRR.

TLC analyses showed that the metabolic pathway and proportions of each metabolite are comparable between immature and mature lettuce samples at all three plantbacks. Based on this and since HPLC and TLC results were similar, it can be concluded from these two analyses that the lettuce extracts were comprised of mainly glucoside of 4HP and malonyl glucoside of 4HP. Isofetamid, PPA, IBA and 4HP were detected at lower levels, up to 6% TRR and 0.007 mg equiv/kg. Unknown metabolites individually accounted for a maximum of 11% TRR and 0.008 mg equiv/kg.

Table 20 Total radioactive residues in rotational crop lettuce (^{14}C-phenyl)

Components	Immature lettuce (TLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.306	93.3	0.116	94.2	0.027	90.3
Isofetamid	*0.001*	*0.3*	*0.002*	*1.4*	*0.002*	*5.2*
PPA	*0.007*	*2.2*	*0.002*	*1.3*	*< 0.001*	*1.3*
Glucoside of 4HP	*0.137*	*41.7*	*0.055*	*44.7*	*0.008*	*26.7*
IBA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.005*	*1.6*	*0.002*	*2.0*	*0.001*	*1.8*
Polar zone [a]	*0.111*	*34.0*	*0.031*	*25.6*	*0.008*	*25.3*
Largest unknown	*0.025*	*7.6*	*0.007*	*5.4*	*0.002*	*6.1*
Other unknowns	*0.005*	*1.5*	*0.012*	*10.4*	*0.003*	*10.4*
Others	*0.013*	*4.0*	*0.002*	*2.0*	*0.001*	*2.5*
Unextracted	0.022	6.7	0.007	5.8	0.003	9.7
Total	0.328	100	0.123	100	0.030	100
Components	Mature lettuce (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR
Extract	0.069	90.1	0.084	94.2	0.033	93.7
Isofetamid	*0.005*	*6.4*	*< 0.001*	*<0.1*	*0.001*	*<0.1*
PPA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*0.4*
Glucoside of 4HP	*0.031*	*40.2*	*0.048*	*54.0*	*0.010*	*26.5*
IBA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.003*	*3.6*	*0.002*	*1.9*	*< 0.001*	*1.8*
Malonyl glucoside of 4HP	*0.009*	*11.4*	*0.018*	*19.9*	*0.004*	*12.3*
Polar zone [a]	*0.008*	*10.9*	*0.005*	*5.9*	*0.009*	*10.2*
Largest unknown	*0.008*	*10.9*	*0.004*	*4.2*	*0.004*	*5.6*
Other unknowns	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*		*4.9*
Others	*0.005*	*6.0*	*0.001*	*1.9*	*0.012*	*12.6*
Unextracted	0.008	9.9	0.005	5.8	0.002	6.3
Total	0.077	100	0.089	100	0.035	100

[a] Comprised of several polar components

The carrot root extracts comprised of mainly isofetamid, malonyl glucoside of 4HP and glucoside of 4HP. PPA, IBA and 4HP were detected at lower levels, up to 8% TRR and 0.015 mg equiv/kg. Unknown metabolites individually accounted for a maximum of 4% TRR and 0.003 mg equiv/kg. The carrot foliage extracts comprised of mainly isofetamid, malonyl glucoside of 4HP, glucoside of 4HP, PPA and 4HP. IBA was detected at lower levels, up to 3% TRR and 0.010 mg equiv/kg. Unknown metabolites individually accounted for a maximum of 15% TRR and 0.029 mg equiv/kg.

Table 21 Total radioactive residues in rotational crop carrot (^{14}C-phenyl)

Components	Immature foliage (TLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.331	83.3	0.309	94.4	0.060	83.9
Isofetamid	*0.016*	*4.0*	*0.008*	*2.3*	*0.004*	*5.6*
PPA	*0.036*	*9.0*	*0.028*	*8.5*	*0.001*	*1.5*
Glucoside of 4HP	*0.039*	*9.8*	*0.016*	*4.9*	*0.004*	*5.4*
IBA	*0.004*	*1.0*	*0.010*	*3.1*	*< 0.001*	*<0.1*
4HP	*0.012*	*3.0*	*0.033*	*10.0*	*< 0.001*	*<0.1*
Polar zone[a]	*0.123*	*30.9*	*0.066*	*20.3*	*0.016*	*22.5*
Largest unknown	*0.030*	*7.6*	*0.034*	*10.4*	*0.008*	*11.6*
Other unknowns	*0.035*	*9.4*	*0.081*	*25.1*	*0.017*	*23.3*
Others	*0.033*	*8.3*	*0.012*	*3.5*	*0.006*	*7.2*
Unextracted	0.066	16.7	0.018	5.6	0.012	16.1
Total	0.397	100	0.327	100	0.072	100

Components	Immature root (TLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.156	80.5	0.089	91.7	0.020	89.9
Isofetamid	*0.029*	*15.1*	*0.014*	*14.6*	*0.003*	*11.9*
PPA	*0.010*	*5.0*	*0.002*	*2.4*	*0.001*	*3.8*
Glucoside of 4HP	*0.023*	*11.7*	*0.007*	*7.0*	*0.001*	*5.7*
IBA	*0.002*	*0.8*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.015*	*7.6*	*0.003*	*3.1*	*< 0.001*	*<0.1*
Polar zone[a]	*0.060*	*30.9*	*0.045*	*46.4*	*0.010*	*42.0*
Largest unknown	*0.003*	*1.7*	*0.003*	*2.7*	*0.001*	*4.0*
Other unknowns	*0.003*	*1.5*	*0.002*	*2.1*	*0.002*	*6.5*
Others	*0.009*	*4.5*	*0.004*	*4.2*	*< 0.001*	*0.4*
Unextracted	0.038	19.5	0.008	8.3	0.002	10.1
Total	0.194	100	0.097	100	0.022	100
Components	Mature foliage (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.197	86.7	0.193	90.6	0.163	84.8
Isofetamid	*0.005*	*2.1*	*0.006*	*2.6*	*0.002*	*1.0*
PPA	*0.003*	*1.3*	*0.002*	*1.0*	*0.001*	*0.7*
Glucoside of 4HP	*0.015*	*6.5*	*0.015*	*7.1*	*0.007*	*3.7*
IBA	*< 0.001*	*<0.1*	*0.002*	*0.9*	*< 0.001*	*<0.1*
4HP	*0.004*	*1.9*	*0.006*	*2.6*	*0.004*	*2.2*
Malonyl glucoside of 4HP	*0.015*	*6.8*	*0.014*	*6.6*	*0.013*	*6.9*
Polar zone[a]	*0.013*	*5.9*	*0.015*	*7.0*	*0.012*	*6.3*
Largest unknown	*0.023*	*10.2*	*0.023*	*10.7*	*0.029*	*14.8*
Other unknowns	*0.037*	*16.5*	*0.016*	*7.2*	*0.026*	*13.6*
Others	*0.063*	*28.3*	*0.078*	*36.5*	*0.043*	*22.3*
Unextracted	0.030	13.3	0.020	9.4	0.029	15.2
Total	0.227	100	0.213	100	0.192	100
Components	Mature root (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.082	89.1	0.057	97.8	0.039	90.3
Isofetamid	*0.036*	*39.9*	*0.002*	*3.3*	*0.002*	*4.6*
PPA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
Glucoside of 4HP	*0.009*	*9.6*	*0.007*	*12.1*	*0.002*	*4.6*
IBA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.003*	*3.0*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
Malonyl glucoside of 4HP	*0.010*	*11.4*	*0.018*	*31.1*	*0.006*	*13.4*
Polar zone[a]	*0.005*	*5.5*	*0.014*	*23.6*	*0.012*	*28.3*
Largest unknown	*0.001*	*1.5*	*0.002*	*3.6*	*0.001*	*3.2*
Other unknowns	*< 0.001*	*<0.1*	*0.001*	*1.2*	*0.001*	*3.1*
Others	*0.009*	*9.3*	*0.009*	*15.1*	*0.008*	*20.1*
Unextracted	0.010	10.9	0.001	2.2	0.004	9.7
Total	0.092	100	0.058	100	0.043	100

[a] Comprised of several polar components

The main component in wheat forage, hay and straw was generally malonyl glucoside of 4HP (4–39% TRR). Isofetamid, glucoside of 4HP, PPA, IBA and 4HP were generally detected at lower levels, up to 12% TRR and 0.081 mg equiv/kg, with the exception of glucoside of 4HP in wheat hay at 120 PBI (10% TRR and 0.238 mg equiv/kg) and PPA in wheat straw at 30 PBI (9% TRR and 0.128 mg equiv/kg). Unknown metabolites individually accounted for a maximum of 8% TRR and 0.119 mg equiv/kg. Wheat grain generally contained malonyl glucoside of 4HP but at less than 4% TRR. No other known metabolites including isofetamid were present. Unknown metabolites individually accounted for a maximum of 6% TRR and 0.004 mg equiv/kg.

Table 22 Total radioactive residues in rotational crop wheat (^{14}C-phenyl)

Components	Forage (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.283	87.7	0.838	95.0	0.151	90.2
Isofetamid	*0.008*	*2.6*	*< 0.001*	*<0.1*	*0.005*	*2.8*
PPA	*0.010*	*3.0*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
Glucoside of 4HP	*0.012*	*3.8*	*0.054*	*6.2*	*0.019*	*11.5*
IBA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.008*	*2.6*	*< 0.001*	*<0.1*	*0.003*	*1.8*
Malonyl glucoside of 4HP	*0.060*	*18.8*	*0.345*	*39.1*	*0.025*	*14.5*
Polar zone	*0.017*	*5.4*	*0.011*	*1.3*	*0.003*	*1.7*
Largest unknown	*0.020*	*6.2*	*0.053*	*6.0*	*0.014*	*8.4*
Other unknowns	*0.142*	*43.6*	*0.342*	*38.6*	*0.074*	*44.2*
Others	*0.004*	*1.4*	*0.001*	*0.1*	*0.002*	*1.4*
Unextracted	0.040	12.3	0.044	5.0	0.017	9.8
Total	0.323	100	0.882	100	0.168	100
Components	Hay (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	1.02	85.4	2.03	88.9	0.553	62.2
Isofetamid	*< 0.001*	*<0.1*	*0.034*	*1.5*	*< 0.001*	*<0.1*
PPA	*0.014*	*1.1*	*0.047*	*2.0*	*< 0.001*	*<0.1*
Glucoside of 4HP	*0.048*	*4.0*	*0.238*	*10.4*	*0.019*	*2.1*
IBA	*0.006*	*0.5*	*0.026*	*1.1*	*< 0.001*	*<0.1*
4HP	*0.008*	*0.7*	*0.130*	*5.7*	*< 0.001*	*<0.1*
Malonyl glucoside of 4HP	*0.193*	*16.1*	*0.514*	*22.5*	*0.196*	*22.1*
Polar zone	*0.020*	*1.7*	*0.017*	*0.8*	*0.033*	*3.7*
Largest unknown	*0.086*	*7.2*	*0.119*	*5.2*	*0.059*	*6.6*
Other unknowns	*0.562*	*46.7*	*0.731*	*32.0*	*0.200*	*22.6*
Others	*0.016*	*1.3*	*0.032*	*1.4*	*0.002*	*0.3*
Unextracted	0.175	14.6	0.253	11.1	0.336	37.8
Total	1.20	100	2.29	100	0.889	100
Components	Straw (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	1.27	88.4	1.22	86.5	0.773	85.4
Isofetamid	*0.006*	*0.4*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
PPA	*0.128*	*9.0*	*0.031*	*2.2*	*0.014*	*1.5*
Glucoside of 4HP	*0.057*	*4.0*	*0.074*	*5.3*	*0.016*	*1.8*
IBA	*0.018*	*1.2*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.039*	*2.7*	*0.081*	*5.8*	*0.029*	*3.3*
Malonyl glucoside of 4HP	*0.147*	*10.3*	*0.059*	*4.2*	*0.104*	*11.4*
Polar zone	*0.013*	*0.9*	*0.045*	*3.2*	*0.022*	*2.4*
Largest unknown	*0.070*	*4.9*	*0.099*	*7.0*	*0.066*	*7.3*
Other unknowns	*0.651*	*45.6*	*0.701*	*49.5*	*0.436*	*48.3*
Others	*0.032*	*2.3*	*0.012*	*0.9*	*0.001*	*0.1*
Unextracted	0.166	11.6	0.190	13.5	0.132	14.6
Total	1.43	100	1.41	100	0.905	100

Components	Grain (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.033	45.5	0.035	51.2	0.021	40.6
Isofetamid	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
PPA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
Glucoside of 4HP	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
IBA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
Malonyl glucoside of 4HP	*0.003*	*3.7*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
Polar zone	*0.011*	*15.1*	*0.002*	*2.8*	*0.002*	*4.3*
Largest unknown	*0.004*	*5.1*	*0.002*	*2.8*	*0.003*	*5.9*
Other unknowns	*0.008*	*10.8*	*0.016*	*22.9*	*0.002*	*9.6*
Others	*< 0.001*	*0.4*	*< 0.001*	*<0.1*	*< 0.001*	*0.3*
Unextracted	0.040	54.5	0.033	48.8	0.030	59.4
Total	0.073	100	0.068	100	0.051	100

Isofetamid was detected in all crop fractions, except wheat grain, at values up to 40% TRR and 0.036 mg equiv/kg. The metabolite malonyl glucoside of 4HP was observed in all crop fractions at values up to 39% TRR (0.514 mg equiv/kg). The glucosides of 4HP PPA, IBA and 4HP were detected in all crop fractions except wheat grain at values up to 54% TRR (0.238 mg equiv/kg), 9% TRR (0.128 mg equiv/kg), 3% TRR (0.026 mg equiv/kg) and 10% TRR (0.130 mg equiv/kg). The unknown metabolites which accounted for highest percent TRR and concentration levels, had maximum values of 15% TRR and 0.119 mg equiv/kg, respectively. The metabolite profile was similar between crop types and between immature and mature harvests.

Isofetamid is unlikely to be present in succeeding crops at notably high levels. The residue in succeeding crops is likely to be comprised of several compounds including isofetamid, the glucoside of 4HP, malonyl glucoside of 4HP, 4HP, IBA and PPA, with levels of each varying depending on the crop type. The concentration of these compounds is likely to be reduced at longer plantback intervals.

Study 2

The residues of [^{14}C-thiophene]-isofetamid in rotational crops were investigated following one treatment of test substance SC formulation, simulating the maximum anticipated seasonal treatment rate according to agricultural practice (Graham, 2012: 8211604). The formulated test substance was applied to bare soil at rates close to the intended value of 2.25 kg ai/ha. The spray volumes were in the intended range of 400–100 L/ha. The succeeding crops (lettuce, carrots and wheat) were sown 30, 120 and 365 DAT (plant back interval: PBI) to bare soil in glasshouse.

Crops were harvested as close as possible to their appropriate growth stages and TRR values were determined for each crop fraction by combustion with LSC. Soil cores were also taken at regular intervals but were not processed further. Crop samples were sequentially extracted with acetonitrile, acetonitrile:water (1:1 v/v) and water (neutral extracts). Selected samples were further extracted by maceration with 0.1 M hydrochloric acid and with 0.1 M sodium hydroxide, which was followed by extraction with acetone. The unextracted radioactivity was quantified by combustion with LSC. Where the unextracted residues, following dilute acid or base extraction, accounted for ≥10% TRR or ≥0.05 mg equiv/kg, harsh extractions were performed. The post-extracted solids were refluxed overnight with 6 M hydrochloric acid followed by 10 M sodium hydroxide. The neutral extracts containing notable levels of radioactivity were combined and prepared for analysis by solid phase extraction (SPE), partition with dichloromethane or direct concentration. The concentrated extracts were analysed by TLC and representative extracts were analysed by HPLC. Enzyme hydrolysis was performed on selected samples in an attempt to deconjugate polar material into known metabolites. Aqueous and organic fractions before and after hydrolysis were analysed by TLC.

Each of the TRR values at 365 PBI were lower than those observed at the 30 and 120 PBIs.

TRRs were generally highest at 30 PBI, with the exception of wheat straw which had highest residues at 120 PBI. The neutral extractions removed up to 93% of the TRR, depending on the crop type and fraction. Dilute acid extracted up to 6% TRR and dilute base and the following acetone extraction combined removed up to a further 16% TRR from the crop fractions. Non-extracted radioactivity ranged from 4% TRR to 66% TRR.

Table 23 Total radioactive residues (TRRs) found in crops for confined rotational crop study

Sample			TRR (mg/kg eq)		
			30 PBI	120 PBI	365 PBI
Lettuce	Immature		0.060	0.037	0.012
	Mature		0.047	0.013	0.006
Carrot	Immature	Foliage	0.089	0.059	0.025
		Root	0.040	0.040	0.013
	Mature	Foliage	0.074	0.059	0.027
		Root	0.040	0.057	0.012
Wheat	Forage		0.212	0.151	0.121
	Hay		1.07	0.761	0.339
	Straw		0.919	1.42	0.309
	Grain		0.075	0.057	0.038

The lettuce extracts comprised of mainly the glucoside of 4HP and malonyl glucoside of 4HP. Isofetamid, PPA and 4HP were each detected at lower levels, up to 5% TRR and 0.003 mg equiv/kg. The metabolites 3-MTCA and 3-MTCAM were not detected. Unknown metabolites individually accounted for a maximum of 4% TRR and 0.002 mg equiv/kg.

Table 24 Total radioactive residues in rotational crop lettuce (^{14}C-thiophene)

Components	Immature lettuce (TLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.056	93.3	0.033	89.2	0.011	88.4
Isofetamid	*0.001*	*1.6*	*0.001*	*2.6*	*< 0.001*	*<0.1*
PPA	*0.002*	*2.8*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
Glucoside of 4HP	*0.032*	*53.5*	*0.016*	*42.4*	*0.002*	*19.0*
3-MTCAM	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
3-MTCA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.003*	*4.7*	*0.002*	*5.0*	*< 0.001*	*<0.1*
Polar zone[a]	*0.014*	*23.1*	*0.006*	*16.6*	*0.005*	*41.2*
Largest unknown	*0.002*	*2.7*	*0.002*	*4.4*	*< 0.001*	*<0.1*
Other unknowns	*0.001*	*1.6*	*0.004*	*11.1*	*< 0.001*	*<0.1*
Others	*0.002*	*2.6*	*0.002*	*4.3*	*< 0.001*	*2.8*
Unextracted	0.004	6.7	0.004	10.8	0.001	11.6
Total	0.060	100	0.037	100	0.012	100
Components	Mature lettuce (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg	% TRR	mg/kg	% TRR	mg/kg	% TRR
Extract	0.042	89.7	0.012	88.2	0.004	73.0
Isofetamid	*0.001*	*2.7*	*< 0.001*	*<0.1*	*NA*	*NA*
PPA	*< 0.001*	*<0.1*	*< 0.001*	*0.4*	*NA*	*NA*
Glucoside of 4HP	*0.025*	*54.6*	*0.004*	*29.8*	*NA*	*NA*
4HP	*0.002*	*3.6*	*< 0.001*	*1.3*	*NA*	*NA*
Malonyl glucoside of 4HP	*0.009*	*18.9*	*0.001*	*6.1*	*NA*	*NA*
Polar zone	*0.004*	*8.3*	*0.004*	*32.6*	*NA*	*NA*
Largest unknown	*< 0.001*	*0.6*	*< 0.001*	*2.3*	*NA*	*NA*
Other unknowns	*< 0.001*	*<0.1*	*< 0.001*	*7.3*	*NA*	*NA*
Others	*< 0.001*	*0.8*	*< 0.001*	*1.5*	*NA*	*NA*
Unextracted	0.005	10.3	0.001	11.8	0.002	27.0
Total	0.047	100	0.013	100	0.006	100

NA= Not analysed due to insufficient radioactivity

[a] Comprised of several polar components

The carrot root extracts comprised of mainly the malonyl glucoside of 4HP and the glucoside of 4HP. Isofetamid, PPA and 4HP were detected at lower levels, up to 12% TRR and 0.004 mg equiv/kg. The metabolites 3-MTCA and 3-MTCAM were not detected. Unknown metabolites individually accounted for a maximum of 7% TRR and 0.004 mg equiv/kg. The carrot foliage extracts comprised of mainly malonyl glucoside of 4HP and glucoside of 4HP. Isofetamid, PPA and 4HP were generally detected at lower levels, up to 7% TRR and 0.006 mg equiv/kg. The metabolites 3-MTCA and 3-MTCAM were not detected. Unknown metabolites individually accounted for a maximum of 9% TRR and 0.007 mg equiv/kg.

Table 25 Total radioactive residues in rotational crop carrot (^{14}C-thiophene)

Components	Immature foliage (TLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.080	90.5	0.047	80.2	0.021	83.0
Isofetamid	*0.003*	*3.3*	*0.004*	*6.3*	*< 0.001*	*1.8*
PPA	*0.006*	*7.0*	*0.002*	*2.6*	*< 0.001*	*<0.1*
Glucoside of 4HP	*0.010*	*10.8*	*0.008*	*12.9*	*0.001*	*5.7*
3-MTCAM	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
3-MTCA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*0.004*	*4.3*	*0.003*	*4.5*	*< 0.001*	*<0.1*
Polar zone[a]	*0.032*	*35.5*	*0.014*	*24.1*	*0.010*	*37.5*
Largest unknown	*0.003*	*3.4*	*0.002*	*4.0*	*0.001*	*5.8*
Other unknowns	*0.012*	*14.3*	*0.007*	*12.2*	*0.003*	*13.3*
Others	*0.002*	*2.3*	*< 0.001*	*0.8*	*< 0.001*	*1.9*
Unextracted	0.008	9.5	0.012	19.8	0.004	17.0
Total	0.088	100	0.059	100	0.025	100
Components	Immature root (TLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.038	93.7	0.034	86.0	0.012	89.3
Isofetamid	*0.001*	*2.7*	*0.004*	*9.0*	*0.002*	*11.9*
PPA	*0.004*	*9.0*	*0.001*	*2.7*	*< 0.001*	*<0.1*
Glucoside of 4HP	*0.006*	*16.1*	*0.005*	*12.5*	*0.001*	*10.2*
3-MTCAM	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
3-MTCA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
4HP	*< 0.001*	*<0.1*	*0.001*	*2.2*	*< 0.001*	*<0.1*
Polar zone[a]	*0.022*	*54.6*	*0.016*	*40.5*	*0.006*	*42.6*
Largest unknown	*0.001*	*3.7*	*< 0.001*	*<0.1*	*0.001*	*6.1*
Other unknowns	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*2.9*
Others	*0.001*	*2.2*	*0.003*	*7.0*	*< 0.001*	*1.3*
Unextracted	0.002	6.3	0.006	14.0	0.001	10.7
Total	0.040	100	0.040	100	0.013	100
Components	Mature foliage (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.052	69.8	0.045	76.2	0.022	81.4
Isofetamid	*< 0.001*	*<0.1*	*0.004*	*6.9*	*< 0.001*	*1.5*
PPA	*0.002*	*3.1*	*< 0.001*	*<0.1*	*0.001*	*3.8*
Glucoside of 4HP	*0.012*	*15.7*	*0.007*	*12.3*	*0.003*	*12.1*
4HP	*0.002*	*2.9*	*0.002*	*3.3*	*< 0.001*	*1.1*
Malonyl glucoside of 4HP	*0.009*	*12.3*	*0.006*	*9.9*	*0.003*	*12.1*
Polar zone	*0.001*	*0.9*	*0.006*	*10.9*	*0.001*	*5.0*
Largest unknown	*0.007*	*9.0*	*0.002*	*3.2*	*0.001*	*4.6*
Other unknowns	*0.014*	*19.4*	*0.005*	*11.8*	*0.006*	*25.8*
Others	*< 0.001*	*0.6*	*< 0.001*	*0.5*	*< 0.001*	*0.1*
Unextracted	0.022	30.2	0.014	23.8	0.005	18.6
Total	0.074	100	0.059	100	0.027	100
Components	Mature root (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR

Components	Immature foliage (TLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.037	92.0	0.053	92.5	0.012	95.9
Isofetamid	*0.002*	*5.5*	*0.003*	*6.2*	*< 0.001*	*4.3*
PPA	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*< 0.001*	*1.8*
Glucoside of 4HP	*0.007*	*18.1*	*0.005*	*9.5*	*< 0.001*	*0.7*
4HP	*0.001*	*2.2*	*0.001*	*2.1*	*< 0.001*	*<0.1*
Malonyl glucoside of 4HP	*0.011*	*28.5*	*0.019*	*34.1*	*0.001*	*7.9*
Polar zone	*0.005*	*13.1*	*0.009*	*16.1*	*0.001*	*8.2*
Largest unknown	*0.002*	*4.2*	*0.004*	*6.5*	*0.001*	*4.9*
Other unknowns	*0.006*	*13.7*	*0.006*	*11.0*	*0.001*	*49.9*
Others	*< 0.001*	*0.6*	*< 0.001*	*0.3*	*< 0.001*	*1.1*
Unextracted	0.003	8.0	0.004	7.5	< 0.001	4.1
Total	0.040	100	0.057	100	0.012	100

[a] Comprised of several polar components

The main component in wheat forage, hay and straw was the malonyl glucoside of 4HP (8–29% TRR). Isofetamid, the glucoside of 4HP, PPA and 4HP were detected at lower levels, up to 15% TRR and 0.133 mg equiv/kg. The metabolites 3-MTCA and 3-MTCAM were not detected. Unknown metabolites individually accounted for a maximum of 14% TRR and 0.080 mg equiv/kg. Wheat grain generally contained isofetamid, malonyl glucoside of 4HP and PPA but at less than 6% TRR. No other known metabolites were present. Unknown metabolites individually accounted for a maximum of 6% TRR and 0.005 mg equiv/kg.

Table 26 Total radioactive residues in rotational crop wheat (^{14}C-thiophene)

Components	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Forage (HPLC analysis)						
Extract	0.201	94.8	0.137	90.9	0.109	89.8
Isofetamid	*0.003*	*1.4*	*0.004*	*2.5*	*0.001*	*0.8*
PPA	*0.009*	*4.3*	*< 0.001*	*<0.1*	*0.002*	*1.4*
Glucoside of 4HP	*0.019*	*8.8*	*0.016*	*10.3*	*0.010*	*8.0*
4HP	*0.002*	*0.8*	*0.004*	*2.8*	*0.003*	*2.5*
Malonyl glucoside of 4HP	*0.058*	*27.4*	*0.040*	*26.1*	*0.034*	*28.2*
Polar zone	*0.004*	*1.8*	*0.006*	*3.9*	*0.007*	*5.5*
Largest unknown	*0.015*	*7.3*	*0.021*	*13.5*	*0.005*	*4.1*
Other unknowns	*0.073*	*35.3*	*0.037*	*23.4*	*0.036*	*30.3*
Others	*0.002*	*0.8*	*< 0.001*	*<0.1*	*0.001*	*1.1*
Unextracted	0.011	5.2	0.014	9.1	0.012	10.2
Total	0.212	100	0.151	100	0.121	100
Components	Hay (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.918	85.6	0.649	85.3	0.264	77.8
Isofetamid	*0.068*	*6.4*	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*
PPA	*0.052*	*4.9*	*0.007*	*1.0*	*< 0.001*	*<0.1*
Glucoside of 4HP	*0.062*	*5.8*	*0.047*	*6.1*	*0.013*	*3.8*
4HP	*0.041*	*3.9*	*0.015*	*2.8*	*0.004*	*1.2*
Malonyl glucoside of 4HP	*0.167*	*15.5*	*0.222*	*29.1*	*0.073*	*21.4*
Polar zone	*0.007*	*0.7*	*0.032*	*4.2*	*0.021*	*6.2*
Largest unknown	*0.080*	*7.5*	*0.046*	*6.0*	*0.013*	*3.7*
Other unknowns	*0.364*	*33.9*	*0.219*	*29.1*	*0.118*	*35.1*
Others	*0.017*	*1.6*	*0.008*	*1.1*	*0.003*	*1.0*
Unextracted	0.154	14.4	0.112	14.7	0.075	22.2
Total	1.07	100	0.761	100	0.339	100

Components	Straw (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.786	85.5	1.22	85.8	0.244	79.0
Isofetamid	*0.013*	*1.5*	*0.003*	*0.2*	*< 0.001*	*<0.1*
PPA	*0.133*	*14.5*	*0.051*	*3.6*	*0.008*	*2.6*
Glucoside of 4HP	*0.061*	*6.6*	*0.131*	*9.2*	*0.016*	*5.2*
4HP	*0.031*	*3.4*	*0.133*	*9.4*	*0.012*	*3.8*
Malonyl glucoside of 4HP	*0.175*	*19.0*	*0.116*	*8.2*	*0.061*	*19.7*
Polar zone	*< 0.001*	*<0.1*	*0.024*	*1.7*	*0.016*	*5.3*
Largest unknown	*0.056*	*6.1*	*0.071*	*5.0*	*0.017*	*5.5*
Other unknowns	*0.219*	*24.0*	*0.524*	*36.9*	*0.085*	*27.7*
Others	*0.009*	*1.0*	*0.014*	*1.0*	*0.004*	*1.3*
Unextracted	0.133	14.5	0.201	14.2	0.065	21.0
Total	0.919	100	1.42	100	0.309	100
Components	Grain (HPLC analysis)					
	30 PBI		120 PBI		365 PBI	
	mg/kg eq	% TRR	mg/kg eq	% TRR	mg/kg eq	% TRR
Extract	0.039	52.4	0.030	53.0	0.013	34.4
Isofetamid	*< 0.001*	*<0.1*	*0.002*	*3.2*	*NA*	*NA*
PPA	*0.004*	*5.6*	*< 0.001*	*0.2*	*NA*	*NA*
Glucoside of 4HP	*< 0.001*	*<0.1*	*< 0.001*	*<0.1*	*NA*	*NA*
4HP	*< 0.001*	*<0.1*	*0.001*	*1.0*	*NA*	*NA*
Malonyl glucoside of 4HP	*0.002*	*2.6*	*< 0.001*	*<0.1*	*NA*	*NA*
Polar zone	*0.009*	*12.4*	*0.005*	*8.5*	*NA*	*NA*
Largest unknown	*0.005*	*6.2*	*0.002*	*3.6*	*NA*	*NA*
Other unknowns	*0.007*	*9.0*	*0.011*	*17.0*	*NA*	*NA*
Others	*0.001*	*0.7*	*< 0.001*	*0.3*	*NA*	*NA*
Unextracted	0.036	47.6	0.027	47.0	0.025	65.6
Total	0.075	100	0.057	100	0.038	100

NA= Not analysed due to insufficient radioactivity

Isofetamid was detected in all crop fractions at values up to 12% TRR and 0.068 mg equiv/kg. The metabolites PPA and the malonyl glucoside of 4HP, were observed in all crop fractions at values up to 15% TRR (0.133 mg equiv/kg) and 34% TRR (0.222 mg equiv/kg), respectively. Glucoside of 4HP and 4HP were detected in all crop fractions except wheat grain at values up to 55% TRR (0.131 mg equiv/kg) and 9% TRR (0.133 mg equiv/kg), respectively. The unknown metabolites which accounted for the highest percent TRR and concentration levels, had maximum values of 14% TRR (equivalent to 0.021 mg/kg) and 0.080 mg equiv/kg (equivalent to 8% TRR), respectively. The metabolite profile was similar between crop types and between immature and mature harvests.

Isofetamid is unlikely to be present in succeeding crops at notably high levels. The residue in succeeding crops is likely to be comprised of several compounds including isofetamid, the glucoside of 4HP, malonyl glucoside of 4HP, 4HP and PPA, with levels of each varying depending on the crop type. The concentration of these compounds is likely to be reduced at later plantback intervals.

Summary of metabolism in succeeding crops

Isofetamid undergoes extensive metabolism in rotated crops. Similar metabolite profiles were obtained for the [^{14}C-phenyl]-isofetamid and [^{14}C-thiophene]-isofetamid, with malonyl glucoside of 4HP and glucoside of 4HP, PPA, 4HP and isofetamid contributing to the total radioactive residues. IBA was detected in crops grown in soil treated with [^{14}C-phenyl]-isofetamid. There was no evidence of the metabolites unique to the thiophene ring. However, as there was fairly extensive formation of non-extracted residue in some crop fractions (particularly grain) it is reasonable to assume that most of the radioactive material had undergone significant metabolism, indicating that it could be further conjugated, encapsulated or incorporated into natural components. The following metabolic pathway was proposed based upon the rotational crop metabolism studies available.

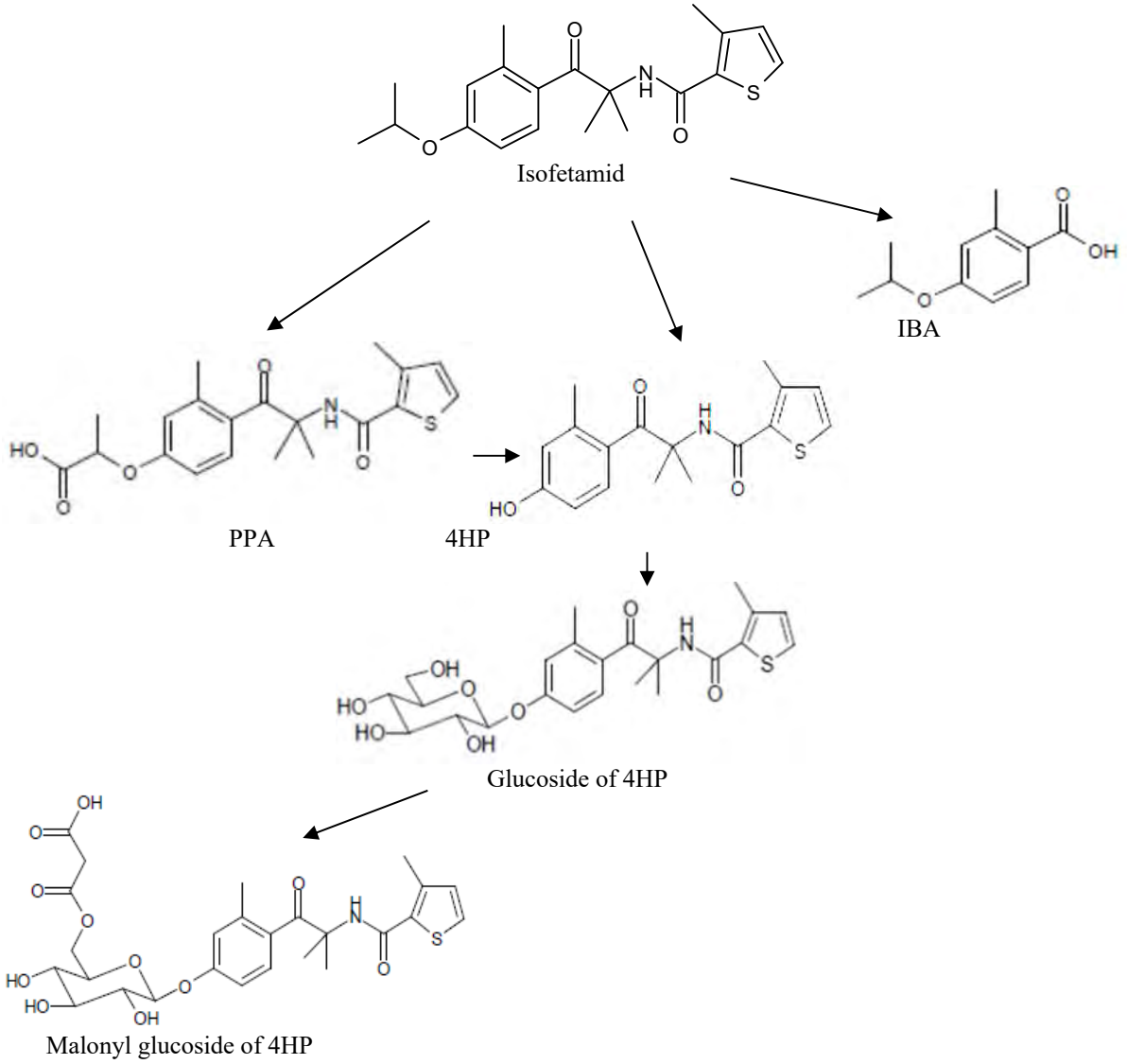


Figure 3 Metabolic Pathway of isofetamid in succeeding crops

Field rotational crop studies

Study in Europe

A field rotational crop study was initiated in Europe in August 2011 to investigate the magnitude of residues in succeeding crops (Cooke, 2013: 8251586). Two foliar applications of isofetamid 400SC (a 402 g/L SC formulation) were applied to lettuce at a nominal application rate of 0.40 kg ai/ha and with a spray interval of 8 to13 days. The trial sites were located in Germany and Spain, in areas of intended commercial usage of the test substance. At each trial site, three plots were treated with the SC formulation and a further three plots remained untreated to serve as controls.

Trial No.	Country	Region	Location	Soil type
8251586/1	Germany	Lower Saxony	Breitenwisch	Loam
8251586/2	Germany	Lower Saxony	Dollern	Sandy Loam
8251586/3	Spain	Tudela	Tudela	Loam

Trial No.	Country	Region	Location	Soil type
8251586/4	Spain	Valencia	Anna	Clay Loam

Rotational crops (spinach, radish and winter barley) were then sown at 30, 120 and 365-day plant-back intervals and grown according to Good Agricultural Practice. Samples of each crop were then harvested at pre-defined growth stages as detailed in the following table:

Crop	Timing / BBCH growth stage	Commodity
Spinach	Immature harvest – BBCH 19–43	Whole plant
	Normal commercial harvest	Leaves
Radish	Immature harvest – BBCH 43–45	Root and top with leaves
	Normal commercial harvest	Root and top with leaves
Winter barley	BBCH 31–33	Forage – whole plant without roots
	BBCH 75–83	Hay – whole plant without roots
	Normal commercial harvest	Grain and straw

Due to failed emergence, or crop damage due to unfavourable weather conditions, the 120–day and 365-day spinach trials in trials 8251586/1 (Germany) and 8251586/2 (Germany), and the 30-day and 120-day spinach trials in trial 8251586/4 (Spain), were repeated.

Samples were extracted with acetonitrile/water mixture, and cleaned-up with a SPE cartridge. All samples were analysed for isofetamid and its metabolite glucoside of 4HP using the validated analytical procedures JSM0119 and CLE 8251586-01V (for barley straw). Isofetamid and glucoside of 4HP were quantified by UPLC-MS/MS. The LOQ was 0.01 mg/kg for both compounds. The intermediate sample extracts were subjected to hydrolysis in order to hydrolyse conjugates of glucoside of 4HP, such as malonyl glucoside of 4HP detected in the confined rotational crops studies (8211603 and 8211604). Following the hydrolysis procedure all samples were analysed again for glucoside of 4HP using the JSM0119 and CLE 8251586-01V methods.

Residues of isofetamid and the glucoside of 4HP in succeeding crop fractions at the 30-day plant-back interval (PBI) were all below the LOQ, with the exception of radish tops with leaves in one trial (Trial 8251586/2 in Germany). In this sample, the residue level was 0.0254 mg/kg, for isofetamid, and <LOQ for glucoside of 4HP. Repeat analysis of this sample, and analysis of the retained sample, confirmed the original results. These residue levels in radish tops with leaves are higher than expected and do not follow the trend for all other samples from the 30-day PBI.

Residue levels of the glucoside of 4HP, prior to and following the hydrolysis procedure, were variable but were in general higher after hydrolysis. This indicated the presence of glucoside of 4HP conjugates, such as malonyl glucoside of 4HP (detected in the confined rotational crops studies (8211603 and 8211604 on this compound) and their subsequent degradation to form the glucoside of 4HP under the hydrolysis conditions. Residues of the glucoside of 4HP after hydrolysis were all below the LOQ, with the exception of radish tops in one trial (Trial 8251586/4 in Spain).

Table 27 Concentration of isofetamid and glucoside of 4HP in the 30-day PBI samples

Crop	Harvest timing	Crop fraction	Residues, mg/kg		
			Isofetamid	Glucoside of 4HP Pre-hydrolysis	Glucoside of 4HP Post-hydrolysis
Spinach	Immature	Whole plant	ND	ND	< 0.01
	Mature	Leaves	< 0.01	< 0.01	< 0.01
Radish	Immature	Root	< 0.01	< 0.01	< 0.01
	Immature	Top with leaves	< 0.01	< 0.01	0.013[b]
	Mature	Root	< 0.01	< 0.01	< 0.01
	Mature	Top with leaves	< 0.01	< 0.01	0.011[b]

Crop	Harvest timing	Crop fraction	Residues, mg/kg		
			Isofetamid	Glucoside of 4HP Pre-hydrolysis	Glucoside of 4HP Post-hydrolysis
Radish[a]	Immature	Top with leaves	0.025	< 0.01	NA
	Immature	Top with leaves	0.029	< 0.01	NA
	Immature	Top with leaves	0.023	< 0.01	0.012
Winter barley	Immature	Forage	< 0.01	< 0.01	< 0.01
	Immature	Hay	< 0.01	< 0.01	< 0.01
	Mature	Straw	< 0.01	ND	ND
	Mature	Grain	< 0.01	< 0.01	< 0.01

ND= Not detected (LOD, 0.004 mg/kg), NA= Not applicable

[a] Trial 8251586/2

[b] Trial 8251586/4

In crops sown 120 days after the second application, residue levels of isofetamid were consistently below the LOQ (0.01 mg/kg), with only one sample (radish top with leaves, trial 8251586/2 in Germany) recording a residue level above the LOD (0.004 mg/kg). Residue levels of the glucoside of 4HP, prior to and following hydrolysis, were variable and occasionally showed slight increases after the procedure, indicating the presence of the glucoside of 4HP conjugates. It should be noted, however, that all the residue levels of the glucoside of 4HP were either not detected (ND) or <LOQ (0.01 mg/kg).

Table 28 Concentration of isofetamid and glucoside of 4HP in the 120-day PBI samples

Crop	Harvest timing	Crop fraction	Residues, mg/kg		
			Isofetamid	Glucoside of 4HP Pre-hydrolysis	Glucoside of 4HP Post-hydrolysis
Spinach	Immature	Whole plant	ND	< 0.01	< 0.01
	Mature	Leaves	ND	< 0.01	< 0.01
Radish	Immature	Root	ND	ND	< 0.01
	Immature	Top with leaves	< 0.01	< 0.01	< 0.01
	Mature	Root	< 0.01	< 0.01	ND
	Mature	Top with leaves	< 0.01	< 0.01	< 0.01
Winter barley	Immature	Forage	< 0.01	< 0.01	< 0.01
	Immature	Hay	ND	ND	ND
	Mature	Straw	< 0.01	ND	ND
	Mature	Grain	ND	ND	ND

ND= Not detected (LOD, 0.004 mg/kg), NA= Not applicable

As expected, isofetamid and glucoside of 4HP residue levels in the crops sown 365 days after the second application were very low. Isofetamid was either not detected, or below the LOQ, in all crop fractions at this plant-back interval.

Table 29 Concentration of isofetamid and glucoside of 4HP in the 365-day PBI samples

Crop	Harvest timing	Crop fraction	Residues, mg/kg		
			Isofetamid	Glucoside of 4HP Pre-hydrolysis	Glucoside of 4HP Post-hydrolysis
Spinach	Immature	Whole plant	ND	ND	< 0.01
	Mature	Leaves	ND	ND	< 0.01
Radish	Immature	Root	ND	< 0.01	< 0.01
	Immature	Top with leaves	ND	< 0.01	< 0.01
	Mature	Root	< 0.01	ND	ND
	Mature	Top with leaves	< 0.01	< 0.01	< 0.01
Winter barley	Immature	Forage	ND	< 0.01	< 0.01
	Immature	Hay	ND	< 0.01	< 0.01
	Mature	Straw	< 0.01	ND	ND
	Mature	Grain	ND	ND	ND

ND= Not detected (LOD, 0.004 mg/kg), NA= Not applicable

With the exception of one crop fraction each in trial 8251586/2 (immature radish tops with leaves at the 30-day plant-back interval) and in trial 8251586/4 (mature radish tops with leaves at the 30-day plant-back interval, post-hydrolysis), residue levels of isofetamid and the glucoside of 4HP were all either lower than the LOQ (0.01 mg/kg) or the LOD (0.004 mg/kg) in all crop fractions, at all plant-back intervals. These data demonstrate that, following application to a primary crop, isofetamid and the glucoside of 4HP are unlikely to be present in succeeding crops under field conditions.

Study in the USA

The study was conducted at two sites in different growing regions in the USA to provide information on the residues of isofetamid and its metabolite glucoside of 4HP appearing in or on rotational crops at harvest following treatment of the growing crop with isofetamid 400SC (Wiedmann, 2013: IB-2011-JLW-013-01-01). The field trial sites consisted of a control (untreated) plot and one plot treated with isofetamid 400SC for each of 3 situations. Thirty day plantback, 120 day plantback and 365 day plantback intervals (PBIs) were tested with representative root crops, leafy vegetables and small grain crops. Three applications of isofetamid 400SC 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. Actual treatments at Suffolk VA were 0.77, 0.76 and 0.78 kg ai/ha for a total of 2.3 kg ai/ha for the 30 day situation and 0.76, 0.75 and 0.75 kg ai/ha, total of 2.3 kg ai/ha for the 120 and 365 day situations. Actual applications at Cheneyville, LA were 0.77, 0.78 and 0.76 kg ai/ha for a total of 2.3 kg ai/ha for the 30 day situation and 0.76, 0.76 and 0.77 kg ai/ha, total of 2.3 kg ai/ha for the 120 and 365 day situations. The application in VA used a backpack sprayer for the applications and the application in LA used a tractor mounted boom. The application spray volumes ranged from 243 to 290 L/ha.

Location	Soil texture	Sand, %	Silt, %	Clay, %	pH	Organic matter, %
Suffolk, VA	Sandy Loam	65	20	15	6.7	3.3
Cheneyville, LA	Silty Loam	36	60	4	5.3	1.2

The sample was blended with acetonitrile:water (80:20 v/v), shaken and centrifuged. The solids reextracted as above with acetonitrile:water (80:20 v/v). The extract was diluted if necessary with acetonitrile:water (20:80 v/v) for analysis of isofetamid and the glucoside of 4HP. For the malonyl glucoside of 4HP an aliquot of the above extract was dried down to ~1 mL using N_2 gas to remove the acetonitrile. Then 2 M HC1 was added and the solution incubated at 40 °C for 2 hours. The acid was neutralized with 6 M NaOH. An aliquot was diluted with acetonitrile for analysis. HPLC-MS/MS was used for quantification. The LOQ for isofetamid and glucoside of 4HP is 0.01 mg/kg based on the lowest fortification and the LOD is 0.005 mg/kg based on the lowest calibration standard. For the malonyl glucoside of 4HP the conversion is only 40% so the LOQ is 0.025 mg/kg and the LOD is 0.0125 mg/kg.

Acceptable recoveries were obtained for all matrices. The 28 concurrent recoveries which included all matrices and which were fortified at 0.01 and 0.10 mg/kg for isofetamid had a mean recovery of 99.9% and a standard deviation of 8.8%. Corresponding recoveries for glucoside of 4HP averaged 101% with a standard deviation of 8.3%. Corresponding recoveries for the malonyl glucoside of 4HP by the hydrolysis procedure averaged 84.7% with a standard deviation of 8.7%. The sampling to extraction interval for the crops ranged from 100–335 days. In a separate study there was no loss of isofetamid or the glucoside of 4HP from 6 crops over a 12 month freezer storage period so the samples in this study were considered stable.

There were no detectable residues of isofetamid, the glucoside of 4HP or the malonyl glucoside of 4HP in the controls from any crop at either site. For the 30 day PBI rotational crops no residues of isofetamid, glucoside of 4HP or malonyl glucoside of 4HP were found in the wheat forage, straw or grain at either site. At the 30 day PBI one turnip root sample (LA site) had 0.01 mg/kg isofetamid and the duplicate sample had a detectable residue of 0.008 mg/kg (<LOQ) for a mean of 0.009 mg/kg or <LOQ at that site. Both 30 day turnip root samples from VA were <LOD. One of two turnip top samples had a detectable 0.014 mg/kg malonyl glucoside of 4HP at LA (LOQ for malonyl glucoside of 4HP is 0.025 mg/kg and the LOD is 0.0125 mg/kg) and <LOD for the VA site samples. Soya beans grown at Suffolk, VA for the 30 day PBI had detectable malonyl glucoside

of 4HP at 0.02 mg/kg which is below the 0.025 mg/kg LOQ. At the LA site lettuce was grown instead of cabbage and no residues were detected in these samples. No isofetamid or glucoside of 4HP residues were found in the 30 day PBI turnip tops, soya beans or lettuce. For the 120 day PBI, no detectable residues of isofetamid, glucoside of 4HP or malonyl glucoside of 4HP were found in the wheat forage, straw or grain at either site. At the 120 day PBI turnip tops and turnip roots showed no detectable residues. Kale (VA) and lettuce (LA) were the leafy vegetables planted at 120 day PBIs. No detectable residues were found in either crop. Since there were no detectable residues in any of the 120 day PBI crops, the 365 day PBI crops were not analysed.

Table 30 Residues of isofetamid, glucoside of 4HP and malonyl glucoside of 4HP in rotational crops

Location	PBI, days	Crop	Crop fraction	Residues, mg/kg		
				Isofetamid	Glucoside of 4HP Pre-hydrolysis	Glucoside of 4HP Post-hydrolysis
Suffolk, VA	30	Turnip	Tops Roots	ND ND	ND ND	ND ND
Suffolk, VA	30	Spring wheat	Forage Straw Grain	ND ND ND	ND ND ND	ND ND ND
Suffolk, VA	30	Soya bean	Forage	ND	ND	< 0.025
Cheneyville, LA	30	Turnip	Tops Roots	ND < 0.01, 0.010	ND ND	< 0.025 ND
Cheneyville, LA	30	Winter wheat	Forage Straw Grain	ND ND ND	ND ND ND	ND ND ND
Cheneyville, LA	30	Lettuce	Leaf	ND	ND	ND
Suffolk, VA	120	Turnip	Tops Roots	ND ND	ND ND	ND ND
Suffolk, VA	120	Winter wheat	Forage Straw Grain	ND ND ND	ND ND ND	ND ND ND
Suffolk, VA	120	Kale	Leaf	ND	ND	ND
Cheneyville, LA	120	Turnip	Tops Roots	ND ND	ND ND	ND ND
Cheneyville, LA	120	Winter wheat	Forage Straw Grain	ND ND ND	ND ND ND	ND ND ND
Cheneyville, LA	120	Lettuce	Leaf	ND	ND	ND

ND= Not detected, <LOD (0.005 mg/kg, 0.0125 mg/kg for malonyl glucoside of 4HP), NA= Not analysed

All values are as received.

Environmental fate in water

The Meeting received information on hydrolytic degradation study. Because isofetamid is intended for use as foliar treatment, hydrolytic degradation study relevant to the current evaluations were reported below (FAO Manual Third edition, 2016).

Hydrolysis

The hydrolytic stability of [^{14}C]-isofetamid was studied in buffered aqueous solution, under sterile conditions, at pH values of 4, 7 and 9 (Fletcher, 2010: 2244/073). Solutions of aqueous buffers were prepared at pH 4, 7 and 9 at *ca* 50 °C and were sterilised by autoclaving. [^{14}C]-isofetamid (in acetonitrile, *ca* 30 µL), was applied to glass vials containing buffer (3 mL) to achieve final concentrations of *ca* 3 µg/mL. Duplicate incubation units were analysed immediately after treatment and at 5 days after treatment.

Radioactivity present in the test solution at each pH and sampling interval was determined by LSC. All samples were analysed for [^{14}C]-isofetamid by HPLC and selected samples were also analysed by TLC to confirm the identity of isofetamid. The potential for adsorption of the test substance to glassware from buffer solutions containing up to 1% acetonitrile was assessed prior to

studying the hydrolysis. Additional vials, treated with non-radiolabeled isofetamid, were incubated concurrently with the test samples and were used to confirm pH and sterility at the end of each incubation.

Sterile conditions were maintained throughout the in-life phase of the incubation. The recovery of radioactivity in buffer solutions in the adsorption test was 95% therefore there was no significant adsorption of isofetamid to the vials. Mean recovery of applied radioactivity in solution was 94–98% at each sampling interval.

Table 31 Identification of applied radioactivity in buffer solutions

Compound	% of applied radioactivity					
	pH 4		pH 7		pH 9	
	0 days	5 days	0 days	5 days	0 days	5 days
Isofetamid	90.3	94.8	92.0	95.1	90.9	95.0
Unknowns	0.2	ND	0.2	ND	0.5	ND
Unresolved background	1.7	1.1	1.7	1.4	1.6	1.3
Total	92.3	95.9	93.9	96.5	92.9	96.4

ND= Not detected

In the test, isofetamid was hydrolytically stable at all pH values after incubation for 5 days and >94% of applied radioactivity was recovered as unchanged isofetamid. There were no degradation products detected at any pH. Isofetamid was confirmed by TLC co-chromatography with an authentic reference standard. The conclusion of the study was that isofetamid was hydrolytically stable at pH values of 4, 7, and 9 at 50 °C over 5 days.

RESIDUE ANALYSIS

Analytical methods

Descriptions of analytical methods together with validation data for residues of isofetamid in plant and animal matrices were submitted to the Meeting. The methods rely on an initial extraction, usually with acetonitrile/water. After column clean-up, the isofetamid and its metabolite the glucoside of 4HP residues are prepared for LC analysis. Isofetamid and the glucoside of 4HP residues can be measured by mass spectrometric detector (MS/MS) with an LOQ of 0.01 mg/kg. Since the methods use standard extraction solvents and standard detection techniques, they have the potential to be incorporated into existing multi-residue methods.

Detailed descriptions of all these analytical methods are presented below.

Plant matrices

Grape, Lettuce, Oilseed rape seed and Dry bean (JSM0119)

Grape, Almond, Lettuce and Dry bean (IB-2011-JLW-007-00-01)

Analyte:	Isofetamid (m/z 360→210 for quantification, 360→125 for confirmation) Glucoside of 4HP (m/z 480→210 for quantification, 480→125 for confirmation)	LC-MS/MS
LOQ:	0.01 mg/kg	
Description	Samples were extracted with acetone (oilseed rape seeds only) or acetonitrile:water (80:20 v:v) mixture (all samples), and cleaned-up with an Oasis HLB solid phase extraction (SPE) cartridge. Quantitation was performed using LC-MS/MS.	

Stone fruits (apricot, cherry, peach, plum) , Grape, Strawberry, Lettuce, Oilseed rape

Analyte:	Isofetamid (m/z 360→210 for quantification, 360→125 for confirmation) Glucoside of 4HP (m/z 480→210 for quantification, 480→125 for confirmation)	LC-MS/MS
LOQ:	0.01 mg/kg	
Description	The residues of isofetamid and glucoside of 4HP were extracted from 20 g of blended homogeneous sample with 180 mL acetonitrile:water (80:20 v/v). The extract was centrifuged and the supernatant liquid was cleaned up by loading onto Oasis HLB SPE cartridges. Isofetamid and glucoside of 4HP were eluted with acetonitrile:water (50:50, v/v) and diluted further with water. Isofetamid and glucoside of 4HP residues were determined by LCMS/MS with positive-ion electrospray ionisation (ESI).	

Grape (IB-2011-JLW-002-01-01), Strawberry (IB-2011-JLW-005-01-01), Lettuce (IB-2011-JLW-006-01-01), Almond (IB-2011-JLW-001-01-01), Canola (IB-2011-JLW-004-01-01)

Analyte:	Isofetamid (m/z 360→210 for quantification, 360→125 for confirmation) Glucoside of 4HP (m/z 480→210 for quantification, 480→125 for confirmation)	LC-MS/MS
LOQ:	0.01 mg/kg	
Description	Samples were chopped in a Robotcoupe Vertical Batch Processor in the presence of dry ice until a completely homogenous sample was obtained. After the dry ice was removed by sublimation, the samples were subsampled for analysis. A 5.0 g aliquot of homogenised grape was weighed out. The sample was blended for 30 sec. with 25 mL of acetonitrile:water (80:20 v/v), shaken for 30 min. and centrifuged. The supernatant liquid was transferred to a 50 mL centrifuged tube and solids re-extracted as above with 20 mL od acetonitrile:water (80:20 v/v). The combined extracts were diluted to 50 mL with acetonitrile:water (80:20 v/v) and filtered through a 0.45 qm filter. The extract was diluted if necessary with acetonitrile:water (20:80 v/v). Isofetamid and glucoside of 4HP residues were determined by LCMS/MS with positive-ion electrospray ionisation (ESI).	

Validation data for methods on plant matrices are summarized in Table 32.

Table 32 Summary of recovery data for isofetamid and glucoside of 4HP fortified into plant matrices

Commodity	Analyte	Fortification mg/kg	N	Range Recovery (%)	Mean recovery (%)	% RSD	Reference Method
Grape (MV)	Isofetamid	0.01 0.1	5 5	70 – 96 84 – 90	86 87	11.2 2.8	JSM0119
	Glucoside of 4HP	0.01 0.1	5 5	75 – 110 93 – 106	89 99	16.5 5.4	
Lettuce (MV)	Isofetamid	0.01 0.1	5 5	89 – 94 82 – 101	91 91	2.3 7.4	
	Glucoside of 4HP	0.01 0.1	5 5	95 – 110 91 – 102	103 95	7.1 5.1	
Oilseed rape, seed (MV)	Isofetamid	0.01 0.1	5 5	71 – 87 86 – 93	80 89	8.9 3.7	

Commodity	Analyte	Fortification mg/kg	N	Range Recovery (%)	Mean recovery (%)	% RSD	Reference Method
	Glucoside of 4HP	0.01 0.1	5 5	96 – 105 104 – 107	102 105	3.6 1.3	
Dry bean (MV)	Isofetamid	0.01 0.1	5 5	71 – 81 80 – 82	76 81	5.9 1.0	
	Glucoside of 4HP	0.01 0.1	5 5	79 – 110 93 – 103	89 99	14.2 3.9	
Grape (ILV)	Isofetamid	0.01 0.1	5 5	88 – 98 90 – 97	93 93	4.2 2.9	IB-2011-JLW-007-00-01 (JSM0119)
	Glucoside of 4HP	0.01 0.1	5 5	87 – 99 94 – 99	94 96	6.2 1.8	
Almond (ILV)	Isofetamid	0.01 0.1	5 5	87 – 95 90 – 95	92 93	3.4 2.2	
	Glucoside of 4HP	0.01 0.1	5 5	90 – 105 101 – 110	95 105	6.2 3.0	
Lettuce (ILV)	Isofetamid	0.01 0.1	5 5	91 -100 91 – 95	96 92	3.2 1.8	
	Glucoside of 4HP	0.01 0.1	5 5	96 – 109 89 – 99	103 95	5.0 4.0	
Dry bean (ILV)	Isofetamid	0.01 0.1	5 5	80 – 88 79 – 83	83 81	3.7 2.0	
	Glucoside of 4HP	0.01 0.1	5 5	79 – 94 80 – 85	88 82	6.1 2.5	
Cherry (CR)	Isofetamid	0.01 0.1	3 3	72 – 92 74 – 90	85 80	13.0 10.6	JSM0068
	Glucoside of 4HP	0.01 0.1	3 3	73 – 89 88 – 100	83 93	10.8 6.9	
Cherry (CR)	Isofetamid	0.01 0.1	3 3	96 – 99 91 – 96	97 93	1.6 2.7	JSM0181
	Glucoside of 4HP	0.01 0.1	3 3	90 – 95 91 – 96	93 94	3.1 3.1	
Cherry (CR)	Isofetamid	0.01 0.1	3 3	76 – 78 90 – 93	77 91	1.5 1.9	JSM0293
	Glucoside of 4HP	0.01 0.1	3 3	81 – 89 89 – 94	88 91	4.7 2.9	
Apricot (CR)	Isofetamid	0.01 0.1	4 3	77 – 103 77 – 89	92 84	12.8 7.6	JSM0067
	Glucoside of 4HP	0.01 0.1	4 3	71 – 109 83 – 103	86 93	20.0 10.8	
Apricot (CR)	Isofetamid	0.01 0.1	3 3	91 – 99 89 – 94	96 91	4.4 2.9	JSM0180
	Glucoside of 4HP	0.01 0.1	3 3	81 – 91 89 – 91	87 90	6.3 1.3	
Plum (CR)	Isofetamid	0.01 0.1 0.3	3 3 2	87 – 107 90 – 95 94, 95	95 92 95	10.9 2.9	JSM0099
	Glucoside of 4HP	0.01 0.1 0.3	3 3 2	73 – 104 93 – 104 91, 106	84 98 99	20.3 5.6	
Plum (CR)	Isofetamid	0.01 0.1 1	3 3 1	93 – 94 87 – 96 88	93 91 -	0.6 4.9	JSM0204
	Glucoside of 4HP	0.01 0.1 1	3 3 1	79 – 91 86 – 98 90	85 90 -	7.1 7.4	

Commodity	Analyte	Fortification mg/kg	N	Range Recovery (%)	Mean recovery (%)	% RSD	Reference Method
Plum (CR)	Isofetamid	0.01 0.1	3 3	72 – 80 82 – 85	76 84	5.3 2.1	JSM0313
	Glucoside of 4HP	0.01 0.1	3 3	71 – 86 81 – 85	76 83	11.0 2.4	
Plum (CR)	Isofetamid	0.01 0.1	4 3	82 – 97 81 – 89	87 86	7.9 5.1	JSM0509
	Glucoside of 4HP	0.01 0.1	4 3	88 – 102 81 – 90	94 87	6.7 5.7	
Peach (CR)	Isofetamid	0.01 0.1 1	4 4 1	79 – 106 79 – 96 98	92 88 -	14.7 8.1	JSM0098
	Glucoside of 4HP	0.01 0.1 1	4 4 1	75 – 94 72 – 102 103	85 92 -	9.5 14.6	
Peach (CR)	Isofetamid	0.01 0.1 1	3 3 1	92 – 98 89 – 97 95	95 94 -	3.2 4.6	JSM0203
	Glucoside of 4HP	0.01 0.1 1	3 3 1	91 – 101 92 – 97 98	95 95 -	5.4 2.8	
Grape (CR)	Isofetamid	0.01 0.1 1 5	3 3 2 1	73 – 75 73 – 92 79, 98 93	74 84 89 -	1.4 11.9	JSM0100
	Glucoside of 4HP	0.01 0.1 1 5	3 3 2 1	79 – 82 89 – 96 77, 100 108	80 92 89 -	1.9 3.8	
Grape (CR)	Isofetamid	0.01 0.1	3 3	76 – 109 89 – 94	91 92	18.2 2.7	JSM0101
	Glucoside of 4HP	0.01 0.1	3 3	79 – 93 89 – 96	85 94	8.7 4.3	
Grape (CR)	Isofetamid	0.01 0.1 1	1 2 1	70 78, 82 87	- 80 -		JSM0102
	Glucoside of 4HP	0.01 0.1 1	1 2 1	71 78, 82 112	- 80 -		
Grape raw juice (CR)	Isofetamid	0.1	1	80	-		
	Glucoside of 4HP	0.1	1	64	-		
Grape clarified juice (CR)	Isofetamid	0.1	1	82	-		
	Glucoside of 4HP	0.1	1	75	-		
Must (CR)	Isofetamid	0.01 1	1 1	77 85	- -		
	Glucoside of 4HP	0.01	1	86	-		
Wine (CR)	Isofetamid	0.01 0.1	1 1	97 91	-		
	Glucoside of 4HP	0.01 0.1	1 1	103 99	-		
Stored wine (CR)	Isofetamid	0.1	4	78-90	83	6.5	
	Glucoside of 4HP	0.1	4	75-90	82	8.6	

Commodity	Analyte	Fortification mg/kg	N	Range Recovery (%)	Mean recovery (%)	% RSD	Reference Method
Grape (CR)	Isofetamid	0.01 0.1 1 2	3 3 1 1	78 – 89 91 – 93 96 91	85 92 - -	7.2 1.3	JSM0208
	Glucoside of 4HP	0.01 0.1 1 2	3 3 1 1	84 – 94 90 – 94 98 91	89 92 - -	5.7 2.3	
Grape (CR)	Isofetamid	0.01 0.1 3	3 4 1	84 – 88 87 – 95 92	86 92 -	2.4 3.7	JSM0209
	Glucoside of 4HP	0.01 0.1 3	3 4 1	73 – 85 80 – 92 94	79 86 -	7.6 5.7	
Grape (CR)	Isofetamid	0.01 0.1	2 3	90, 93 90 – 95	92 92	 2.7	JSM0210
	Glucoside of 4HP	0.01 0.1	2 3	85, 89 85 – 91	87 89	 3.6	
Grape juice (CR)	Isofetamid	0.01 0.1	1 1	98 94	- -		
	Glucoside of 4HP	0.01 0.1	1 1	91 92	- -		
Raisins (CR)	Isofetamid	0.1 1.0	1 1	96 96	- -		
	Glucoside of 4HP	0.1 1.0	1 1	87 95	- -		
Wine (CR)	Isofetamid	0.1	2	91, 96	94		
	Glucoside of 4HP	0.1	2	91, 98	95		
Grape (MV)	Isofetamid	0.01 0.10	3 3	100 – 104 104 – 109	103 106	2.3 2.4	IB-2011-JLW-002-01-01
	Glucoside of 4HP	0.01 0.10	3 3	88 – 94 97 – 105	91 100	3.1 4.1	
Grape (CR)	Isofetamid	0.01 0.10 0.984 2.44 4.9	6 1 1 1 3	88 – 100 107 110 96 93 – 109	95 - - - 103	5.4 8.5	
	Glucoside of 4HP	0.01 0.10 0.984 2.44 4.9	6 1 1 1 3	82 – 107 100 105 96 96 – 115	95 - - - 108	8.8 9.6	
Strawberry (CR)	Isofetamid	0.01 0.1 0.5	3 3 1	93 – 97 91 – 97 95	95 94 -	2.1 3.2	JSM0179
	Glucoside of 4HP	0.01 0.1 0.5	3 3 1	92 – 98 94 – 98 98	95 96 -	3.2 2.1	
Strawberry (CR)	Isofetamid	0.01 0.1 1	3 3 1	85 – 100 84 – 90 89	95 87 -	8.9 3.4	JSM0188 ISK-G301TO 305-11
	Glucoside of 4HP	0.01 0.1 1	3 3 1	78 – 95 84 – 86 92	88 85 -	10.0 1.2	

Commodity	Analyte	Fortification mg/kg	N	Range Recovery (%)	Mean recovery (%)	% RSD	Reference Method
Strawberry (CR)	Isofetamid	0.01 0.1 1	3 4 1	84 – 108 86 – 94 89	93 92 -	14.1 4.0	JSM0189
	Glucoside of 4HP	0.01 0.1 1	3 4 1	78 – 88 87 – 98 97	83 93 -	6.0 4.9	
Strawberry (CR)	Isofetamid	0.01 0.1 1	3 3 1	97 – 107 90 – 92 89	101 91 -	5.1 1.3	JSM0265
	Glucoside of 4HP	0.01 0.1 1	3 3 1	79 – 89 84 – 94 93	85 88 -	6.1 6.3	
Strawberry (CR)	Isofetamid	0.01 0.1	3 3	80 – 104 86 – 94	89 91	15.0 4.8	JSM0275 ISK-G211TO 214-12
	Glucoside of 4HP	0.01 0.1	3 3	85 – 96 90 – 96	90 94	6.1 3.7	
Strawberry (CR)	Isofetamid	0.01 0.1	3 3	79 – 92 85 – 89	86 87	7.6 2.3	JSM0527 ISK-G601TO 604-13
	Glucoside of 4HP	0.01 0.1	3 3	71 – 87 73 – 84	77 78	11.7 7.0	
Strawberry (MV)	Isofetamid	0.01 0.1	3 3	94 – 97 104 – 106	95 105	1.5 1.0	IB-2011-JLW-05-01-01
	Glucoside of 4HP	0.01 0.1	3 3	90 – 101 100 – 104	95 102	5.9 2.0	
Strawberry (CR)	Isofetamid	0.01 0.1 2.5	4 1 3	91 – 103 101 104 – 109	96 - 106	5.4 2.5	
	Glucoside of 4HP	0.01 0.1 2.5	4 1 3	87 – 105 98 96 - 102	95 - 98	7.9 3.4	
Lettuce (CR)	Isofetamid	0.01 0.1 20	3 3 1	70 – 87 78 – 90 89	76 84 -	12.6 7.1	JSM0247
	Glucoside of 4HP	0.01 0.1	3 3	74 – 80 72 – 90	77 80	4.0 11.5	
Lettuce (CR)	Isofetamid	0.01 0.1 10	3 3 1	72 – 78 81 – 87 92	75 84 -	4.1 3.6	JSM0249 ISK-G501TO 504-11
	Glucoside of 4HP	0.01 0.1	3 3	83 – 85 84 – 90	84 87	1.2 3.5	
Lettuce (CR)	Isofetamid	0.01 0.1 1.0 20	3 3 2 1	74 – 89 79 – 95 87, 91 81	81 85 89 -	9.5 10.6	JSM0250 ISK-G505TO 508-11
	Glucoside of 4HP	0.01 0.1 1.0	3 3 2	76 – 82 81 – 91 91, 93	79 85 92	3.9 6.2	
Lettuce (CR)	Isofetamid	0.01 0.1	3 3	73 62 – 73	73 69	0 8.5	JSM0266
	Glucoside of 4HP	0.01 0.1	3 3	71 – 76 64 – 72	74 69	3.4 6.3	
Lettuce (CR)	Isofetamid	0.01 0.1 10	3 3 1	77 – 81 73 – 92 91	79 84 -	2.5 11.9	JSM0274
	Glucoside of 4HP	0.01 0.1	3 3	79 – 86 70 – 90	82 83	4.6 13.3	

Commodity	Analyte	Fortification mg/kg	N	Range Recovery (%)	Mean recovery (%)	% RSD	Reference Method
Lettuce (CR)	Isofetamid	0.01 0.1 10	3 3 1	84 – 93 79 – 90 83	89 85 -	5.1 6.6	JSM0276 ISK-G201TO 205-12
	Glucoside of 4HP	0.01 0.1	3 3	76 – 89 77 – 87	81 83	9.0 6.4	
Lettuce (MV)	Isofetamid	0.01 0.1	3 3	94 – 99 98 – 103	96 101	2.9 2.5	IB-2011-JLW-006-01-01
	Glucoside of 4HP	0.01 0.1	3 3	95 – 101 98 – 103	98 101	3.2 2.4	
Lettuce (CR)	Isofetamid	0.01 0.1 5.0	11 1 10	61 – 96 102 85 – 105	85 - 98	12.6 6.5	
	Glucoside of 4HP	0.01 0.1 5.0	11 1 10	83 – 100 104 94 – 105	94 - 98	5.2 3.6	
Almond nutmeats (MV)	Isofetamid	0.01 0.1	3 3	84 – 89 91 – 103	86 98	3.0 6.3	IB-2011-JLW-001-01-01
	Glucoside of 4HP	0.01 0.1	3 3	102 – 107 92 – 103	104 98	2.8 5.6	
Almond nutmeats (CR)	Isofetamid	0.01 0.1	2 2	100, 111 109, 115	105 112		
	Glucoside of 4HP	0.01 0.1	2 2	99, 123 112, 115	111 114		
Almond hulls (MV)	Isofetamid	0.01 0.1	3 3	91 – 93 89 – 91	92 90	1.1 1.4	
	Glucoside of 4HP	0.01 0.1	3 3	102 – 106 88 – 96	104 92	1.9 4.2	
Almond hulls (CR)	Isofetamid	0.01 0.1 0.4	2 2 1	93, 95 94, 99 91	94 96 -		
	Glucoside of 4HP	0.01 0.1 0.4	2 2 1	91, 92 84, 96 88	91 90 -		
Oilseed rape, whole plant without roots (CR)	Isofetamid	0.1 5	3 1	77 – 84 70	80 -	4.8	JSM0090
	Glucoside of 4HP	0.1	3	70 – 91	78	14.9	
Oilseed rape, pods (CR)	Isofetamid	0.05	1	87	-		
	Glucoside of 4HP	0.05	1	90	-		
Oilseed rape, seeds (CR)	Isofetamid	0.01	3	69 – 88	77	12.6	
	Glucoside of 4HP	0.01	3	70 – 95	80	16.2	
Canola, seed (MV)	Isofetamid	0.01 0.1	3 3	91 – 93 94 – 95	92 95	0.9 0.4	IB-2011-JLW-004-01-01
	Glucoside of 4HP	0.01 0.1	3 3	87 – 94 88 – 92	90 90	4.3 2.2	
Canola, meal (MV)	Isofetamid	0.01 0.1	3 3	87 – 90 91 – 94	89 92	2.0 1.8	
	Glucoside of 4HP	0.01 0.1	3 3	87 – 88 84 – 86	87 85	0.6 1.3	
Canola, oil (MV)	Isofetamid	0.01 0.1	3 3	88 – 95 86 – 87	90 86	4.1 0.5	
	Glucoside of 4HP	0.01 0.1	3 3	97 – 105 101 – 102	101 102	4.2 0.6	

Commodity	Analyte	Fortification mg/kg	N	Range Recovery (%)	Mean recovery (%)	% RSD	Reference Method
Canola, seed (CR)	Isofetamid	0.01 0.1 0.2 0.4	7 4 2 1	84 – 97 87 – 103 84, 86 91	85 96 85 -	10.0 7.1	
	Glucoside of 4HP	0.01 0.1 0.2 0.4	7 4 2 1	90 – 110 88 – 99 91, 92 105	97 94 91 -	6.6 5.4	
Canola, meal (CR)	Isofetamid	0.01 0.1	1 1	87 90	- -		
	Glucoside of 4HP	0.01 0.1	1 1	89 85	- -		
Canola, oil (CR)	Isofetamid	0.01 0.1 0.4	1 1 2	97 91 104, 106	- - 105		
	Glucoside of 4HP	0.01 0.1 0.4	1 1 2	104 98 90, 95	- - 92		

CR: Concurrent Recovery, MV: Method Validation, ILV: Independent Laboratory Validation

Animal matrices

Milk, Muscle, Liver, Kidney, Fat and Eggs (8256542)

Analyte:	Isofetamid (m/z 360→210 for quantification, 360→125 for confirmation) 4HP (m/z 318→125 for quantification, 318→96.9 for confirmation) PPA (m/z 390→210 for quantification, 390→182 for confirmation) 5-HPPA (m/z 406→198 for quantification, 406→226 for confirmation)	LC-MS/MS
LOQ:	0.01 mg/kg	
Description	Samples were homogenised with acetonitrile and water (15:2 v:v), and DisQuE extraction mixture was added. The samples were mixed and then centrifuged. An aliquot was diluted in formate buffer and centrifuged. Quantitation was performed using LC-MS/MS.	

Validation data for methods on animal matrices are summarized in Table 33.

Table 33 Summary of Recovery Data for isofetamid and its metabolites fortified into animal matrices

Commodity	Analyte	Fortification mg/kg	N	Range of Recovery (%)	Mean recovery (%)	% RSD	Reference
Bovine milk (MV)	Isofetamid	0.01 0.10	5 5	82 – 92 94 – 100	86 95	4.6 2.7	8256542
	4HP	0.01 0.10	5 5	78 – 87 89 – 94	83 91	4.1 2.0	

Commodity	Analyte	Fortification mg/kg	N	Range of Recovery (%)	Mean recovery (%)	% RSD	Reference
	PPA	0.01 0.10	5 5	71 – 83 87 – 92	79 89	6.2 2.3	
	5-HPPA	0.01 0.10	5 5	87 – 93 87 – 92	90 90	2.6 2.1	
Bovine muscle (MV)	Isofetamid	0.01 0.10	5 5	86 – 93 93 – 99	90 96	3.0 2.3	
	4HP	0.01 0.10	5 5	88 – 93 91 – 94	90 93	2.5 1.5	
	PPA	0.01 0.10	5 5	81 – 88 85 – 86	84 86	3.3 0.6	
	5-HPPA	0.01 0.10	5 5	60 – 68 80 – 90	64 83	4.5 4.9	
Bovine liver (MV)	Isofetamid	0.01 0.10	5 5	86 – 91 91 – 93	88 92	2.1 0.9	
	4HP	0.01 0.10	5 5	91 – 96 93 – 99	94 96	2.7 2.7	
	PPA	0.01 0.10	5 5	78 – 86 84 – 90	82 87	3.9 3.2	
	5-HPPA	0.01 0.10	5 5	68 – 79 78 – 81	74 79	5.3 1.6	
Bovine kidney (MV)	Isofetamid	0.01 0.10	5 5	81 – 92 90 – 96	87 93	5.0 2.6	
	4HP	0.01 0.10	5 5	86 – 92 88 – 91	89 90	2.4 1.5	
	PPA	0.01 0.10	5 5	77 – 83 79 – 84	80 81	3.1 2.5	
	5-HPPA	0.25 0.50	5 5	73 – 77 81 – 86	75 83	2.4 2.2	
Bovine fat (MV)	Isofetamid	0.01 0.10	5 5	91 – 99 87 – 96	96 93	3.1 3.8	
	4HP	0.01 0.10	5 5	91 – 99 94 – 97	95 96	3.1 1.1	
	PPA	0.01 0.10	5 5	86 – 87 90 – 93	87 91	0.5 1.2	
	5-HPPA	0.01 0.10	5 5	89 – 94 90 – 99	91 95	2.5 3.8	
Eggs (MV)	Isofetamid	0.01 0.10	5 5	83 – 89 85 – 90	87 88	2.6 2.2	
	4HP	0.01 0.10	5 5	88 – 94 88 – 95	91 93	2.4 3.1	
	PPA	0.01 0.10	5 5	78 – 88 81 – 87	84 85	4.4 3.2	
	5-HPPA	0.01 0.10	5 5	79 – 87 77 – 81	83 79	4.4 1.9	

Stability of pesticide residues in stored analytical samples

The Meeting received data on the storage stability of isofetamid and metabolite glucoside of 4HP residues in almond, oilseed rape seed, grape, lettuce, potato and dry bean samples for plant commodities stored frozen.

The freezer stability study of isofetamid and glucoside of 4HP was conducted on almonds, oilseed rape seeds, grapes, lettuce, potatoes and dry beans (Brewin, 2012: JSM0212). Homogenised samples of each matrix were fortified with each analyte individually at 0.1 mg/kg and stored frozen at approximately -20°C for a period of up to 12 months, in the dark. Samples were analysed after storage using HPLC-MS/MS method validated in the study No. JSM0119. The LOQ was 0.01 mg/kg.

Table 34 Recovery of isofetamid from stored fortified samples of plant matrices

Storage interval	Recovery (%) [0.1 mg/kg fortification]		
	Procedural	% remaining	Mean
Almonds			
Day 0	-	95, 96, 97	96
1 month	93	85, 86, 87	86
3 months	88	93, 95, 96	95
6 months	89	87, 90, 92	90
12 months	83	85, 88, 90	88
Oilseed rape seeds			
Day 0	-	88, 91, 93	91
1 month	94	94, 96, 98	96
3 months	81	86, 86, 86	86
6 months	82	81, 84, 86	84
12 months	82	81, 84, 87	84
Grapes			
Day 0	-	96, 97, 97	97
1 month	94	94, 95, 95	95
3 months	90	92, 94, 95	94
6 months	82	86, 87, 87	87
12 months	90	86, 87, 87	87
Lettuce			
Day 0	-	102, 104, 105	104
1 month	100	99, 101, 102	101
3 months	90	94, 96, 97	96
6 months	86	86, 89, 92	89
12 months	89	84, 86, 87	86
Potatoes			
Day 0	-	99, 101, 102	101
1 month	96	98, 99, 99	99
3 months	86	90, 94, 97	94
6 months	84	83, 84, 85	84
12 months	84	81, 83, 85	83
Dry beans			
Day 0	-	74, 75, 75	75
1 month	85	83, 84, 84	84
3 months	83	86, 87, 87	87
6 months	80	80, 81, 82	81
12 months	77	78, 79, 80	79

Actual storage periods were 30 days (1 month), 92 days (3 months), 182 days (6 months) and 366 days (12 months).

Table 35 Recovery of glucoside of 4HP from stored fortified samples of plant matrices

Storage interval	Recovery (%) [0.1 mg/kg fortification]		
	Procedural	% remaining	Mean
Almonds			
Day 0	-	91, 92, 93	92
1 month	91	92, 93, 93	93
3 months	84	82, 83, 84	83
6 months	91	86, 87, 88	87
12 months	85	90, 91, 91	91
Oilseed rape seeds			
Day 0	-	84, 85, 86	85
1 month	85	79, 81, 83	81
3 months	74	62, 62, 62	62
6 months	80	65, 67, 68	67
12 months	78	71, 72, 72	72
Grapes			
Day 0	-	92, 93, 93	93
1 month	93	98, 100, 101	100

Storage interval	Recovery (%) [0.1 mg/kg fortification]		
	Procedural	% remaining	Mean
3 months	87	84, 86, 88	86
6 months	81	81, 83, 84	83
12 months	86	84, 85, 86	85
Lettuce			
Day 0	-	92, 93, 94	93
1 month	98	100, 100, 100	100
3 months	91	82, 85, 88	85
6 months	88	85, 86, 86	86
12 months	87	85, 87, 89	87
Potatoes			
Day 0	-	93, 94, 95	94
1 month	97	97, 98, 98	98
3 months	91	88, 88, 88	88
6 months	90	84, 86, 88	86
12 months	84	80, 82, 83	82
Dry beans			
Day 0	-	90, 91, 91	91
1 month	93	90, 92, 93	92
3 months	85	78, 79, 79	79
6 months	92	88, 88, 88	88
12 months	82	83, 84, 85	84

Actual storage periods were 30 days (1 month), 92 days (3 months), 182 days (6 months) and 366 days (12 months).

USE PATTERN

Isofetamid is registered in Canada and the USA for the control of fungal pathogens belonging to *Ascomycetes* and *Deuteromycetes* on grape, strawberry, lettuce, almond and oilseed rape. The Meeting received labels from Canada and USA. A draft label proposal for the EU zone was submitted to the Meeting. The information available to Meeting on registered uses of isofetamid is summarized in Table below.

Table 36 Registered uses of isofetamid for crops

Crop	Country	Formulation		Application					PHI, days and/or Application timing
		Type	Conc. of isofetamid	Method	Rate kg ai/ha	Volume L/ha	No. max	Application interval	
Grapes	Canada	SC	400 g/L	Foliar	0.58-0.64	200-1000	3	14	14
Grapes, Crop Subgroup 13-07F[b]	USA	SC	400 g/L	Foliar	0.58-0.64 Max 1.9 /year	468-935	ns	7-14	14
Low growing berry, Crop Subgroup 13-07G[b]	Canada	SC	400 g/L	Foliar	0.39-0.50	200-1000	5	7-14	0
Low growing berry, Crop Subgroup 13-07G[b]	USA	SC	400 g/L	Foliar	0.39-0.45 Max 1.6 /year	468-935 Aerial: 47-94	ns	14	0
Lettuce head and leaf	Canada	SC	400 g/L	Foliar	0.36	200-1000	2	14	14
Lettuce head and leaf	USA	SC	400 g/L	Foliar	0.36 Max 0.72 /year	468 Aerial: 47-94	ns	14	14

Crop	Country	Formulation		Application					PHI, days and/or Application timing
		Type	Conc. of isofetamid	Method	Rate kg ai/ha	Volume L/ha	No. max	Application interval	
Almond	USA	SC	400 g/L	Foliar	0.39-0.50 Max 2.0 /year	468-935 Aerial: 47-94	ns	7-14	Typically applications are started preventatively at pink bud and continued through petal fall. Do not apply after first cover.
Rapeseed, Crop Subgroup 20A[c]	Canada	SC	400 g/L	Foliar	0.30-0.35	200-1000	2	14	20-40% flowering (BBCH 62-64) and near the end of flowering (BBCH 67-69)
Rapeseed (Canola), Crop Subgroup 20A[c]	USA	SC	400 g/L	Foliar	0.30-0.35 Max 0.71 /year	468-935 Aerial: 47-94	ns	14	20-40% flowering (BBCH 62-64) and near the end of flowering (BBCH 67-69)

ns: not specified

Rotational crop restrictions in Canada and USA: Do not plant other crops not registered for the products within 30 days after the last application.

[a] Crop Subgroup 13-07 F (Small fruit vine climbing subgroup except fuzzy kiwifruit): Amur river grape; gooseberry; grape; kiwifruit, hardy; maypop; schisandra berry; and cultivars, varieties, and/or hybrids of these.

[b] Crop Subgroup 13-07G (Low growing berry subgroup): Bearberry; bilberry; blueberry, lowbush; cloudberry; cranberry; lingonberry; muntries; partridgeberry; strawberry; and cultivars, varieties, and/or hybrids of these.

[c] Crop Subgroup 20A (Rapeseed subgroup): Borage; crambe; cuphea; echium; flax seed; gold of pleasure; hare's ear mustard; lesquerella; lunaria; meadowfoam; milkweed; mustard seed; oil radish; poppy seed; rapeseed (*Brassica napus, B. campestris, and Crambe abyssinica* (oilseed-producing varieties only which include canola and crambe)); sesame; sweet rocket; and cultivars, varieties, and/or hybrids of these.

RESIDUES RESULTING FROM SUPERVISED TRIALS ON CROPS

The Meeting received information on isofetamid supervised field trials for the following crops.

Group	Commodity	Table
Stone fruits	Cherries	Table 37
	Plum	Table 38
	Apricot	Table 39
	Peach	Table 40
Berries and other small fruits	Grapes	Table 41, 42
	Strawberry	Table 43, 44
Leafy vegetables (including Brassica leafy vegetables)	Lettuce	Table 45, 46
Tree nuts	Almonds	Table 47
Oilseed	Oilseed Rape	Table 48, 49

Isofetamid formulations were applied for foliar treatments. Each of the field trial sites generally consisted of untreated control plot and treated plot. Application rates and spray concentrations have generally been rounded to two significant figures.

Residue values from the trials, which have been used for the estimation of maximum residue levels, STMRs and HRs, are underlined.

Laboratory reports included method validation with procedural recoveries from spiking at residue levels similar to those occurring in samples from the supervised trials. Date of analyses and duration of residue sample storage were also provided. Although trials included control plots, no

control data are recorded in the tables except when residues were found in samples from control plots. Residue data are not corrected for percent recovery.

Conditions of the supervised residue trials were generally well reported in detailed field reports. Most field reports provided data on the sprayers used, plot size, field sample size and sampling date.

The residue concentrations are reported for isofetamid and the glucoside of 4HP. Since the residue values were expressed as mg of the analyte/kg sample, the glucoside of 4HP needed to be converted into isofetamid equivalenst. The conversion factor is 0.75 (359.48/479.54 = 0.7496) for glucoside of 4HP. Residues for the glucoside of 4HP <LOQ are not converted.

Total residues for estimation of STMRs are calculated by summing up the concentrations of isofetamid and the glucoside of 4HP. In case that the residues of isofetamid were found at high levels, the glucoside of 4HP was also detected and the ratio of glucoside of 4HP depends on the commodity.

The method for calculation of the total residues for plant commodities is illustrated below.

Isofetamid	Glucoside of 4HP	Total
0.85	0.06	0.90 (0.85 + 0.06 × 0.75)
0.19	< 0.01	0.20 (0.19 + 0.01 × 0.75)
< 0.01	0.03	0.03 (0.01 + 0.03 × 0.75)
< 0.01	< 0.01	< 0.02 (0.01 + 0.01)

Stone fruits

Cherries

The Meeting received data from eight supervised residue trials (at harvest trials/end-point) on sweet cherry which were conducted in Europe (Schäufele, 2011 and 2012). In each trial, 3 foliar applications of a SC formulation (400 g/L isofetamid) were made to cherry trees. The application was made 47–68 days prior to the normal harvest of mature fruits.

The cherry samples were analysed for residues of isofetamid and glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The maximum storage interval for field-treated samples was 123 days.

Table 37 Residues of isofetamid and glucoside of 4HP on sweet cherry from supervised trials in Europe

Cherry, Sweet country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Ref: JSM0068 Schäufele, 2011 Sampling to analysis: 57-123 days										
France (South), 2010 Maguio (Badacsony)	SC	0.30 0.30 0.33	922 946 1016	0.032 0.032 0.032	55 65 69	3	52	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
Italy, 2010 Ruvo di Plugia/ Bari (Ferrovia)	SC	0.33 0.32 0.33	1013 993 1003	0.033 0.033 0.033	55 64-65 67	3	56	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
Ref: JSM0181 Schäufele, 2012 Sampling to analysis: 43-59 days										
France (South), 2011 Saulce sur Rhône (New moon)	SC	0.32 0.32 0.34	996 985 1050	0.032 0.0320.032	55 65 67	3	47	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
Italy, 2011 Crevalcore (Ferrovia)	SC	0.32 0.33 0.31	1003 1013 978	0.032 0.032 0.032	55 65 69	3	52	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02

Cherry, Sweet country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Ref: JSM0293 Schäufele, 2012 Sampling to analysis: 48-59 days										
Germany, 2012 Volkach Fahr (Sam)	SC	0.32 0.31 0.34	492 484 529	0.064 0.064 0.064	55 61 65	3	59	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
		0.26 0.25 0.26	499 485 502	0.051 0.051 0.051	55 61 65	3	59	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
Germany, 2012 Sommerhausen (Regina)	SC	0.30 0.33 0.34	474 523 533	0.064 0.064 0.064	55 61 65-67	3	68	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
		0.33 0.33 0.33	512 519 517	0.064 0.064 0.064	55 60 65-67	3	68	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
Germany, 2012 Neuenschleuse (Merchand)	SC	0.31 0.32 0.33	475 503 508	0.064 0.0640.064	55 65 67	3	58	< 0.01, < 0.01	0.01, 0.01	0.02, 0.02
								< 0.01, < 0.01	0.01, 0.01	0.02, 0.02
		0.21 0.22 0.22	487 527 525	0.042 0.042 0.042	55 65 67	3	58	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
Germany, 2012 Frankfurt/Oder OT Markendorf (Sam)	SC	0.32 0.32 0.32	989 992 1003	0.032 0.032 0.032	55 63 67	3	60	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
		0.38 0.39 0.41	992 1000 1051	0.039 0.039 0.039	55 63 67	3	60	< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02
								< 0.01, < 0.01	< 0.01, < 0.01	< 0.02, < 0.02

Portion analysed: Flesh without stones (up), Whole fruits (down)

Plum

The Meeting received data from 16 residue trials (eight decline and eight at harvest trials) on plums conducted in Europe (Schäufele, 2011 and 2012). In each trial, 3 foliar applications of a SC formulation (400 g/L isofetamid) were made to plum trees.

The plum samples were analysed for residues of isofetamid and glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The maximum storage interval for field-treated samples was 90 days.

Table 38 Residues of isofetamid and glucoside of 4HP on plum from supervised trials in Europe

Plum country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Ref: JSM0099 Schäufele, 2011 Sampling to analysis: 49-63 days										
France (South), 2010 Clairac (Prune d'Ente 70)	SC	0.39 0.37 0.39	537 515 537	0.072 0.072 0.072	77 78-81 78-81	3	-0 0 4 6 11 14	NA NA 0.15, 0.21 0.15, 0.21 0.14, 0.17 0.14, 0.19	NA NA < 0.01, 0.02 0.02, 0.02 0.02, 0.02 0.03, 0.03	NA NA 0.16, 0.23 0.17, 0.23 0.16, 0.19 0.16, 0.21

Plum country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
							-0 0 4 6 11 14	0.08, 0.12 0.19, 0.22 0.14, 0.19 0.14, 0.19 0.13, 0.16 0.13, 0.18	0.01, 0.02 0.01, 0.01 < 0.01, 0.02 0.02, 0.02 0.02, 0.02 0.03, 0.03	0.09, 0.14 0.20, 0.23 0.15, 0.21 0.16, 0.21 0.15, 0.18 0.15, 0.20
Italy, 2010 Aguscello/ Ferrara (TC Sun)	SC	0.36 0.36 0.36	993 989 1001	0.036 0.036 0.036	77 77-79 81-83	3	-0 0 3 7 11 14	0.03, 0.03 0.04, 0.04 0.02, 0.03 0.03, 0.04 0.02, 0.02 0.02, 0.02	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.04, 0.04 0.05, 0.05 0.03, 0.04 0.04, 0.05 0.03, 0.03 0.03, 0.03
							-0 0 3 7 11 14	0.03, 0.03 0.04, 0.04 0.02, 0.03 0.03, 0.04 0.02, 0.02 0.02, 0.02	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.04, 0.04 0.05, 0.05 0.03, 0.04 0.04, 0.05 0.03, 0.03 0.03, 0.03
Ref: JSM0204 Schäufele, 2012 Sampling to analysis: 32-90 days										
France (South), 2011 Mas Grenier (Ente 707)	SC	0.36 0.39 0.37	605 639 619	0.060 0.060 0.060	79-81 81-85 87-89	3	-0 0 3 7 10	0.30, 0.34 0.42, 0.59 0.35, 0.50 0.31, 0.42 0.31, 0.50	< 0.01, < 0.01 < 0.01, 0.01 < 0.01, 0.01 0.01, 0.01 0.01, 0.01	0.31, 0.35 0.43, 0.60 0.36, 0.51 0.32, 0.43 0.32, 0.51
							-0 0 3 7 10	0.27, 0.31 0.38, 0.54 0.32, 0.46 0.28, 0.38 0.29, 0.46	< 0.01, < 0.01 < 0.01, 0.01 < 0.01, 0.01 0.01, 0.01 0.01, 0.01	0.28, 0.32 0.39, 0.55 0.33, 0.47 0.29, 0.39 0.30, 0.47
Italy, 2011 Aguscello/ Ferrara (Angeleno)	SC	0.37 0.35 0.36	1012 978 996	0.036 0.036 0.036	77-81 79-81 83-85	3	-0 0 3 7 10	0.10, 0.11 0.09, 0.15 0.08, 0.08 0.04, 0.06 0.04, 0.05	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.11, 0.12 0.10, 0.16 0.09, 0.09 0.05, 0.07 0.05, 0.06
							-0 0 3 7 10	0.10, 0.11 0.09, 0.15 0.08, 0.08 0.04, 0.06 0.04, 0.05	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.11, 0.12 0.10, 0.16 0.09, 0.09 0.05, 0.07 0.05, 0.06
France (South), 2011 L'Honor de Cos (Bavay)	SC	0.36 0.36 0.35	598 604 586	0.060 0.060 0.060	75 77 85	3	7	0.12, 0.14 0.11, 0.13	< 0.01, < 0.01 < 0.01, < 0.01	0.13, 0.15 0.12, 0.14
Italy, 2011 Codrignano/ Borgo Tossignano (President)	SC	0.36 0.36 0.36	999 1001 987	0.036 0.036 0.036	81-83 83-85 85-87	3	6	0.14, 0.15 0.13, 0.14	0.01, 0.02 0.01, 0.02	0.15, 0.17 0.14, 0.16
Spain, 2011 Turis (Black Amber)	SC	0.39 0.36 0.35	960 895 868	0.040 0.040 0.040	81 81-85 85-87	3	7	0.03, 0.04 0.03, 0.04	< 0.01, < 0.01 < 0.01, < 0.01	0.04, 0.05 0.04, 0.05
Spain, 2011 Quatretonda (Black Gold)	SC	0.36 0.34 0.35	985 952 971	0.036 0.036 0.036	79-81 81 85	3	6	0.11, 0.14 0.10, 0.13	< 0.01, < 0.01 < 0.01, < 0.01	0.12, 0.15 0.11, 0.14
Ref: JSM0313 Schäufele, 2012 Sampling to analysis: 17-29 days										

Plum country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Germany, 2012 Volkach (Jojo)	SC	0.38 0.37 0.33	627 616 553	0.060 0.060 0.060	85 85 89-91	3	-0 0 2 6 9	0.08 0.36, 0.37 0.31 0.18, 0.20 0.19	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.09 0.37, 0.38 0.32 0.19, 0.21 0.20
							-0 0 2 6 9	0.08 0.34, 0.35 0.30 0.17, 0.19 0.18	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.09 0.35, 0.36 0.31 0.18, 0.20 0.19
		0.34 0.33 0.33	621 601 601	0.055 0.055 0.055	85 85 89-91	3	-0 0 2 6 9	0.14 0.42, 0.50 0.27 0.15, 0.17 0.23	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 0.01	0.15 0.43, 0.51 0.28 0.16, 0.18 0.24
							-0 0 2 6 9	0.13 0.38, 0.47 0.26 0.14, 0.16 0.22	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 0.01	0.14 0.39, 0.48 0.27 0.15, 0.17 0.23
Germany, 2012 Sommerhousen (Presenta)	SC	0.38 0.37 0.38	735 726 742	0.051 0.051 0.051	85 85 85-89	3	-0 0 4 7 10	0.04 0.16, 0.17 0.17 0.08, 0.10 0.06	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.05 0.17, 0.18 0.18 0.09, 0.11 0.07
							-0 0 4 7 10	0.04 0.15, 0.16 0.16 0.08, 0.09 0.06	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.05 0.16, 0.17 0.17 0.09, 0.10 0.07
		0.40 0.44 0.46	651 717 750	0.062 0.062 0.062	85 85 85-89	3	-0 0 4 7 10	0.04 0.20, 0.24 0.18 0.14, 0.15 0.09	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.05 0.21, 0.25 0.19 0.15, 0.16 0.10
							-0 0 4 7 10	0.04 0.19, 0.23 0.17 0.13, 0.14 0.08	< 0.01 < 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.05 0.20, 0.24 0.18 0.14, 0.15 0.09
Germany, 2012 Fahr (top)	SC	0.36 0.33 0.33	506 458 460	0.072 0.072 0.072	85 85 85-89	3	6	0.19, 0.19 0.18, 0.18	< 0.01, < 0.01 < 0.01, < 0.01	0.20, 0.20 0.19, 0.19
		0.24 0.27 0.26	470 518 498	0.052 0.052 0.052	85 85 85-89	3	6	0.11, 0.12 0.10, 0.11	< 0.01, < 0.01 < 0.01, < 0.01	0.12, 0.13 0.11, 0.12
Germany, 2012 Büchelberg (Hauszwetschge)	SC	0.38 0.38 0.38	531 533 522	0.072 0.072 0.072	85 85 85-89	3	8	0.19, 0.21 0.18, 0.20	< 0.01, < 0.01 < 0.01, < 0.01	0.20, 0.22 0.19, 0.21
		0.49 0.49 0.48	534 537 524	0.092 0.092 0.092	85 85 85-89	3	8	0.15, 0.15 0.14, 0.14	< 0.01, < 0.01 < 0.01, < 0.01	0.16, 0.16 0.15, 0.15
Ref: JSM0509 Schäufele, 2013 Sampling to analysis: 14-50 days										

Plum country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Germany, 2013 Volkach (Cacaks Schöne)	SC	0.37 0.35 0.37	608 590 613	0.060 0.060 0.060	81 85 87	3	0 4 8 11	0.22, 0.23 0.15 0.15, 0.16 0.11	< 0.01, 0.01 0.01 0.01, 0.02 0.01	0.23, 0.24 0.16 0.16, 0.18 0.12
							0 4 8 11	0.21, 0.22 0.14 0.14, 0.15 0.11	< 0.01, 0.01 0.01 0.01, 0.02 0.01	0.22, 0.23 0.15 0.15, 0.17 0.12
		0.28 0.30 0.30	592 617 614	0.048 0.048 0.048	81 85 87	3	0 4 8 11	0.20, 0.21 0.13 0.10, 0.11 0.08	< 0.01, 0.01 < 0.01 0.01, 0.02 0.02	0.21, 0.22 0.14 0.11, 0.13 0.10
							0 4 8 11	0.19, 0.20 0.12 0.10, 0.11 0.08	< 0.01, 0.01 < 0.01 0.01, 0.02 0.02	0.20, 0.21 0.13 0.11, 0.13 0.10
Germany, 2013 Volkach (Elene)	SC	0.36 0.37 0.37	590 611 609	0.060 0.060 0.060	81-84 85 85	3	0 4 7 10	0.40, 0.52 0.47 0.35, 0.40 0.24	< 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.41, 0.53 0.48 0.36, 0.41 0.25
							0 4 7 10	0.38, 0.49 0.44 0.33, 0.28 0.23	< 0.01, < 0.01 < 0.01 < 0.01, < 0.01 < 0.01	0.39, 0.50 0.45 0.34, 0.29 0.24
		0.61 0.63 0.65	587 616 629	0.103 0.103 0.103	81-84 85 85	3	0 4 7 10	1.1, 1.1 0.77 0.58, 0.65 0.51	< 0.01, < 0.01 < 0.01 < 0.01, 0.01 0.01	1.1, 1.1 0.78 0.59, 0.66 0.52
							0 4 7 10	1.0, 1.1 0.73 0.55, 0.62 0.49	< 0.01, < 0.01 < 0.01 < 0.01, 0.01 0.01	1.0, 1.1 0.74 0.56, 0.63 0.50
Hungary, 2013 Velence (Besztercei)	SC	0.35 0.35 0.35	984 977 977	0.036 0.036 0.036	79 81 87	3	7	0.22, 0.24 0.20, 0.23	< 0.01, < 0.01 < 0.01, < 0.01	0.23, 0.25 0.21, 0.24
		0.43 0.43 0.43	999 1000 996	0.043 0.043 0.043	79 81 87	3	7	0.14, 0.17 0.13, 0.16	< 0.01, < 0.01 < 0.01, < 0.01	0.15, 0.18 0.14, 0.17
Hungary, 2013 Gárdony (President)	SC	0.36 0.35 0.34	988 977 957	0.036 0.036 0.036	75 81 85	3	7	0.12, 0.14 0.11, 0.13	0.01, 0.02 0.01, 0.02	0.12, 0.16 0.12, 0.15
		0.43 0.44 0.42	1001 1010 964	0.043 0.043 0.043	75 81 85	3	7	0.21, 0.22 0.20, 0.21	0.01, 0.02 0.01, 0.02	0.22, 0.24 0.21, 0.23

Portion analysed: Flesh without stones (up), Whole fruits (down)
-0: on the day of the last application, directly before the application took place
NA: Not available, the samples were not mature enough to separate the stones from the flesh, therefore the entire fruits with stone were homogenized and analysed.

Apricot

The Meeting received data from eight residue trials (at harvest trials) on apricot which were conducted in Europe (Schäufele, 2011 and 2012). In each trial, 3 foliar applications of a SC formulation (400 g/L isofetamid) were made to apricot trees. The application was made 82–128 days prior to the normal harvest of mature fruits.

The apricot samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The maximum storage interval for field-treated samples was 101 days.

Table 39 Residues of isofetamid and glucoside of 4HP on apricot from supervised trials in Europe

Apricot country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Ref: JSM0067 Schäufele, 2011 Sampling to analysis: 42-99 days										
Spain, 2010 Turis (Mitger)	SC	0.30 0.30 0.33	941 941 1018	0.032 0.032 0.032	55 57-59 61-62	3	84	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02
France (South), 2010 Aubord (Jmbocot)	SC	0.29 0.31 0.33	906 960 1014	0.033 0.033 0.033	55 57 65	3	90	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02
France (South), 2010 Beaucaire (Fardao)	SC	0.31 0.32 0.31	952 986 944	0.033 0.033 0.033	55 65 69	3	128	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02
Italy, 2010 Poggio Renatico /Ferrara (Portici)	SC	0.32 0.33 0.34	988 1004 1031	0.033 0.033 0.033	55 65 71	3	89	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02
Ref: JSM0180 Schäufele, 2012 Sampling to analysis: 66-101 days										
France (South), 2011 Eurre (Bergeron)	SC	0.31 0.31 0.32	955 969 983	0.032 0.032 0.032	55 59 65	3	104	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02
Italy, 2011 Aguscello (Pisana)	SC	0.32 0.32 0.32	1006 989 983	0.032 0.032 0.032	55 65 69	3	95	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02
Spain, 2011 Godelleta (Mitger)	SC	0.33 0.32 0.33	1019 983 1042	0.032 0.032 0.032	55 62 67	3	82	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02
Spain, 2011 Quatretonda (Tadeo)	SC	0.33 0.33 0.33	1019 1013 1037	0.032 0.032 0.032	55 61 67	3	90	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02

Portion analysed: Flesh without stones (up), Whole fruits (down)

Peach

The Meeting received data from eight residue trials (four decline and four at harvest trials) on apricots conducted in Europe (Schäufele, 2011 and 2012). In each trial, 3 foliar applications of a SC formulation (400 g/L isofetamid) were made to peach trees.

The peach samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The maximum storage interval for field-treated samples was 97 days.

Table 40 Residues of isofetamid and glucoside of 4HP on peach from supervised trials in Europe

Peach country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Ref: JSM0098 Schäufele, 2011 Sampling to analysis: 54-85 days										
France (South), 2010 Maguio (Ryan sun)	SC	0.34 0.36 0.36	473 498 503	0.072 0.072 0.072	75 81 85	3	-0 0 2 7 9 14	0.24, 0.33 0.54, 0.78 0.41, 0.52 0.19, 0.29 0.12, 0.16 0.11, 0.22	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.25, 0.34 0.55, 0.79 0.42, 0.53 0.20, 0.30 0.13, 0.17 0.12, 0.23

Peach country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
							-0 0 2 7 9 14	0.23, 0.31 0.52, 0.74 0.39, 0.50 0.18, 0.28 0.12, 0.15 0.11, 0.21	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.24, 0.32 0.53, 0.75 0.40, 0.51 0.19, 0.29 0.13, 0.16 0.12, 0.22
Italy, 2010 Poggio Renatico (Suncrest)	SC	0.36 0.36 0.36	1004 992 988	0.036 0.036 0.036	76 78-81 81-83	3	-0 0 3 7 10 14	0.06, 0.11 0.19, 0.26 0.11, 0.14 0.07, 0.08 0.04, 0.05 0.02, 0.02	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, 0.01 < 0.01, < 0.01 0.01, 0.01	0.07, 0.12 0.20, 0.27 0.12, 0.15 0.08, 0.09 0.05, 0.06 0.03, 0.03
							-0 0 3 7 10 14	0.06, 0.10 0.18, 0.24 0.10, 0.13 0.07, 0.08 0.04, 0.05 0.02, 0.02	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, 0.01 < 0.01, < 0.01 0.01, 0.01	0.07, 0.11 0.19, 0.25 0.11, 0.14 0.08, 0.09 0.05, 0.06 0.03, 0.03
France (South), 2010 Redessam (Emmanuelle)	SC	0.37 0.36 0.35	517 496 483	0.072 0.072 0.072	75 78 81	3	-0 0 4 7 11	0.39, 0.53 1.1, 1.1 0.37, 0.64 0.38, 0.47 0.30, 0.42	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.40, 0.54 1.1, 1.1 0.38, 0.65 0.39, 0.48 0.31, 0.43
							-0 0 4 7 11	0.35, 0.49 0.98, 1.0 0.34, 0.58 0.35, 0.43 0.28, 0.39	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.36, 0.50 0.99, 1.0 0.35, 0.59 0.36, 0.44 0.29, 0.40
Italy, 2010 Codrignano Locality/ Borgo Tossignano (Kaweah)	SC	0.36 0.36 0.37	1000 1004 1014	0.036 0.036 0.036	76 79 81-83	3	-0 0 3 7 9 15	0.09, 0.16 0.13, 0.19 0.12, 0.15 0.03, 0.08 0.07, 0.08 0.06, 0.07	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.10, 0.17 0.14, 0.20 0.13, 0.16 0.04, 0.09 0.08, 0.09 0.07, 0.08
							-0 0 3 7 9 15	0.09, 0.15 0.12, 0.18 0.11, 0.14 0.03, 0.08 0.07, 0.08 0.06, 0.07	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.10, 0.16 0.13, 0.19 0.12, 0.15 0.04, 0.09 0.08, 0.09 0.07, 0.08
Ref: JSM0203 Schäufele, 2012 Sampling to analysis: 55-97 days										
France (South), 2011 Eurre (Coraline)	SC	0.35 0.37 0.31	961 1022 851	0.036 0.036 0.036	75 77 79	3	7	0.15, 0.16 0.14, 0.15	< 0.01, < 0.01 < 0.01, < 0.01	0.16, 0.17 0.15, 0.16
Italy, 2011 Poggio Renatico (Maria Marta)	SC	0.36 0.35 0.36	983 976 989	0.036 0.036 0.036	75 77-81 85	3	7	0.06, 0.14 0.06, 0.13	< 0.01, < 0.01 < 0.01, < 0.01	0.07, 0.15 0.07, 0.14
Spain, 2011 Turis (Spring Crest)	SC	0.38 0.38 0.39	1038 1043 1075	0.036 0.036 0.036	73 75 81-85	3	7	0.34, 0.34 0.32, 0.32	< 0.01, < 0.01 < 0.01, < 0.01	0.35, 0.35 0.33, 0.33
Spain, 2011 Quatretonda (Catherine)	SC	0.36 0.36 0.37	803 799 818	0.045 0.045 0.045	75 78 81-85	3	7	0.10, 0.18 0.09, 0.16	< 0.01, < 0.01 < 0.01, < 0.01	0.11, 0.19 0.10, 0.17

Portion analysed: Flesh without stones (up), Whole fruits (down)

-0: on the day of the last application, directly before the application took place

Berries and other small fruits

Grapes

The Meeting received data from from 25 supervised residue trials (12 decline and 13 at harvest trials) on grapes conducted in Europe (Schäufele, 2011 and 2012). Eight trials (four decline and four at harvest trials) were conducted in Northern Europe and 17 trials (eight decline and nine at harvest trials) were in Southern Europe. In each trial, 2 foliar applications of a SC formulation (400 g/L isofetamid) were made to grape vines.

The grape samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The maximum storage interval for field-treated samples was 115 days.

Table 41 Residues of isofetamid and glucoside of 4HP on grapes from supervised trials in Europe

Grapes country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Ref: JSM0100 Schäufele, 2011 Sampling to analysis: 44-102 days										
Germany, 2010 Sommerhausen (Domina) Red wine grape	SC	0.63 0.59	680 644	0.092 0.092	83 85	2	0 15 21 28 35	1.4 0.57 0.98 0.93 1.1	< 0.01 < 0.01 0.01 0.02 0.01	1.4 0.58 0.99 0.95 1.1
France (North), 2010 Genille (Chenin) White wine grape	SC	0.61 0.63	806 833	0.075 0.075	80 85	2	0 13 20 27 34	0.56 0.27 0.18 0.22 0.13	< 0.01 0.01 0.02 0.02 0.01	0.57 0.28 0.20 0.24 0.14
France (South), 2010 Nages et Solorgues (Chardonnay) White wine grape	SC	0.58 0.58	481 485	0.12 0.12	79 81-85	2	0 14 20 27 36	0.85 0.41 0.30 0.36 0.27	0.01 0.02 0.03 0.04 0.05	0.86 0.43 0.32 0.39 0.31
Italy, 2010 Imola (Sangiovese) Red wine grape	SC	0.61 0.59	812 783	0.075 0.075	81 85	2	0 14 21 28 34	0.34 0.22 0.15 0.13 0.07	< 0.01 0.01 < 0.01 < 0.01 < 0.01	0.35 0.23 0.16 0.14 0.08
Italy, 2010 Capurso/ Bari (Black pearl) Red table grape	SC	0.62 0.59	620 588	0.10 0.10	83 85	2	0 14 21 28 35	2.6, 2.6 2.7, 3.0 3.0, 3.1 2.3, 2.5 3.0, 3.2	0.01, 0.02 0.02, 0.02 0.02, 0.02 0.02, 0.02 0.03, 0.03	2.6, 2.6 2.7, 3.0 3.0, 3.1 2.3, 2.5 3.0, 3.2
Ref; JSM0101 Schäufele, 2011 Sampling to analysis: 28-76 days										
Germany, 2010 Iphofen (Müller Thurgau) White wine grape	SC	0.61 0.62	661 667	0.092 0.092	79 81	2	18	0.49	0.02	0.51
		1.2 1.2	659 665	0.19 0.19	79 81	2	18	1.0	0.02	1.0
France (North), 2010 Chervey (Pinot Noir) Red wine grape	SC	0.61 0.60	806 795	0.075 0.075	79 85	2	21	0.36	0.01	0.37
		1.2 1.2	810 812	0.15 0.15	79 85	2	21	0.72	0.02	0.74
France (South), 2010 Argellieres (Mourvedre) Red wine grape	SC	0.60 0.60	398 396	0.15 0.15	85 85	2	20	< 0.01	< 0.01	< 0.02
		1.2 1.2	396 398	0.30 0.30	85 85	2	20	2.2	< 0.01	2.2
Spain, 2010 Turis (Malvasia) White wine grape	SC	0.60 0.61	805 815	0.075 0.075	77 79-81	2	21	0.22	< 0.01	0.23
Spain, 2010 Turis (Moscatel)	SC	0.66 0.59	879 790	0.075 0.075	79 83	2	21	0.17	0.07	0.22

Grapes country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
White table grape										
Spain, 2011 Agost (Red Globe) Red table grape	SC	0.66 0.56	876 749	0.075 0.075	77-79 83	2	0 7 14 21 28	1.9 0.92 1.0 0.38 0.65	0.16 0.13 0.23 0.16 0.32	2.0 1.0 1.2 0.50 0.89
Italy, 2011 Palombaio (Italia) White table grape	SC	0.61 0.60	807 801	0.075 0.075	76 78	2	0 7 14 21 28	2.6 2.0 2.2 1.3 1.1	< 0.01 0.04 0.06 0.06 0.09	2.6 2.0 2.2 1.3 1.2
Greece, 2011 Nea Fili (Sultanina) White table grape	SC	0.59 0.60	783 799	0.075 0.075	77 79	2	0 7 14 20 27	2.0 1.9 1.3 1.4 1.2	0.03 0.04 0.05 0.07 0.05	2.0 1.9 1.3 1.5 1.2
Spain, 2011 Estacion Blanca (Napoleon) Red table grape	SC	0.58 0.64	767 856	0.075 0.075	79 81-83	2	21	0.87	0.04	0.90
Italy, 2011 Noicattaro (Red Globe) Red table grape	SC	0.60 0.58	795 775	0.075 0.075	77 78	2	21	1.3	0.15	1.4
Greece, 2011 Kariani (Thompson Seedless) White table grape	SC	0.62 0.59	823 779	0.075 0.075	77 79	2	20	0.78	0.04	0.81
Ref: JSM0209 Schäufele, 2012 Sampling to analysis: 27-83 days										
Germany, 2011 Groβlangheim (Regent) Red wine grape	SC	0.63 0.63	627 629	0.10 0.10	79-81 83-85	2	0 14 21 28 35	3.7 3.2 3.0 1.3 2.1	0.04 0.12 0.12 0.13 0.17	3.7 3.3 3.1 1.4 2.2
France (North), 2011 Chaintré (Chardonnay) White wine grape	SC	0.61 0.60	604 595	0.10 0.10	77-79 79	2	0 14 21 28 35	1.3 0.67 0.48 0.37 0.34	0.02 0.05 0.06 0.09 0.10	1.3 0.71 0.53 0.44 0.42
France (South), 2011 Fronton (Sauvignon) White wine grape	SC	0.61 0.63	504 523	0.12 0.12	77 79-81	2	0 14 21 28 35	2.9 0.87 0.69 0.72 0.51	0.03 0.04 0.05 0.09 0.08	2.9 0.90 0.73 0.79 0.57
Italy, 2011 Palombaio Bitonto (Uva di Troia) Red wine grape	SC	0.62 0.61	819 804	0.075 0.075	79 83	2	0 14 21 28 35	3.0 0.84 1.0 1.3 0.90	0.04 0.03 0.06 0.08 0.08	3.0 0.86 1.0 1.4 0.96
Ref: JSM0210 Schäufele, 2012 Sampling to analysis: 27-83 days										
Germany, 2011 Marktbreit (Bacchus) White wine grape	SC	0.54 0.63	633 741	0.085 0.085	77 81	2	21	1.38	0.10	1.5

Grapes country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
France (North), 2011 La Chapelle de Guinchay (Carignan) Red wine grape	SC	0.61 0.62	604 613	0.10 0.10	77 81-83	2	21	0.39	0.02	0.41
France (South), 2011 Fronton (Garmay) Red wine grape	SC	0.63 0.64	523 532	0.12 0.12	77-79 83-85	2	21	1.39	0.12	1.5
France (South), 2011 Nimes (Grenache) Red wine grape	SC	0.61 0.63	504 522	0.12 0.12	79 81-83	2	21	0.25	0.02	0.27
Spain, 2011 Turis (Moscatel) White wine grape	SC	0.60 0.63	795 833	0.075 0.075	77 81-83	2	21	0.52	0.12	0.61

Portion analysed: grape bunches

The trials were conducted at 15 sites in grape growing regions in the USA (14 sites) and Canada (1 site) (Wiedmann, 2012: IB-2011- JLW-002- 01-01). Three applications of isofetamid 400 g/L SC formulation at about 10-day intervals were made to the treated plots at a target rate 0.65 kg ai/ha. The total application rate ranged from 1.9–2.2 kg ai/ha. The spray application volumes ranged from 786–1815 L/ha.

The grape samples were analysed for residues of isofetamid and glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. Grapes were fortified over the range of 0.01-5.0 mg/kg for isofetamid and glucoside of 4HP. The averages and standard deviations for isofetamid and the glucoside of 4HP in grapes (n=18) were 101 ± 6.8 and 98.3 ± 8.5%, respectively. The sampling to extraction interval for the grapes ranged from 168- 218 days.

Table 42 Residues of isofetamid and glucoside of 4HP on grapes from supervised trials in Canada and USA

Grapes country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.		Isofetamid	Glucoside of 4HP	Total
Canada, GAP	SC	0.58-0.64			14	3	14			
USA, GAP	SC	0.58-0.64 max. 1.9 kg ai/ha/year			7-14		14			
USA, 2011 Dundee/NY (Concord)	SC	0.66 0.670.66	938 952 944	81 83 85	- 10 11	3	14	0.95, 1.2 mean 1.1	0.02, 0.02 mean 0.02	0.96, 1.2 Mean 1.1
USA, 2011 Orefield/PA (Concord)	SC	0.66 0.65 0.66	1518 1498 1518	79 83 85	- 13 9	3	9 14 19 24 28	0.14, 0.15 0.12, 0.12 mean 0.12 0.07, 0.08 0.06, 0.06 0.06, 0.08	0.04, 0.04 0.02, 0.04 mean 0.03 0.03, 0.03 0.02, 0.03 0.04, 0.04	0.16, 0.17 0.14, 0.15 mean 0.14 0.09, 0.10 0.07, 0.08 0.09, 0.10
USA, 2011 Comstock Park/MI (Concord)	SC	0.65 0.65 0.65	1160 1135 1144	Immature fruit Immature fruit 80% mature	- 10 10	3	14	0.60, 0.85 mean 0.73	0.06, 0.06 mean 0.06	0.64, 0.90 mean 0.77
Canada, 2011 Branchton/Ontario (Concord)	SC	0.73 0.74 0.74	1456 1470 1469	77-79 81-83 84	- 10 10	3	14	0.15, 0.19 mean 0.17	< 0.01, < 0.01 mean < 0.01	0.16, 0.20 mean 0.18
USA, 2011 Oregon/WI (Concord)	SC	0.75 0.60 0.66	864 1069 797	Not recorded 80% mature 90-95% mature	- 11 10	3	14	1.5, 1.6 mean 1.5	0.02, 0.02 mean 0.02	1.5, 1.6 mean 1.6

Grapes country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.		Isofetamid	Glucoside of 4HP	Total
USA, 2011 Orland/CA (Rubired)	SC	0.65 0.64 0.65	934 930 936	34 day PHI 24 day PHI 14 day PHI	- 10 10	3	14	1.3, 2.6 mean 1.9	0.10, 0.06 mean 0.08	1.4, 2.6 mean 2.0
USA, 2011 Arbuckle/CA (Muscat)	SC	0.65 0.65 0.65	936 937 939	34 day PHI 24 day PHI 14 day PHI	- 10 10	3	14	0.48, 1.2 mean 0.84	0.06, 0.11 mean 0.09	0.53, 1.3 mean 0.91
USA, 2011 Sanger/CA (Flame Seedless)	SC	0.73 0.65 0.65	1030 899 905	Veraison +11 days +20 days	- 11 9	3	14	0.42, 0.56 mean 0.49	0.04, 0.03 mean 0.04	0.45, 0.59 mean 0.52
USA, 2011 Madera/CA (Ruby Red) Wine	SC	0.66 0.67 0.68	935 952 965	79 83 85	- 10 10	3	16	0.16, 0.18 mean 0.17	0.04, 0.02 mean 0.03	0.18, 0.20 mean 0.19
USA, 2011 Lindsay/CA (Globe) Table	SC	0.65 0.67 0.66	785 809 797	86 86 89	- 10 11	3	14	0.79, 0.86 mean 0.82	0.14, 0.15 mean 0.15	0.89, 0.97 mean 0.93
USA, 2011 Dinuba/CA (Ruby Red) Wine	SC	0.66 0.65 0.66	1811 1722 1785	87 87 88-89	- 9 10	3	14	0.41, 0.62 mean 0.51	0.01, 0.01 mean 0.01	0.42, 0.63 mean 0.52
USA, 2011 Selma/CA (Crimson)	SC	0.66 0.65 0.65	789 785 794	85 88 88	- 11 9	3	14	0.77, 0.89 mean 0.83	0.01, < 0.01 mean < 0.01	0.78, 0.90 mean 0.84
USA, 2011 Kingsburg/CA (Thompson) Table	SC	0.66 0.65 0.65	1528 1518 1537	85 85 85	- 9 10	3	14	0.49, 0.59 mean 0.54	0.04, 0.06 mean 0.05	0.52, 0.64 mean 0.58
USA, 2011 Ephrata/WA (White Riesling)	SC	0.65 0.65 0.65	934 931 944	79 81 83	- 10 10	3	14	0.83, 0.91 mean 0.87	0.01, 0.02 mean 0.02	0.84, 0.92 mean 0.88
USA, 2011 Granger/WA (Riesling)	SC	0.66 0.65 0.65	957 947 933	Grapes touching Immature fruit Immature grapes	- 10 10	3	9 14 19 24 29	0.56, 0.62 0.55, 0.69 mean 0.62 0.64, 0.71 mean 0.67 0.50, 0.57 0.51, 0.75	0.02, 0.02 0.03, 0.03 mean 0.03 0.03, 0.03 mean 0.03 0.03, 0.03 0.03, 0.04	0.58, 0.64 0.57, 0.71 mean 0.64 0.66, 0.72 mean 0.69 0.52, 0.59 0.53, 0.78

Portion analysed: grape bunches

Strawberry

The Meeting received data from 24 residue trials on strawberry conducted in Europe (2011 to 2013). Sixteen trials were conducted in Northern Europe and eight trials were in Southern Europe. In each trial, 2 foliar applications of a SC formulation (400 g/L isofetamid) were made to strawberries.

The strawberry samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The maximum storage interval for field-treated samples was 163 days.

Table 43 Residues of isofetamid and glucoside of 4HP on strawberry from supervised trials in Europe

Strawberry country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Ref: JSM0179 Schäufele, 2012 Sampling to analysis: 55-112 days										
Italy, 2011 Poggio Renatico (Alba) Outdoor	SC	0.48 0.47	800 788	0.060 0.060	81 85-89	2	-0 0 1 3	0.03, 0.03 0.14, 0.18 0.15, 0.15 0.10, 0.10	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.04, 0.04 0.15, 0.19 0.16, 0.16 0.11, 0.11

Strawberry country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Italy, 2011 Policoro (Najad) Polytunnel	SC	0.47 0.51	782 844	0.060 0.060	88-89 88-89	2	-0 0 1 3	0.12, 0.20 0.29, 0.31 0.20, 0.41 0.18, 0.19	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.13, 0.21 0.30, 0.32 0.21, 0.42 0.19, 0.20
Spain, 2011 Bollullos par del Condado (Sabrina) Polytuunel	SC	0.47 0.47	387 393	0.12 0.12	87-89 87-89	2	-0 0 1 3	0.09, 0.11 0.37, 0.41 0.30, 0.34 0.22, 0.29	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.10, 0.12 0.38, 0.42 0.31, 0.35 0.23, 0.30
Spain, 2011 Quatretonda (Camarosa) Outdoor	SC	0.47 0.47	387 390	0.12 0.12	87 87-89	2	-0 0 1 3	0.09, 0.13 0.70, 0.75 0.61, 0.65 0.51, 0.57	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.10, 0.14 0.71, 0.76 0.62, 0.66 0.52, 0.58
Ref: JSM0188, ISK-G301TO305-11 Brewin, 2012 Sampling to analysis: 43-163 days										
Netherlands, 2011 Siebengewald (Elsanta) Indoor	SC	0.48 0.48	604 600	0.080 0.080	85 85-87	2	0 1 3	0.77 0.58 0.69	< 0.01 < 0.01 < 0.01	0.78 0.59 0.70
Belgium, 2011 Nivelles (Darselect) Indoor	SC	0.49 0.47	610 593	0.080 0.080	85 87	2	0 1 3	0.60 0.40 0.40	< 0.01 < 0.01 < 0.01	0.61 0.41 0.41
France (North), 2011 Vivy (Darselect) Outdoor	SC	0.47 0.51	485 527	0.096 0.096	89 89	2	0 1 3	0.34 0.28 0.22	< 0.01 < 0.01 < 0.01	0.35 0.29 0.23
Belgium, 2011 Ittre (Lambada) Indoor	SC	0.49 0.49	608 608	0.080 0.080	85 87-89	2	1 3	0.39 0.34	< 0.01 < 0.01	0.40 0.35
France, (North) 2011 Chouze Sur Loire (Mara) Indoor	SC	0.48 0.47	498 492	0.096 0.096	87 87	2	1 3	0.25 0.32	< 0.01 < 0.01	0.26 0.33
Ref: JSM0189 Schäufele, 2012 Sampling to analysis: 34-57 days										
Germany, 2011 Oberpleichfeld (Darselect) Outdoor	SC	0.49 0.49	512 509	0.096 0.096	87 87-89	2	-0 0 1 3	0.17 0.35 0.24 0.22	< 0.01 < 0.01 < 0.01 < 0.01	0.18 0.36 0.25 0.23
Germany, 2011 Untersteinbach (Sonata) Outdoor	SC	0.48 0.46	596 571	0.080 0.080	87 89	2	1 3	0.15 0.18	< 0.01 < 0.01	0.16 0.19
Germany, 2011 Goch-Kessel (Elsanta) Outdoor	SC	0.49 0.49	813 810	0.060 0.060	83-85 87-89	2	1 3	0.50 0.44	< 0.01 < 0.01	0.51 0.45
Ref: JSM0265 Schäufele, 2012 Sampling to analysis: 34-78 days										
Italy, 2012 Poggio Renatico (Asia) Outdoor	SC	0.47 0.46	483 480	0.096 0.096	81-85 85-87	2	1 3	0.20, 0.25 0.12, 0.17	< 0.01, < 0.01 < 0.01, < 0.01	0.21, 0.26 0.13, 0.18
France (South), 2012 Bessières (Mara des Bois) Outdoor	SC	0.49 0.49	503 507	0.096 0.096	81 87	2	1 3	0.20, 0.31 0.13, 0.21	< 0.01, < 0.01 < 0.01, < 0.01	0.21, 0.32 0.14, 0.22

Strawberry country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Spain, 2012 Bollullos par del Condado (Splendor) Polytunnel	SC	0.49 0.48	613 600	0.080 0.080	87 87	2	1 3	0.76, 1.0 0.59, 0.70	< 0.01, < 0.01 < 0.01, < 0.01	0.77, 1.0 0.60, 0.71
France (South), 2012 Cambes (Gariguette) Hydroponic cultivation	SC	0.47 0.50	486 517	0.096 0.096	85 87	2	1 3	1.8, 1.9 1.9, 2.2	< 0.01, < 0.01 < 0.01, < 0.01	1.8, 1.9 1.9, 2.2
Ref: JSM0275, ISK-G211 TO214-12 Miller, 2012 Sampling to analysis: 17-69 days										
Germany, 2012 Kalkar-Wisselward (Sonata) Outdoor	SC	0.49 0.48	405 402	0.12 0.12	85 87	2	0 1 3	0.51 0.30 0.17	< 0.01 < 0.01 < 0.01	0.52 0.31 0.18
Germany, 2012 Goch-Kessel (Lambada) Outdoor	SC	0.48 0.49	402 405	0.12 0.12	85 87	2	0 1 3	0.12 0.11 0.12	< 0.01 < 0.01 < 0.01	0.13 0.12 0.13
Belgium, 2012 Ittre (Lambada) Outdoor	SC	0.49 0.49	615 613	0.080 0.080	85 87	2	1 3	0.33 0.26	< 0.01 < 0.01	0.34 0.27
Netherlands, 2012 Siebengewald (Elsanta) Outdoor	SC	0.49 0.48	405 402	0.12 0.12	85 87	2	1 3	0.64 0.36	< 0.01 < 0.01	0.65 0.37
Ref: JSM0527 ISK-G601, TO604-13 Loriau, 2013 Sampling to analysis: 69-107 days										
Belgium, 2013 Mont-Sainte-Geneviève (Darselect) Indoor	SC	0.49 0.48	607 600	0.080 0.080	73-81 87	2	1 3	0.18 0.23	< 0.01 < 0.01	0.19 0.24
France (North), 2013 Allonnes (Cijosè) Indoor	SC	0.46 0.47	497 507	0.092 0.092	65 83	2	1 3	0.31 0.25	< 0.01 < 0.01	0.32 0.26
Belgium, 2013 Ittre (Lambada) Indoor	SC	0.49 0.48	618 605	0.080 0.080	81 87	2	0 1 3	0.16 0.16 0.11	< 0.01 < 0.01 < 0.01	0.17 0.17 0.12
Netherlands, 2013 Siebengewald (Elegance) Indoor	SC	0.52 0.48	547 500	0.096 0.096	81-83 85-87	2	0 1 3	1.1 0.72 0.60	< 0.01 < 0.01 < 0.01	1.1 0.73 0.61

Portion analysed: fruits

-0: on the day of the last application, directly before the application took place

The trials were conducted at 11 sites in strawberry growing regions in the USA (10 sites) and Canada (1 site). Five applications (4 at one site) of isofetamid 400 g/L SC formulation were made to the treated plots at about 7-days intervals at a target rate 0.47 kg ai/ha. The total application rate ranged from 2.3–2.4 kg ai/ha. The spray application volumes ranged from 196–364 L/ha (Wiedmann, 2012: IB-2011- JLW-005- 01-01).

The strawberry samples were analysed for residues of isofetamid and glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. Strawberries were fortified over the range of 0.01–

2.6 mg/kg for isofetamid and the glucoside of 4HP (n=14) were 100 ± 5.7 and 97.5 ± 5.2%, respectively. The sampling to extraction interval for the strawberries ranged from 42–202 days.

Table 44 Residues of isofetamid and glucoside of 4HP on strawberries from supervised trials in Canada and USA

Strawberry country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.		Isofetamid	Glucoside of 4HP	Total
Canada, GAP	SC	0.39-0.50			7-14	5	0			
USA, GAP	SC	0.39-0.45 max. 1.6 kg ai/ha/year			14		0			
USA, 2012 New Tripoli/PA (Earliglow)	SC	0.47 0.47 0.47 0.46 0.48 (2.3)	236 235 235 228 238	65-67 67-73 65-73 65-85 87	- 7 7 7 8	5	0 1 3 7	0.45, 0.48 mean <u>0.47</u> 0.18, 0.23 0.13, 0.16 0.06, 0.07	0.01, < 0.01 mean 0.01 < 0.01, < 0.01 0.01, 0.01 0.01, 0.01	0.46, 0.48 mean 0.47 0.19, 0.24 0.14, 0.17 0.07, 0.08
USA, 2012 Jeffersonville/GA (Jewel)	SC	0.46 0.47 0.47 0.46 0.46 (2.3)	325 327 328 324 325	71 73 85 87 89	- 7 7 8 6	5	0	0.29, 0.35 mean <u>0.32</u>	< 0.01, < 0.01 mean < 0.01	0.30, 0.35 mean 0.32
USA, 2012 Winter Garden/FL (Camerosa)	SC	0.46 0.46 0.46 0.46 0.46 (2.3)	218 215 216 218 215	81 85 87 87 87	- 7 7 7 7	5	0	2.3, <u>3.1</u> mean <u>2.7</u>	0.01, 0.01 mean 0.01	2.3, 3.1 mean 2.7
Canada, 2012 St. Marc sar Richelieu/Quebec (Seascape)	SC	0.46 0.46 0.47 0.47 0.47 (2.3)	243 246 249 249 249	71-73 73-81 73-85 81-85 87	- 7 6 8 7	5	0	0.44, 0.51 mean <u>0.48</u>	< 0.01, < 0.01 mean < 0.01	0.45, 0.52 mean 0.48
USA, 2012 Oregon/WI (Jewel)	SC	0.48 0.47 0.47 0.47 0.48 (2.4)	274 270 244 278 275	Early bloom Late bloom Fruit set Early ripening Mature fruit	- 7 7 7 7	5	0	0.13, 0.20 mean <u>0.16</u>	< 0.01, < 0.01 mean < 0.01	0.14, 0.20 mean 0.17
USA, 2012 Deerfield[a]/MI (Governor Simcoe)	SC	0.94 0.47 0.47 0.47 (2.3)	196 198 191 198	86 87 88 89	- 6 6 6	4	0	0.33, 0.72 mean 0.53	< 0.01, < 0.01 mean < 0.01	0.34, 0.72 mean 0.53
USA, 2012 Deerfield[b]/MI (Allstar)	SC	0.47 0.48 0.47 0.48 0.47 (2.4)	196 201 198 196 196	81 85 87 88 89	- 7 8 6 6	5	0	0.27, 0.35 mean <u>0.31</u>	< 0.01, < 0.01 mean < 0.01	0.28, 0.36 mean 0.32
USA, 2012 Porterville/CA (Albion)	SC	0.47 0.47 0.47 0.47 0.47 (2.3)	364 364 365 363 363	81-85 82-85 82-87 82-87 85-89	- 7 7 8 5	5	0	0.43, 0.56 mean <u>0.50</u>	0.02, 0.02 mean 0.02	0.44, 0.58 mean 0.51
USA, 2012 Sanger/CA (Albion)	SC	0.48 0.48 0.47 0.46 0.47 (2.4)	287 287 279 278 283	Mature Mature Mature Mature Mature	- 7 7 7 8	5	0	0.45, 0.63 mean <u>0.54</u>	< 0.01, < 0.01 mean < 0.01	0.46, 0.64 mean 0.55

Strawberry country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.		Isofetamid	Glucoside of 4HP	Total
USA, 2012 Santa Maria/CA (Monterey)	SC	0.46 0.46 0.47 0.47 0.47 (2.3)	280 270 292 295 284	73 73 81 85 87	- 6 7 7 7	5	0	1.0, 1.1 mean 1.0	< 0.01, < 0.01 mean < 0.01	1.0, 1.1 mean 1.0
USA, 2012 Hillsboro/OR (Fern)	SC	0.47 0.47 0.47 0.47 0.47 (2.3)	234 235 234 237 236	Bloom to Red fruits	- 7 7 7 7	3	0	1.1, 1.3 mean 1.2	0.02, 0.03 mean 0.02	1.1, 1.3 Mean 1.2

Portion analysed: fruits

[a] From Deerfield, head west on Deerfield Rd. for 6.5 miles. The site is on the left at intersection of Grosvenor Hwy and Deerfield Rd. Application date: 6/8 – 6/26, 2012

[b] From Deerfield, head west on Deerfield Rd. for 7.5 miles. Turn south onto Rogers Hwy and go 0.7 miles. Turn west on Pope Rd and the site is on the right. Application date: 5/30 – 6/26, 2012

Leafy vegetables (including Brassica leafy vegetables)

Lettuce

The Meeting received data from 26 residue trials (11 decline and 15 at harvest trials) on lettuce which were conducted in Europe (2011 and 2012). Sixteen trials (seven decline and nine at harvest trials) were conducted in Northern Europe and 10 trials (four decline and six at harvest trials) were in Southern Europe. In each trial, 2 foliar applications of a SC formulation (400 g/L isofetamid) were made to lettuce.

The lettuce samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The maximum storage interval for field-treated samples was 137 days.

Table 45 Residues of isofetamid and glucoside of 4HP on lettuce from supervised trials in Europe

Lettuce country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Leaf lettuce	Ref: JSM0247 Schäufele, 2012 Sampling to analysis: 72-124 days									
France (South), 2011 Merville (Funtasia) Batavia Outdoor	SC	0.39 0.42	482 522	0.080 0.080	19 42	2	0 3 7 14 21	14 3.4 0.98 0.14 0.04	0.05 0.10 0.09 0.03 0.01	14 3.5 1.0 0.16 0.05
Italy, 2011 Cavazzana Luisa (Susibel) Gentilina Outdoor	SC	0.40 0.41	393 410	0.10 0.10	16 42	2	0 3 7 14 21	17 0.88 0.10 0.05 < 0.01	0.05 0.09 0.05 0.03 < 0.01	17 0.95 0.14 0.07 < 0.02
Italy, 2011 Bitonto (Gentilina) Gentilina Outdoor	SC	0.44 0.44	655 650	0.067 0.067	19-20 42-43	2	0 3 7 14 21	14 7.5 0.54 0.09 0.05	< 0.01 0.01 0.01 < 0.01 < 0.01	14 7.5 0.55 0.10 0.06
Spain, 2011 Meliana (Filipus) Romana Outdoor	SC	0.37 0.37	373 365	0.10 0.10	42 45	2	0 2 7 14 22	9.1 1.4 0.15 0.02 < 0.01	0.12 0.14 0.11 0.05 0.02	9.2 1.5 0.23 0.06 0.03
Leaf lettuce	Ref: JSM0249, ISK-G501 TO504-11 Brewin, 2012 Sampling to analysis: 82-103 days									

Lettuce country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Germany, 2011 Goch-Nierswalde (Livorno) Field	SC	0.39 0.41	389 411	0.10 0.10	23 41	2	0 3 7 14 21	9.2 7.1 2.8 2.0 0.43	0.02 0.04 0.05 0.06 0.03	9.2 7.1 2.9 2.0 0.45
France (North), 2011 Tinqueux (Quelio) Field	SC	0.40 0.39	300 280	0.13 0.14	44 45	2	21	0.29	0.06	0.34
Germany, 2011 Goch-Nierswalde (Cavernet) Field	SC	0.41 0.42	408 417	0.10 0.10	23 41	2	21	0.45	0.03	0.47
Leaf lettuce	Ref: JSM0250, ISK-G505 TO508-11 Brewin, 2012 Sampling to analysis: 63-137days									
France, 2011 Saint Genouph (Kitonia) Indoor	SC	0.41 0.43	311 322	0.13 0.13	43 46	2	0 3 7 14 21	18 12 13 7.3 4.0	0.03 0.02 0.04 0.04 0.02	18 12 13 7.3 4.0
Netherlands, 2011 Aijen (Aleppo rz) Indoor	SC	0.42 0.41	421 406	0.10 0.10	19 41	2	0 3 7 14 21	11 10 7.1 4.4 2.6	0.04 0.05 0.07 0.03 0.02	11 10 7.2 4.4 2.6
France, 2011 La Chapelle de Guinchay (Arcadia) Indoor	SC	0.42 0.42	313 317	0.13 0.13	15-16 45-46	2	21	10, 13	0.08, 0.09	10, 13
UK, 2011 Wellesbourne (Bowl) Indoor	SC	0.41 0.42	307 317	0.13 0.13	16-18 42	2	21	28, 32	0.09, 0.09	28, 32
Head & leaf lettuce	Ref: JSM0266 Schäufele, 2012 Sampling to analysis: 49-111 days									
Italy, 2012 Granarolo Emilia (Fungsong) Head lettuce Outdoor	SC	0.39 0.41	383 403	0.10 0.10	43 44	2	21	0.01	0.02	0.03
France (South), 2012 Saint-Jory (Model) Head lettuce Outdoor	SC	0.42 0.42	420 420	0.10 0.10	43 45	2	21	< 0.01	< 0.01	< 0.02
Spain, 2012 Almenara (Sirmai) Oak leaf lettuce Outdoor	SC	0.40 0.41	600 607	0.067 0.067	17-18 19	2	20	0.02	< 0.01	0.03
Spain, 2012 Blanca (Baby) Baby lettuce Outdoor	SC	0.40 0.42	395 415	0.10 0.10	15 18-19	2	20	< 0.01	< 0.01	< 0.02
Head & leaf lettuce	Ref: JSM0274 Schäufele, 2012 Sampling to analysis: 34-117 days									
Italy, 2012 Granarolo Emilia (Jazzie) Head lettuce	SC	0.39 0.39	386 386	0.10 0.10	43 46	2	21	< 0.01	< 0.01	< 0.02

Lettuce country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.		Isofetamid	Glucoside of 4HP	Total
Plactic tunnel										
Spain, 2012 Valencia (Cervantes) Head lettuce Romana Greenhouse	SC	0.38 0.42	375 419	0.10 0.10	18 19	2	20	0.01	< 0.01	0.02
France (North), 2012 Flavy le Martel (Justine) Head lettuce Greenhouse	SC	0.41 0.41	310 310	0.13 0.13	15 19	2	20	0.04	< 0.01	0.05
Germany, 2012 Goch-Nierswalda (Lollo Bionda) Lollo Bionda Greenhouse	SC	0.41 0.41	307 304	0.13 0.13	17 43	2	0 3 7 14 20	31 20 15 6.8 3.7	0.02 0.05 0.06 0.07 0.10	31 20 15 6.8 3.8
Netherlamds, 2012 Siebengewald (Lollo Bionda) Lollo Bionda Greenhouse	SC	0.42 0.40	312 300	0.13 0.13	19 30	2	0 2 7 14 21	11 9.0 1.6 0.11 < 0.01	< 0.01 < 0.01 < 0.01 < 0.01 < 0.01	11 9.0 1.6 0.12 < 0.02
Germany, 2012 Goch-Nierswalde (Lollo Bionda) Lollo Bionda Greenhouse	SC	0.42 0.39	317 292	0.13 0.13	19 25	2	21	0.02	< 0.01	0.03
Leaf lettuce	Ref: JSM0276, ISK-G201 TO205-12 Brewin, 2012						Sampling to analysis: 11-53 days			
Netherlamds, 2012 Siebengewald (Lollo Bionda) Outdoor	SC	0.42 0.43	317 320	0.13 0.13	19 45	2	0 3 7 14 21	4.5 0.33 0.07 0.03 < 0.01	0.02 0.02 0.02 0.01 < 0.01	4.6 0.35 0.09 0.04 < 0.02
France (North), 2012 Ambillou (Guetary) Outdoor	SC	0.39 0.40	290 300	0.13 0.13	19 43	2	0 3 7 14 21	13 5.0 0.98 0.28 0.10	0.06 0.10 0.19 0.13 0.08	13 5.1 1.1 0.38 0.16
Germany, 2012 Goch-Kessel (Lollo Rosso) Outdoor	SC	0.40 0.40	303 297	0.13 0.13	19 33	2	21	0.03	< 0.01	0.04
UK, 2012 Bicester (Green Salad Bowl) Outdoor	SC	0.38 0.41	283 312	0.13 0.13	14 14-16	2	21	0.22	0.11	0.30
UK, 2012 Warwick (Green Salad Bowl) Outdoor	SC	0.41 0.42	307 320	0.13 0.13	16-18 47	2	21	0.03	0.02	0.05

Portion analysed: whole plants

The trials were conducted at 11 sites for head lettuce and 12 sites for leaf lettuce in lettuce growing regions in the USA (20 sites) and Canada (3 sites). Two applications of isofetamid 400 g/L SC formulation at about 9 to 10-day intervals were made to the treated plots at a target rate 0.36 kg ai/ha. The total application rate ranged from 0.70–0.76 kg ai/ha. The spray application volumes ranged from 187–409 L/ha (Wiedmann, 2012: IB-2011- JLW-006- 01-01).

The lettuce samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. Lettuce was fortified over the range of 0.01–5.2 mg/kg for isofetamid and the glucoside of 4HP. The averages and standard deviations for concurrent recoveries of isofetamid and the glucoside of 4HP in lettuce (n=28) were 92.8 ± 10.2 and 97.1 ± 4.7%, respectively. The sampling to extraction interval for the lettuce ranged from 23–139 days.

Table 46 Residues of isofetamid and glucoside of 4HP on lettuce from supervised trials in Canada and USA

Lettuce country, year (variety)	Application						DALA Days	Portion analysed	Residues, mg/kg		
	For m	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.			Isofetamid	Glucoside of 4HP	Total
Canada, GAP	SC	0.36			14	2	14				
USA, GAP	SC	0.36 max. 0.72 kg ai/ha/year			14		14				
USA, 2012 Germansville/PA (Ithaca) Head lettuce	SC	0.37 0.36 (0.73)	285 282		- 9	2	13	w	< 0.01, 0.01 mean <u>0.01</u>	< 0.01, < 0.01 mean < 0.01	< 0.02, 0.02 mean 0.02
								w/o	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Seven Springs/NC (Green Vision) Leaf lettuce	SC	0.36 0.37 (0.73)	287 296	39 48	- 10	2	14	all	0.31, 0.47 mean <u>0.39</u>	0.27, 0.28 mean 0.28	0.52, 0.68 mean 0.60
USA, 2011 Bradenton/FL (Summertime) Head lettuce	SC	0.37 0.38 (0.76)	371 409	Vegetative Vegetative	- 10	2	13	w	0.15, 0.27 mean <u>0.21</u>	0.04, 0.07 mean 0.06	0.18, 0.32 mean 0.25
								w/o	< 0.01, 0.02 mean 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, 0.03 mean 0.02
USA, 2011 Bradenton/FL (Green Tower - Romaine) Leaf lettuce	SC	0.35 0.36 (0.71)	345 387	Vegetative Vegetative	- 10	2	13	all	0.73, 0.78 mean <u>0.76</u>	0.22, 0.22 mean 0.22	0.90, 0.95 mean 0.92
USA, 2012 Verona/WI (Sylvesta) Head lettuce	SC	0.37 0.36 (0.73)	248 260	Vegetative	- 9	2	13	w	0.31, 0.38 mean <u>0.34</u>	0.07, 0.08 mean 0.08	0.36, 0.44 mean 0.40
								w/o	0.05, 0.06 mean 0.05	0.03, 0.03 mean 0.03	0.07, 0.08 mean 0.07
USA, 2012 Verona/WI (Black Seeded Simpson) Leaf lettuce	SC	0.37 0.36 (0.73)	253 255	Vegetative Vegetative	- 10	2	14	all	0.14, 0.16 mean <u>0.15</u>	0.02, 0.02 mean 0.02	0.16, 0.17 mean 0.17
Canada, 2012 Branchton/Ontario (Caliente M.I.) Butterhead lettuce	SC	0.38 0.35 (0.73)	295 268	29-41 41-43	- 10	2	14	w	0.15, 0.19 mean <u>0.17</u>	0.07, 0.09 mean 0.08	0.21, 0.26 mean 0.23
								w/o	0.01, 0.01	< 0.01,	0.02,

Lettuce country, year (variety)	Application						DALA Days	Portion analysed	Residues, mg/kg		
	For m	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.			Isofetamid	Glucoside of 4HP	Total
									mean 0.01	0.02 mean 0.01	0.03 mean 0.02
USA, 2012 Seymour/IL (Green Ice) Leaf lettuce	SC	0.38 0.37 (0.75)	243 237	47 48	- 10	2	14	all	0.03, 0.07 mean 0.05	0.02, 0.02 mean 0.02	0.05, 0.08 mean 0.07
Canada, 2012 St-Marc-sur-Richelieu/Quebec (Rapsody) Head lettuce	SC	0.35 0.35 (0.71)	243 244	18-19 41	- 10	2	14	w	< 0.01, < 0.01 mean < 0.01	0.10, 0.10 mean 0.10	0.08, 0.09 mean 0.08
								w/o	< 0.01, < 0.01 mean < 0.01	0.02, 0.03 mean 0.02	0.02, 0.03 mean 0.03
Canada, 2012 St-Marc-sur-Richelieu/Quebec (Green Tower) Leaf lettuce	SC	0.36 0.34 (0.70)	245 237	18-19 19	- 10	2	14	all	< 0.01, < 0.01 mean < 0.01	0.01, 0.01 mean 0.01	0.02, 0.02 mean 0.02
USA, 2012 Sharon/ND (Romaine) Leaf lettuce	SC	0.36 0.36 (0.72)	278 280	18 20	- 9	2	14	all	0.06, 0.10 mean 0.08	< 0.01, < 0.01 mean < 0.01	0.07, 0.10 mean 0.09
USA, 2011 Kerman/CA (Crisphead) Head lettuce	SC	0.36 0.36 (0.72)	279 280	45 47	- 9	2	14	w	2.1, 4.7 mean 3.4	0.02, 0.03 mean 0.02	2.2, 4.7 mean 3.5
								w/o	0.84, 0.97 mean 0.90	0.01, 0.01 mean 0.01	0.85, 0.98 mean 0.91
USA, 2011 Kerman/CA (Tahema) Leaf lettuce	SC	0.36 0.36 (0.72)	282 279	33 35	- 10	2	14	all	1.4, 1.4 mean 1.4	0.18, 0.16 mean 0.17	1.5, 1.5 mean 1.5
USA, 2011 Porterville/CA (Vandenberg) Head lettuce	SC	0.36 0.36 (0.72)	280 277	42 47	- 9	2	14	w	0.33, 0.36 mean 0.35	0.04, 0.05 mean 0.04	0.36, 0.40 mean 0.38
								w/o	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2012 King City/CA (Hornet) Leaf lettuce	SC	0.36 0.37 (0.73)	307 306	46 48	- 10	2	13	all	< 0.01, 0.02 mean 0.01	< 0.01, 0.02 mean 0.01	< 0.02, 0.03 mean 0.03
USA, 2012 Sanger/CA (Great Lakes) Head lettuce	SC	0.36 0.36 (0.72)	278 281	42 45	- 10	2	14	w	0.22, 0.36 mean 0.29	0.02, 0.05 mean 0.03	0.24, 0.39 mean 0.32
								w/o	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2012 Sanger/CA (Salad Bowl) Leaf lettuce	SC	0.37 0.36 (0.73)	288 281	33 45	- 10	2	14	all	0.84, 0.91 mean 0.88	0.13, 0.11 mean 0.12	0.94, 1.0 mean 0.97
USA, 2012 Santa Maria/CA (N/A)	SC	0.37 0.36 (0.72)	281 278	43 46	- 10	2	14	w	0.33, 0.35 mean 0.34	0.02, 0.02 mean 0.02	0.34, 0.36 mean

Lettuce country, year (variety)	Application						DALA Days	Portion analysed	Residues, mg/kg		
	For m	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.			Isofetamid	Glucoside of 4HP	Total
Head lettuce											0.35
								w/o	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2012 Santa Maria/CA (Romaine Greenthunder) Leaf lettuce	SC	0.35 0.37 (0.72)	270 285	42 45	- 10	2	14	all	< 0.01, 0.02 mean 0.01	0.01, 0.01 mean 0.01	0.02, 0.02 mean 0.02
USA, 2011 Corning/CA (N/A) Head lettuce	SC	0.36 0.35 (0.71)	188 187		- 10	2	14	w	0.82, 1.9 mean 1.4	< 0.01, 0.01 mean 0.01	0.83, 1.9 mean 1.4
								w/o	0.03, 0.05 mean 0.04	< 0.01, < 0.01 mean < 0.01	0.03, 0.06 mean 0.05
USA, 2011 Corning/CA (Sun Valley) Leaf lettuce	SC	0.35 0.35 (0.71)	187 187		- 10	2	14	all	4.7, 5.2 mean 4.9	0.11, 0.11 mean 0.11	4.7, 5.3 mean 5.0
USA, 2012 Santa Maria[3)]/CA (Oso flaco) Head lettuce	SC	0.36 0.34 (0.70)	267 285	42 50% Head	- 9	2	13	w	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
								w/o	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2012 Santa Maria/CA (Bergham Green) Leaf lettuce	SC	0.37 0.34 (0.71)	272 284	33 25-30% rosette	- 9	2	9 13 19 24 28	all	0.08, 0.10 0.01, 0.01 mean 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.03, 0.03 0.02, 0.02 mean 0.02 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.10, 0.13 0.02, 0.03 mean 0.02 < 0.02, < 0.02 < 0.02, < 0.02 < 0.02, < 0.02

Portion analysed; w: with wrapper leaves, w/o: without wrapper leaves, all: whole plant

Tree nuts

Almonds

The trials were conducted at five sites in almond growing regions in the USA. Four applications of isofetamid 400 g/L SC formulation were made at approximately 10-day intervals to the treated plots at a target rate 0.50 kg ai/ha. The total application rate ranged from 1.99–2.02 kg ai/ha. The spray application volumes ranged from 1038–1441 L/ha (Wiedmann, 2012: IB-2011- JLW-001- 01-01).

The Almond samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. Nutmeat fortifications for almond were performed over the range of 0.01–0.10 mg/kg for isofetamid and the glucoside of 4HP. The average recoveries and standard deviations for isofetamid and glucoside of 4HP in almond nutmeats (n=10) were 98.8 ±

11.0 and 105.1 ± 9.1%, respectively. The sampling to extraction interval for nutmeats ranged from 113–175 days.

Table 47 Residues of isofetamid and glucoside of 4HP on almond nutmeats from supervised trials in USA

Almonds country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS	App. interval	no.		Isofetamid	Glucoside of 4HP	Total
USA, GAP	SC	0.39-0.50 max. 2.0 kg ai/ha/year			7-14					
USA, 2011 Chico/CA (Non-Pareil)	SC	0.50 0.50 0.50 0.50 (2.0)	1038 1038 1038 1038	[a]	- 10 10 14	4	158	< 0.01, < 0.01 mean ≤ 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Orland/CA (Non-Pareil)	SC	0.50 0.50 0.50 0.50 (2.0)	1038 1038 1038 1038	[b]	- 13 10 10	4	159 169 179 189	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 mean ≤ 0.01	< 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 < 0.02, < 0.02 < 0.02, < 0.02 < 0.02, < 0.02 mean < 0.02
USA, 2011 Wasco/CA (Fritz)	SC	0.55 0.45 0.49 0.50 (2.0)	1412 1394 1384 1412	[c]	- 10 9 10	4	217	< 0.01, < 0.01 mean ≤ 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Coalinga/CA (Non-Pareil)	SC	0.51 0.50 0.50 0.50 (2.0)	1441 1422 1422 1403	[d]	- 9 11 10	4	172	< 0.01, < 0.01 mean ≤ 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Turlock/CA (Padres)	SC	0.50 0.50 0.51 0.50 (2.0)	1412 1394 1422 1403	[e]	- 9 10 8	4	198	< 0.01, < 0.01 mean ≤ 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02

Portion analysed: nutmeats

[a] 1: Bud break green tip to popcorn 10%, 2: Bud break full bloom to popcorn, 3: Full bloom, 4: Petal fall

[b] 1: Bud break/green tip, 2: Full bloom, 3: Petal fall, 4: Nut development

[c] 1: Blossom break, 2: Full bloom, 3: Lots of petals on ground, leaves beginning to show, all buds have opened. 4: Still a few blossoms on trees, many leaves, many nuts forming from BB to large peanut sized.

[d] 1: 5 years old trees at blossom break, 2: Bloom, 3: Full bloom (most buds have bloomed), petals have begun to fall, 4: Many new leaves; many petals on ground; small, raisin-sized fruits (nuts) forming

[e] 1: Blossom break, 2: Full bloom ~90% of blossoms open, just starting to fall, 3: Many petals on ground, flowers present but ready to fall, very small nuts forming. BB sized to small raisin sized. Many leaves present, about 1" long and 3/8~1/2" wide. 4: Many leaves up to 3.5 inches long and 1 inch wide. Most petals fallen; only a few still hanging on. Nuts from BB to olive pit sized.

Oilseed

Rape seed

The Meeting received data from seven trials (three decline and four at harvest trials) on oilseed rape which were conducted in Europe. Five trials (two decline and three at harvest trials) were conducted in Northern Europe and two trials (one decline and one at harvest trial) were in Southern Europe. In each trial, a foliar application of a SC formulation (400 g/L isofetamid) was made to oilseed rape.

The oilseed rape samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. The sampling to extraction interval for oilseed rape ranged from 9–98 days.

Table 48 Residues of isofetamid and glucoside of 4HP on oilseed rape from supervised trials in Europe

Rape seed country, year (variety)	Application						DALA Days	Portion analysed	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	kg ai/hL	BBCH	no.			Isofetamid	Glucoside of 4HP	Total
Ref: JSM0090 Schäufele, 2011 Sampling to analysis: 9-98 days											
Germany, 2010 Dettelbach-Effeldorf (Visby)	SC	0.32	313	0.10	65	1	0 14 27 34 42	Whole plant without roots	1.8 0.10 0.01 < 0.01 < 0.01	< 0.01 0.02 < 0.01 < 0.01 < 0.01	1.8 0.12 0.02 < 0.02 < 0.02
							34 42	Pods	< 0.01 < 0.01	< 0.01 < 0.01	< 0.02 < 0.02
							84	Seeds	< 0.01	< 0.01	< 0.02
Germany, 2010 Volkach (Visby)	SC	0.33	324	0.10	65	1	75	Seeds	< 0.01	< 0.01	< 0.02
Germany, 2010 Goch-Nierswalde (Billy)	SC	0.31	311	0.10	65	1	72	Seeds	< 0.01	< 0.01	< 0.02
France (North), 2010 Rouvres-Saint-Jean (Adriana)	SC	0.30	302	0.10	65	1	0 14 28 35 42	Whole plant without roots	1.6 0.30 0.08 0.08 0.03	< 0.01 0.01 < 0.01 < 0.01 < 0.01	1.6 0.31 0.09 0.09 0.04
							28 35 42	Pods	< 0.01 < 0.01 < 0.01	< 0.01 < 0.01 < 0.01	< 0.02 < 0.02 < 0.02
							83	Seeds	< 0.01	< 0.01	< 0.02
France (North), 2010 Clery-saint-Andre (Catalina)	SC	0.31	309	0.10	65-67	1	76	Seeds	< 0.01	< 0.01	< 0.02
France (South), 2010 Saint Porquier (Coquelicot)	SC	0.32	322	0.10	65	1	0 14 28 36 42	Whole plant without roots	2.2 0.03 0.02 < 0.01 < 0.01	< 0.01 < 0.01 < 0.01 < 0.01 < 0.01	2.2 0.04 0.03 < 0.02 < 0.02
							28 36 42	Pods	< 0.01 < 0.01 < 0.01	< 0.01 < 0.01 < 0.01	< 0.02 < 0.02 < 0.02
							71	Seeds	< 0.01	< 0.01	< 0.02
France (South), 2010 Barry D'Islemande (Corali)	SC	0.30	300	0.10	65	1	64	Seeds	< 0.01	< 0.01	< 0.02

The trials were conducted at 17 sites in oilseed rape growing regions in Canada and the USA. Two applications of isofetamid 400 g/L SC formulation at 6 to 29-day intervals were made to the treated plots at a target rate 0.30 kg ai/ha. The total annual application rate ranged from 0.59–0.67 kg ai/ha. The spray application volumes ranged from 193–242 L/ha (Wiedmann, 2012: IB-2011- JLW-004- 01-01).

The oilseed rape samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. Oilseed rape (canola) was fortified over the range of 0.01–0.42 mg/kg for isofetamid and the glucoside of 4HP. The averages and standard deviations for

isofetamid and the glucoside of 4HP in canola (n=38) were 90.8 ± 6.6 and 94.1 ± 6.7%, respectively. The sampling to extraction interval for the canola seed ranged from 52–176 days.

Table 49 Residues of isofetamid and glucoside of 4HP on oilseed rape from supervised trials in Canada and USA

Oilseed rape country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.		Isofetamid	Glucoside of 4HP	Total
Canada, GAP	SC	0.30-0.35			14	2	BBCH 62-64 67-69			
USA, GAP	SC	0.30-0.35 max. 0.71 kg ai/ha/year			14					
USA, 2012 Seven Springs/NC (Colza D'Hiver)	SC	0.31 0.30 (0.61)	234 234	25% Flower 67	- 15	2	38	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Northwood/ND (Invigor LL 8440)	SC	0.31 0.30 (0.61)	225 235	64 68	- 8	2	19 32 33 40	0.01, 0.01 mean 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 mean < 0.01 < 0.01, < 0.01 < 0.01, < 0.01 < 0.01, < 0.01	0.02, 0.02 mean 0.02 < 0.02, < 0.02 < 0.02, < 0.02 < 0.02, < 0.02
USA, 2011 McVille/ND (Invigor LL 8440)	SC	0.30 0.30 (0.60)	235 235	62 67	- 12	2	35	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Carrington/ND (Invigor LL 8440)	SC	0.30 0.32 (0.61)	232 230	62 69	- 13	2	42	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Velva/ND (DKL 52-41)	SC	0.30 0.31 (0.61)	235 238	62 69	- 15	2	33	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Ephrata/WA (73-45 RR)	SC	0.30 0.30 (0.59)	232 234	63 69	- 16	2	35	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
USA, 2011 Jerome/ID (A7191/Cultivar 274)	SC	0.31 0.30 (0.61)	206 195	64 67	- 11	2	33	< 0.01, 0.01 mean 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, 0.02 mean 0.02
USA, 2011 Hermiston/OR (05-M9-EXP)	SC	0.30 0.30 (0.60)	235 234	63 Bloom complete	- 22	2	27	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2011 Fort Saskatchewan/ Alberta (72-65 RR)	SC	0.30 0.31 (0.61)	201 209	64 67	- 12	2	58	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2011 Kipp/Alberta (9553 RR Canola)	SC	0.29 0.31 (0.60)	193 203	62-64 67-69	- 17	2	60	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2-11 Monarch/Alberta (9553 RR Canola)	SC	0.30 0.31 (0.61)	199 204	62-64 65-69	- 6	2	48	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2011 Alvena/ Saskatchewan (Roundup Ready)	SC	0.34 0.34 (0.67)	242 240	62-64 69	- 20	2	41	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2011 Blaine Lake/ Saskatchewan (71-45 RR)	SC	0.31 0.30 (0.61)	204 202	60-64 67-76	- 29	2	35	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2011 Rosthern/ Saskatchewan (5770)	SC	0.30 0.30 (0.60)	201 198	62-64 69-75	- 21	2	25 32 40	< 0.01, < 0.01 < 0.01, < 0.01	< 0.01, < 0.01 < 0.01, < 0.01	< 0.02, < 0.02 < 0.02, < 0.02

Oilseed rape country, year (variety)	Application						DALA Days	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS (BBCH)	App. interval	no.		Isofetamid	Glucoside of 4HP	Total
							46	0.01, 0.01 mean 0.01 < 0.01, < 0.01	< 0.01, < 0.01 mean < 0.01 < 0.01, < 0.01	0.02, 0.02 mean 0.02 < 0.02, < 0.02
Canada, 2011 Carberry/Manitoba (In Vigor L130)	SC	0.31 0.30 (0.61)	206 202	64 69	- 14	2	36	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2011 Minto/ Manitoba (71-45 RR)	SC	0.31 0.31 (0.61)	205 203	63 67	- 9	2	43	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02
Canada, 2011 Boissevain/ Manitoba (71-45 RR)	SC	0.31 0.30 (0.60)	204 196	64 67	- 6	2	43	< 0.01, < 0.01 mean < 0.01	< 0.01, < 0.01 mean < 0.01	< 0.02, < 0.02 mean < 0.02

Portion analysed: seed

Almond hulls

The Meeting received data from five supervised residue were conducted in almond growing regions of the USA. Four applications of isofetamid 400 g/L SC formulation were made at approximately 10-day intervals to the treated plots at a target rate 0.50 kg ai/ha. The total application rate ranged from 1.99–2.02 kg ai/ha. The spray application volumes ranged from 1038–1441 L/ha (Wiedmann, 2012: IB-2011- JLW-001- 01-01).

The Almond samples were analysed for residues of isofetamid and the glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. Almond hulls were fortified over the range of 0.01–0.4 mg/kg for isofetamid and the glucoside of 4HP. The averages and standard deviations for isofetamid and the glucoside of 4HP in almond hulls (n=11) were 92.5 ± 2.8 and 94.5 ± 7.1%, respectively. The sampling to extraction interval for the almond hulls ranged from 94–159 days.

Table 50 Residues of isofetamid and glucoside of 4HP on almond hulls from supervised trials in USA

Almonds country, year (variety)	Application						DALA Days	DW %	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS	App. interval	no.			Isofetamid	Glucoside of 4HP	Total
USA, GAP	SC	0.39-0.50 max. 2.0 kg ai/ha/year			14						
USA, 2011 Chico/CA (Non-Pareil)	SC	0.50 0.50 0.50 0.50 (2.0)	1038 1038 1038 1038	[a] [b]	- 10 10 14	4	158		< 0.01, < 0.01 mean < 0.01	0.03, 0.04 mean 0.04	0.03, 0.04 mean 0.04
								86, 87	< 0.01, < 0.01 mean < 0.01	0.04, 0.04 mean 0.04	0.04, 0.04 mean 0.04
USA, 2011 Orland/CA (Non-Pareil)	SC	0.50 0.50 0.50 0.50 (2.0)	1038 1038 1038 1038	[c] [d]	- 13 10 10	4	159 169 179 189		0.19, 0.23 mean 0.21 0.02, 0.03 < 0.01, < 0.01 < 0.01, < 0.01	0.12, 0.15 mean 0.14 0.15, 0.13 0.03, 0.03 0.03, 0.03	0.28, 0.35 mean 0.31 0.14, 0.12 0.03, 0.04 0.03, 0.03
							159 169 179 189	53, 51 63, 67 80, 81 79, 83	0.36, 0.46 mean 0.41 0.03, 0.04 < 0.01, < 0.01 < 0.01, < 0.01	0.23, 0.31 mean 0.27 0.23, 0.20 0.04, 0.04 0.03, 0.03	0.54, 0.68 mean 0.61 0.21, 0.19 0.04, 0.04 0.03, 0.04
USA, 2011 Wasco/CA	SC	0.55 0.45	1412 1394	[e] [a]	- 10	4	217		< 0.01, < 0.01 mean < 0.01	0.04, 0.04 mean 0.04	0.04, 0.04 mean 0.04

Almonds country, year (variety)	Application						DALA Days	DW %	Residues, mg/kg		
	Form	kg ai/ha	water, L/ha	GS	App. interval	no.			Isofetamid	Glucoside of 4HP	Total
(Fritz)		0.49 0.50 (2.0)	1384 1412		9 10			76, 73	< 0.01, < 0.01 mean <u>≤ 0.01</u>	0.05, 0.06 mean 0.05	0.05, 0.05 mean 0.05
USA, 2011 Coalinga/CA (Non-Pareil)	SC	0.51 0.50 0.50 0.50 (2.0)	1441 1422 1422 1403	[b] [c]	- 9 11 10	4	172		< 0.01, < 0.01 mean < 0.01	0.03, 0.03 mean 0.03	0.03, 0.03 mean 0.03
								78, 67	< 0.01, < 0.01 mean <u>≤ 0.01</u>	0.04, 0.05 mean 0.05	0.04, 0.05 mean 0.04
USA, 2011 Turlock/CA (Padres)	SC	0.50 0.50 0.51 0.50 (2.0)	1412 1394 1422 1403	[d]	- 9 10 8	4	198		< 0.01, < 0.01 mean < 0.01	0.04, 0.04 mean 0.04	0.04, 0.04 mean 0.04
								43, 42	< 0.01, < 0.01 mean <u>≤ 0.01</u>	0.10, 0.10 mean 0.10	0.08, 0.09 mean 0.08

Portion analysed: hulls, as received basis (up), dry weight basis (down)

[a-e] refer to footnotes of Table 43

FATE OF RESIDUES IN STORAGE AND PROCESSING

In Processing

The Meeting received information on high temperature hydrolysis of isofetamid and the fate of isofetamid residues during the processing of wine grapes and rape seeds.

Grape and oilseed rape of the crops that the Meeting received information on supervised field trials may be processed prior to consumption. Processing factors have been calculated for isofetamid residues in grapes and rape seeds.

High temperature hydrolysis

The hydrolytic stability of [^{14}C]-isofetamid was studied under conditions representative of food processing (Lewis, 2009: 2244/077). The conditions used are summarized below.

Temperature, °C	Time, min	pH	Process Represented
90	20	4	Pasteurisation
100	60	5	Baking, Brewing, Boiling
120	20	6	Sterilisation

Two radiolabeled forms of [^{14}C]-isofetamid were used for the study labeled in the phenyl or the thiophene ring system. Solutions of aqueous buffers were prepared at pH 4, 5 and 6 at 80 °C. The vials of buffer solutions were pre-heated to about 80 °C and [^{14}C]-isofetamid was injected. The test substance concentration in the incubates was about 1 mg/L. Duplicate incubation units were analysed immediately after test article application and after incubation for the required time. Radioactivity present in each test solution was determined by LSC. All samples were analysed for [^{14}C]-isofetamid by HPLC and selected samples were also analysed by one dimensional TLC to confirm the identity of isofetamid.

Most of the applied radioactivity was recovered in solution and the overall recovery of radioactivity was high. There were no differences between labels or between the start and end of incubation.

Table 51 Identification of radioactivity under the conditions for processing simulation

Conditions	Label	Recovery of Applied Radioactivity [1 mg/L]			
		Isofetamid	Unknowns	Unresolved Background	Total

pH 4, 90 °C, 20min	Phenyl Thiophene	96.9, 99.8 97.8, 98.4	ND, ND ND, ND	1.7, 1.3 0.5, 1.6	98.6, 101.1 98.3, 100.0
pH 5, 100 °C, 60 min	Phenyl Thiophene	96.0, 97.0 96.8, 98.0	ND, ND ND, ND	1.2, 1.3 1.1, 1.2	97.2, 98.3 97.9, 99.2
pH 6, 120 °C, 20 min	Phenyl Thiophene	97.3, 97.9 94.6, 96.6	ND, ND ND, ND	0.4, 0.6 1.7, 0.6	97.7, 98.5 96.3, 97.2

ND = Not Detected

There was no observed degradation of isofetamid under any of the conditions. Isofetamid was stable to simulated processing procedures and no degradation would be expected during food processing involving pasteurisation, baking, brewing, boiling or sterilization.

Grapes

A processing study was conducted in Europe to quantify the residues of isofetamid and its metabolite glucoside of 4HP in processed commodities of wine grapes resulting from two applications at the maximum label rate and at the two-fold rate of the SC formulation containing 400 g/L isofetamid applied on a 21 day interval with a PHI of 21 days (Schäufele, 2011: JSM0102 and Schäufele, 2012: JSM0210). Samples for processing purposes were generated from grapes collected from the untreated plot and from the treated plots at 18 DALA from trial in Germany and at 20–21 DALA from the rest of the trials. From each plot two samples were taken for processing purposes. One sample was intended for wine and grape juice production, the other sample was intended for raisin production. The wine grapes were processed into grape juice, young wine at bottling, stored wine (1 year storage) and raisins.

The analysis was conducted using analytical methods that had been validated in the study JSM0119. The analytical method employed for determination of residues of isofetamid and glucoside of 4HP in grape bunches, grape juice, young wine, stored wine, raisins and all intermediate and side products comprised extraction using a water/acetonitrile mixture. An aliquot was subjected to clean-up using an Oasis HLB solid phase extraction cartridge, prior to quantitation by HPLC-MS/MS. The LOQ for isofetamid and the glucoside of 4HP in each commodity was 0.01 mg/kg and the LOD was 0.004 mg/kg. The levels of recovery from fortified samples which were analysed along with the test samples ranged from 70 to 102% for isofetamid and ranged from 71 to 112%, with the exception of one value (64%) for the glucoside of 4HP. The sampling to extraction interval for the processed commodities of wine grapes ranged from 2–34 days.

The grapes were crushed and pressed on the day of arrival. The juice was sulphurized with 50 mg SO_2/L and clarified over night. Afterwards approximately 40 kg separated must were taken for the wine making from each plot. The remaining juice was filtered and pasteurized (85–87 °C). The separated must was filled into 2 glass balloons and mixed with yeasts. After fermentation, the young wine (AF wine) and the yeast (Lees) samples were taken. The wine was mixed with Bentonite/L. After the ripening of the wine, a further separation was made. Afterwards the wine was filtered and bottled. The samples of wine at bottling and those retained samples were collected from all plots. The retained bottles from each plot were stored in the cellar at cellar temperature for one year.

The grapes for raisin processing procedure were dried in a dry chamber at 45 ± 1 °C until raisin ripeness. Afterwards the raisins were separated from the stalks. The raisins were dried to the final raisin ripeness (3 days).

Table 52 Residues of isofetamid and glucoside of 4HP in processed commodities of grapes

country, year (variety)	Application					DALA Days	Commodity	Residues, mg/kg			Processing factor	
	kg ai/ha	water, L/ha	kg ai/hL	GS (BBCH)	no.			Isofetamid	Glucoside of 4HP	Total	Isofetamid	Total

country, year (variety)	Application					DALA Days	Commodity	Residues, mg/kg			Processing factor	
	kg ai/ha	water, L/ha	kg ai/hL	GS (BBCH)	no.			Isofetamid	Glucoside of 4HP	Total	Isofetamid	Total
Germany, 2010 Iphofen (Müller-Thurgau) White wine grape	0.61 0.62	661 667	0.0920.092	79 81	2	18	Grape bunches Grape juice Young wine Aged wine	0.62 0.28 0.22 016	0.02 < 0.01 < 0.01 < 0.01	0.64 0.29 0.23 0.17	 0.45 0.35 0.26	 0.45 0.36 0.26
							Grape bunches Raisins	0.55 1.5	0.02 0.26	0.57 1.7	 2.7	 3.0
	1.2 1.2	659 665	0.19 0.19	79 81	2	18	Grape bunches Must Wet pomace Must deposit Clarified must Grape juice AF wine Lees Young wine Aged wine	0.92 0.95 1.9 3.5 0.72 0.69 0.56 2.5 0.62 0.44	0.02 < 0.01 0.08 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01	0.94 0.96 2.0 3.5 0.73 0.70 0.57 2.5 0.63 0.45	 1.0 2.1 3.8 0.78 0.75 0.61 2.7 0.67 0.48	 1.0 2.1 3.8 0.78 0.75 0.61 2.7 0.67 0.48
							Grape bunches Dried stems Raisins	1.1 18 7.1	0.04 0.27 0.37	1.1 18 7.3	 17 6.5	 16 6.5
France (North), 2010 Chervey (Pinot Noir) Red wine grape	0.61 0.60	806 795	0.075 0.075	79 85	2	22	Grape bunches Grape juice Young wine Aged wine	0.25 0.03 0.07 0.05	0.01 < 0.01 < 0.01 < 0.01	0.26 0.04 0.08 0.06	 0.12 0.28 0.20	 0.15 0.30 0.22
							Grape bunches Raisins	0.33 0.72	0.01 0.04	0.34 0.75	 2.2	 2.2
	1.2 1.2	810 812	0.15 0.15	79 85	2	22	Grape bunches Stems Crushed grapes Raw juice Wet pomace Sediments Clarified juice Grape juice	0.80 1.6 0.81 0.10 3.6 0.25 0.09 0.09	0.02 0.06 0.02 0.01 0.03 0.02 0.02 0.02	0.82 1.6 0.83 0.18 3.6 0.27 0.11 0.11	 2.0 1.0 0.13 4.5 0.31 0.11 0.11	 2.0 1.0 0.21 4.4 0.33 0.13 0.13
							Grape bunches Stems Must AF wine Wet pomace MLF wine Lees Sediments Young wine Aged wine	0.80 1.8 0.84 0.28 3.0 0.19 0.71 0.24 0.17 0.16	0.02 0.04 0.02 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01	0.82 1.8 0.86 0.29 3.0 0.20 0.72 0.25 0.18 0.17	 2.2 1.1 0.35 3.7 0.24 0.89 0.30 0.21 0.20	 2.2 1.0 0.35 3.7 0.24 0.88 0.30 0.22 0.21
							Grape bunches Dried stems Raisins	0.83 8.4 2.0	0.03 0.11 0.06	0.85 8.5 2.1	 10 2.4	 10 2.4
France (South), 2010 Argelliers (Mourvedre) Red wine grape	0.60 0.60	398 396	0.15 0.15	85 85	2	20	Grape bunches Grape juice Young wine Aged wine	< 0.01 0.01 < 0.01 < 0.01	< 0.01 < 0.01 < 0.01 < 0.01	< 0.02 0.02 < 0.02 < 0.02	- - -	- - -
							Grape bunches Raisins	0.47 0.53	< 0.01 < 0.01	0.48 0.54	 1.1	 1.1

country, year (variety)	Application					DALA Days	Commodity	Residues, mg/kg			Processing factor	
	kg ai/ha	water, L/ha	kg ai/hL	GS (BBCH)	no.			Isofetamid	Glucoside of 4HP	Total	Isofetamid	Total
	1.2 1.2	396 398	0.30 0.30	85 85	2	20	Grape bunches Stems Crushed grapes Raw juice Wet pomace Sediments Clarified juice Grape juice	0.36 1.1 0.26 0.05 1.6 0.07 0.04 0.04	< 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01	0.37 1.2 0.27 0.06 1.7 0.08 0.05 0.05	 3.0 0.72 0.14 4.4 0.19 0.11 0.11	 3.0 0.73 0.16 4.6 0.21 0.13 0.13
							Grape bunches Stems Must AF wine Wet pomace MLF wine Lees Sediments Young wine Aged wine	0.36 0.42 0.16 0.09 1.1 0.08 0.17 0.09 0.06 0.08	< 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01	0.37 0.43 0.17 0.10 1.1 0.09 0.18 0.10 0.07 0.09	 1.2 0.44 0.25 2.9 0.22 0.47 0.25 0.17 0.22	 1.2 0.46 0.27 2.9 0.24 0.48 0.27 0.18 0.24
							Grape bunches Dried stems Raisins	< 0.01 < 0.01 < 0.01	< 0.01 < 0.01 < 0.01	< 0.02 < 0.02 < 0.02	 - -	 - -
Spain, 2010 Turis (Malvasia) White wine grape	0.61 0.61	805 815	0.075 0.075	77 79-81	2	22	Grape bunches Grape juice Young wine Aged wine	0.18 0.03 0.07 0.07	0.01 0.01 < 0.01 < 0.01	0.19 0.04 0.08 0.08	 0.17 0.39 0.39	 0.20 0.41 0.41
							Grape bunches Raisins	0.27 0.40	0.02 0.03	0.29 0.42	 1.5	 1.5
France (South), 2011 Nimes (Grenache) Red wine grape	0.61 0.63	504 522	0.12 0.12	79 81-83	2	21	Grape bunches Grape juice Young wine Aged wine	0.23 0.03 0.07 0.06	0.02 0.01 0.01 0.01	0.25 0.04 0.08 0.07	 0.13 0.30 0.26	 0.15 0.32 0.28
							Grape bunches Raisins	0.18 0.41	0.02 0.03	0.20 0.43	 2.3	 2.2

AF wine: After alcoholic fermentation, MLF wine: After malolactic fermentation, Young wine: At bottling

Aged wine: 1 year after bottling

Rape seed

A processing study was conducted in the USA to determine the potential for concentration of residues of isofetamid and its metabolite glucoside of 4HP in processing fractions of rape seed (Wiedmann, 2012: IB-2011-JLW-004-01-01). At the test location, two applications of a SC formulation containing 400 g/L isofetamid at 8 day-interval was made to rape at a 10× application rate (total 6.1 kg ai/ha). Rape seed samples harvested from the plot treated at an exaggerated rate (10×) were harvested 26 days after treatment and were processed in a way that simulates industrial practice to produce into rape seed meal and refined oil.

The processing fractions of rape seed were analysed for residues of isofetamid and glucoside of 4HP using HPLC-MS/MS. The LOQ was 0.01 mg/kg. Processing fractions of rape seed were fortified over the range of 0.01–0.42 mg/kg for isofetamid and glucoside of 4HP. The sampling to extraction interval for the processing fractions ranged from 47–71 days.

Table 53 Residues of isofetamid and glucoside of 4HP in processed commodities of rape seeds

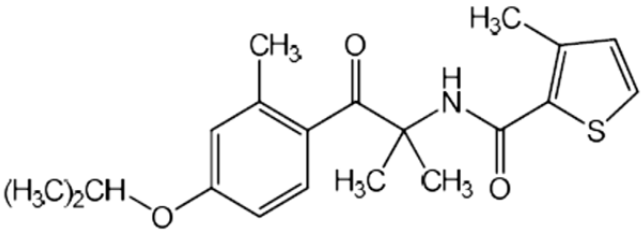
country, year (variety)	Application				DALA Days	Commodity	Residues, mg/kg			Processing factor	
	kg ai/ha	water, L/ha	GS (BBCH)	no.			Isofetamid	Glucoside of 4HP	Total	Isofetamid	Total
USA, 2011 Northwood/ND (Invigor LL 8440)	3.2 3.0 (6.1)	231 231	64 68	2	26	Seed Meal Refined oil	0.11, 0.12, 0.16 mean 0.13 0.02, 0.02 mean 0.02 0.26, 0.26 mean 0.26	< 0.01 (3) < 0.01 (2) < 0.01 (2)	mean 0.13 mean 0.03 mean 0.27	0.17 2.0	0.22 2.0

APPRAISAL

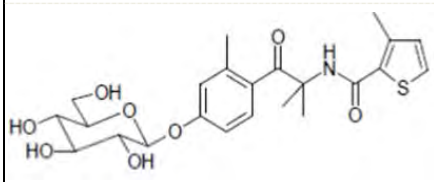
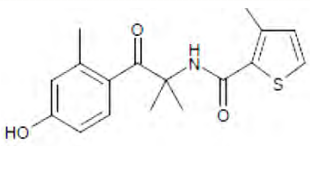
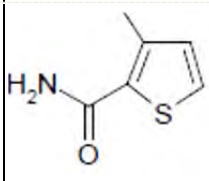
Isofetamid is a broad-spectrum fungicide belonging to the SDHI (Succinate Dehydrogenase Inhibitors) group. It inhibits succinate dehydrogenase in complex II of fungal mitochondrial respiration. Isofetamid is a locally systemic fungicide, which can control fungal pathogens belonging to *Ascomycetes* and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

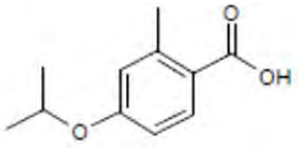
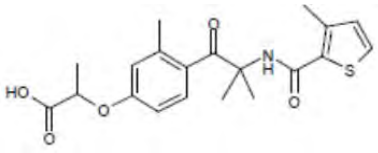
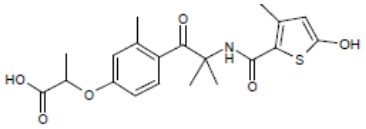
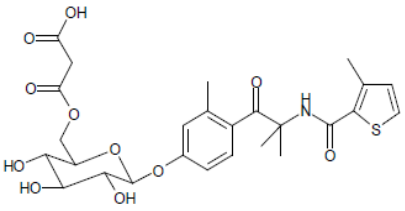
The Meeting received information on identity, animal and plant metabolism, environment fate in water, rotational crops, analytical methods, storage stability, use pattern, supervised trials, and fate of residues in processing.

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	4HP	3-MTCAM
 Synonym: GPTC *N*-(1,1-dimethyl-2-[4-(□-D-glucopyranosyl)oxy-2-methylphenyl]-2-oxoethyl)- 3-methylthiophene-2-carboxamide	 *N*-[1,1-dimethyl-2-(4-hydroxy-2-methylphenyl)-2-oxoethyl]-3-methylthiophene-2-carboxamide	 3-methyl-2-thiophene carboxamide
IBA	PPA	5-HPPA

 2-methyl-4-(2-propyloxy) benzoic acid	 2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido) propanoyl]phenoxy]propanoic acid	 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-(□-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

Commodity		Recommended MRL, mg/kg	STMR or STMR-P, mg/kg	HR or HR-P, mg/kg
CCN	Name	New		
TN 0660	Almonds	0.01*	0.01	0.01
AM 0660	Almond hulls	0.8 (dry weight basis)	0.01 (dry weight basis)	-
DF 0269	Dried grapes (= Currants, Raisins and Sultanas)	7	1.7	5.98
MO 0105	Edible offal (Mammalian)	0.07	0.058	0.058
PE 0112	Eggs	0.01*	0	0
VL 0482	Lettuce, Head	5	0.29	4.7
VL 0483	Lettuce, Leaf	7	0.115	5.2
FB 2009	Low growing berries (includes all commodities in this subgroup)	4	0.49	3.1
MF 0100	Mammalian fats (except milk fats)	0.02	0.012	0.012
MM 0095	Meat (from mammals other than marine mammals)	0.02 (fat)	0.012 fat 0.01 muscle	0.012 fat 0.01 muscle
ML 0106	Milks	0.01*	0.003	0.003
PO 0111	Poultry, Edible offal of	0.01*	0	0
PF 0111	Poultry fats	0.01*	0	0
PM 0110	Poultry meat	0.01*	0	0
SO 0495	Rape seed	0.015	0.01	-
OR 0495	Rape seed oil, edible	0.03	0.02	-
FB 2008	Small fruit vine climbing (includes all commodities in this subgroup)	3	0.73	2.6

* at or about the LOQ.

For calculating dietary exposure

Commodity Name	STMR or STMR-P, mg/kg
Grape juice	0.095
Grape must	0.77

Commodity Name	STMR or STMR-P, mg/kg
Grape wet pomace	2.7
Rape seed meal	0.0017
Red wine	0.15
White wine	0.28

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.

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