5.15 FLUBENDIAMIDE (242)

TOXICOLOGY

Flubendiamide is the International Organization for Standardization (ISO)–approved name for 3-iodo-*N'*-(2-mesyl-1,1-dimethylethyl)-*N*-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-*o*-tolyl}phthalamide (International Union of Pure and Applied Chemistry [IUPAC]), which has the Chemical Abstracts Service (CAS) No. 272451-65-7. Flubendiamide is an insecticide that operates by a highly specific biochemical mode of action. It is a ryanodine receptor agonist, which activates ryanodine-sensitive intracellular calcium release channels in neuromuscular junctions, leading to an overstimulation of these cells. Flubendiamide does not bind to mammalian type 1, 2 and 3 ryanodine receptors.

Flubendiamide is being evaluated for the first time by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) at the request of the Codex Committee on Pesticide Residues (CCPR).

All critical studies complied with good laboratory practice (GLP).

Biochemical aspects

After administration of a single oral dose (2 mg/kg body weight [bw]) of [^{14}C]flubendiamide to rats, about 23–34% of the radiolabel was absorbed. Peak plasma concentrations were reached within 6–12 h. Plasma half-lives were 12.6 and 37.6 h in males and females, respectively. The radiolabel was widely distributed, with highest concentrations in liver, adrenals, fat and kidneys. Male rats showed slightly higher peak organ and tissue levels than females, but also had a more rapid clearance of residues. After a single high oral dose of 200 mg/kg bw, plasma and tissue levels in rats were only slightly higher than after 2 mg/kg bw, indicating saturated absorption. Repeated oral dosing with 2 mg/kg bw for 14 days did not affect metabolism and excretion in rats; whereas residue levels in males were similar to those observed after a single dose of 2 mg/kg bw, residue levels in females were considerably higher, indicating a considerable potential for accumulation in female rats. Excretion occurred predominantly through bile and faeces. Urinary excretion was 1.7% and 0.4% of the 2 mg/kg bw dose in males and females, respectively. In mice, male rats (but not female rats), dogs and humans, flubendiamide can be readily metabolized by oxidation of the methyl groups linked to the aniline ring and at the alkyl bridge between the amide and sulfonyl functions, resulting in the corresponding alcohol, aldehyde and benzoic acid derivatives, followed by formation of glucuronide conjugates of hydroxylated metabolites. As female rats have very limited capability to oxidize these methyl groups, in these animals, flubendiamide is metabolized by direct conjugation with glutathione, leading to further amino acid conjugates with cysteine and glycine. This metabolic pathway is less efficient than the oxidation route, leading to a less rapid excretion of flubendiamide in female rats. Small but significant amounts of flubendiamide-iodophthalimide were detected in the fat extract of both male and female rats, implying the hydrolysis of the amide bond between the phthalic acid ring and the thioalkylamine moiety.

The observed sex difference in clearance and metabolism in rats (both are slower in females) was further investigated. Liver microsomes from mice (both sexes), male rats, dogs (both sexes) and humans (both sexes) efficiently caused hydroxylation of flubendiamide to flubendiamide-benzyl alcohol as a first step of metabolism. Female rat microsomes, however, have very limited capability to oxidize the methyl moieties.

Toxicological data

The acute toxicity of flubendiamide is low in rats (oral and dermal median lethal dose [LD$_{50}$] > 2000 mg/kg bw; inhalation median lethal concentration [LC$_{50}$] > 0.0685 mg/L, maximum achievable

concentration). Flubendiamide is not irritating to the skin and eyes of rabbits and is not a skin sensitizer (Magnusson and Kligman test in guinea-pigs).

In repeated-dose studies with rodents, the most sensitive target was the liver, followed by the thyroid and the red blood cell system (rats only). In general, female rats were more sensitive than males to the effects of flubendiamide. This is likely due to the fact that female rats are poor metabolisers of flubendiamide.

A 28-day mechanistic study in female rats showed that flubendiamide induces liver enzyme activity (uridine diphosphate–glucuronosyltransferase [UDPGT] and ethoxyresorufin *O*-deethylase [EROD]) and an increase in cytochrome P450 content in liver and serum thyroid stimulating hormone (TSH) levels. The mechanistic study was not adequate to elucidate the mode of action of thyroid activation in rodents.

The repeated-dose toxicity of flubendiamide was investigated in mice (28-day and 13-week studies), rats (28-day, 3-month and 1-year studies) and dogs (3-month and 1-year studies). The overall no-observed-adverse-effect level (NOAEL) from the 28-day and 13-week studies in mice was 200 ppm (equal to 26.9 mg/kg bw per day), based on dark coloured liver, fatty changes in centrilobular hepatocytes and hepatocyte hypertrophy at 1000 ppm (equal to 123 mg/kg bw per day).

In the 28-day, 3-month and 1-year oral feeding studies with flubendiamide in rats, the lowest NOAEL was 50 ppm (equal to 2.0 mg/kg bw per day), based on liver effects (increased liver weights, dark coloured and enlarged livers, periportal fatty changes, hepatocyte hypertrophy and foci of cellular alterations [basophilic cell type], clinical chemistry changes), haematological effects (decreased haematocrit, haemoglobin, erythrocyte count, mean corpuscular volume and mean corpuscular haemoglobin, indicative of microcytic anaemia and possibly reactive haematopoiesis) and thyroid effects (follicular cell hypertrophy) observed at 2000 ppm (equal to 79 mg/kg bw per day), observed in the 1-year study. Similar effects had been observed in the 28-day and 3-month studies in rats at 200 ppm (equal to 13–15 mg/kg bw per day). After cessation of treatment in the 3-month rat study, liver, thyroid and red blood cell effects were partially or fully reversible after a 4-week recovery period.

In repeated-dose studies in dogs, the most sensitive targets were the liver, blood and adrenals. In a 3-month and a 1-year study in dogs, the NOAEL was 100 ppm, equal to 2.6 and 2.2 mg/kg bw per day, respectively, based on increased alkaline phosphatase levels and shortened activated prothrombin time (both studies), increased adrenal weights and adrenal cortical hypertrophy (3-month study) and increased liver weights (1-year study) observed at 2000 and 1500 ppm, equal to 53 and 35 mg/kg bw per day, respectively.

In an 18-month feeding study in mice, the NOAEL was 50 ppm (equal to 4.4 mg/kg bw per day), based on increased liver weight, centrilobular hypertrophy, centrilobular microvesicular fatty change, enlarged thyroid, increased thyroid weights, increased incidence of thyroid follicular cell hypertrophy and hydropic change and increased large size follicles in both sexes, diffuse microvesicular and macrovesicular fatty change in the liver of females, and discoloration of the liver in males observed at 1000 ppm (equal to 93 mg/kg bw per day). No effect of flubendiamide on tumour incidence was found.

In a 2-year feeding study in rats, the NOAEL was 50 ppm (equal to 1.7 mg/kg bw per day), based on increased liver weights and periportal fatty change (both sexes), increased incidence of hair loss, dark coloured and enlarged livers, hepatocyte hypertrophy, increased kidney weight and increased incidence of thyroidal follicular cell hypertrophy in females, and decreased eosinophil count in males observed at 1000 ppm (equal to 34 mg/kg bw per day). No treatment-related effect on tumour incidence was found.

The Meeting concluded that flubendiamide is not carcinogenic in rodents.

Flubendiamide was tested for genotoxicity in an adequate range of in vitro and in vivo studies. No evidence for genotoxicity was observed in any test.

The Meeting concluded that flubendiamide is unlikely to be genotoxic.

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

One-generation and two-generation studies of reproductive toxicity in rats were available. The overall NOAEL for parental toxicity was 50 ppm (equal to 3.9 mg/kg bw per day), based on dark coloured livers in parental females and increased liver weights in F_1 females observed in a one-generation study of reproductive toxicity observed at 200 ppm (equal to 15 mg/kg bw per day). No reproductive toxicity was seen at 2000 ppm (equal to 162 mg/kg bw per day), the highest relevant dose tested. The overall NOAEL for offspring toxicity (combined data from the one- and two-generation studies of reproductive toxicity) was 200 ppm, equal to 15 mg/kg bw per day (i.e., the maternal compound intake), based on dark coloured livers and increased liver weight, decreased spleen and thymus weights, delayed balano-preputial separation, enlargement of eyeballs, synechia, haemorrhage, keratitis, iritis, cataract, hydropic degeneration of basal layer of the corneal epithelium and/or corneal epithelial vacuolation at 2000 ppm (equal to 131–149 mg/kg bw per day).

No effects on the eye were observed in special perinatal ocular toxicity studies in female mice in which the animals received flubendiamide at doses up to and including 1395 mg/kg bw per day.

In a developmental toxicity study in rats, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on the small increases in absolute and relative liver weights at 1000 mg/kg bw per day. The NOAEL for developmental toxicity was 1000 mg/kg bw per day, the highest dose tested.

In a developmental study in rabbits, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on increased incidences of loose stools, reduced food consumption on gestation days 27–28 and a tendency to a reduced body weight gain during the latter part of gestation. The NOAEL for developmental toxicity was 1000 mg/kg bw per day, the highest dose tested.

No evidence for a teratogenic effect of flubendiamide was observed in rats or rabbits.

The Meeting concluded that it could not exclude the possibility that flubendiamide induces eye anomalies due to exposure during gestation or early postnatal life or the possibility that the effects on the developing eye are the result of a single exposure to flubendiamide.

In an oral (gavage) study of acute neurotoxicity in rats in which flubendiamide was given by gavage, the NOAEL was 2213 mg/kg bw, the highest dose tested.

In a dietary developmental neurotoxicity study in rats, no neurotoxic effects were observed at doses up to 12 000 ppm (equal to 980 mg/kg bw per day), the highest dose tested. The NOAEL for maternal toxicity was 120 ppm (equal to 9.9 mg/kg bw per day), based on increases in absolute and relative liver weights at 1200 ppm (equal to 100 mg/kg bw per day). The NOAEL for offspring toxicity was 120 ppm (equal to 9.9 mg/kg bw per day), based on effects on the eye (increased incidences of enlarged eyeballs and general ocular opacities), decreased preweaning body weight and delayed balano-preputial separation at 1200 ppm (equal to 100 mg/kg bw per day).

It is noted that in the developmental neurotoxicity study and in the studies of reproductive toxicity, effects on the eye were observed, whereas in developmental toxicity studies in rats and rabbits, no effects on the eye were found. This suggests that the effects on the development of the eyes occur after birth, although it cannot be excluded that the initial lesion occurs during gestation.

In a 28-day dietary immunotoxicity study in rats, the NOAEL for immunotoxicity was 400 ppm (equal to 34 mg/kg bw per day), based on a decrease in CD45 lymphocytes in both sexes and a decrease in immunoglobulin A antibody titres in females at 4000 ppm (equal to 336 mg/kg bw per day). These effects are considered secondary changes due to liver toxicity. The NOAEL was 40 ppm (equal to 4 mg/kg bw per day), based on decreases in food intake, haemoglobin and haematocrit and increases in liver weights at 400 ppm (equal to 34 mg/kg bw per day).

Occupational medical surveillance of workers exposed to flubendiamide has not revealed any adverse effects.

In studies of acute oral toxicity, the flubendiamide metabolites flubendiamide-des-iodo and flubendiamide-3-OH had LD_{50}s of greater than 2000 mg/kg bw. These metabolites gave negative results in a test for reverse mutation in bacteria.

The Meeting concluded that the existing database on flubendiamide is sufficient to characterize the potential hazards to fetuses, infants and children.

The Meeting noted that new studies are being performed to better characterize the risk to humans of the effects of flubendiamide on the developing eye observed in rats.

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) for flubendiamide of 0–0.02 mg/kg bw on the basis of a NOAEL of 50 ppm (equal to 1.7 mg/kg bw per day), based on effects on the liver (both sexes), kidney, thyroid and hair loss (females) and decreased eosinophil count (males) observed in a 2-year feeding study in rats, and on the basis of a NOAEL of 100 ppm (equal to 2.2 mg/kg bw per day), based on increased alkaline phosphatase levels, shortened activated prothrombin time and increased liver weights observed in a 1-year study in dogs. A safety factor of 100 was applied.

The Meeting established an acute reference dose (ARfD) of 0.2 mg/kg bw, based on an overall NOAEL of 15 mg/kg bw per day for effects on the developing eye observed in one- and two-generation reproductive toxicity studies and a developmental neurotoxicity study in rats. A safety factor of 100 was applied.

Although the eye effects became apparent after birth, it is not clear whether the initial lesion occurs during gestation or postnatally. It cannot be excluded that the effects on eye development are the result of a single prenatal or postnatal exposure to flubendiamide.

A toxicological monograph was prepared.

Levels relevant for risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	50 ppm, equal to 4.4 mg/kg bw per day	1000 ppm, equal to 93 mg/kg bw per day
		Carcinogenicity	10 000 ppm, equal to 937 mg/kg bw per day[b]	—
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	50 ppm, equal to 1.7 mg/kg bw per day	1000 ppm, equal to 34 mg/kg bw per day
		Carcinogenicity	20 000 ppm, equal to 705 mg/kg bw per day[b]	—
	One- and two-generation studies of reproductive toxicity[a]	Parental toxicity	50 ppm, equal to 3.9 mg/kg bw per day[c]	200 ppm, equal to 15 mg/kg bw per day[c]
		Offspring toxicity	200 ppm, equal to 15 mg/kg bw per day[c]	2000 ppm, equal to 131 mg/kg bw per day[c]
		Reproductive toxicity	2000 ppm, equal to 162 mg/kg bw per day	20 000 ppm, equal to 1636 mg/kg bw per day
	Developmental toxicity study[d]	Maternal toxicity	100 mg/kg bw per day	1000 mg/kg bw per day
		Embryo and fetal toxicity	1000 mg/kg bw per day[b]	—
	Acute neurotoxicity	Neurotoxicity	2213 mg/kg bw per day[b]	—

Species	Study	Effect	NOAEL	LOAEL
	study[d]			
	Developmental neurotoxicity study[a]	Maternal toxicity	120 ppm, equal to 9.9 mg/kg bw per day	1200 ppm, equal to 100 mg/kg bw per day
		Offspring toxicity	120 ppm, equal to 9.9 mg/kg bw per day	1200 ppm, equal to 100 mg/kg bw per day
Rabbit	Developmental toxicity study[d]	Maternal toxicity	100 mg/kg bw per day	1000 mg/kg bw per day
		Embryo and fetal toxicity	1000 mg/kg bw per day[b]	—
Dog	One-year study of toxicity[a]	Toxicity	100 ppm, equal to 2.2 mg/kg bw per day	1500 ppm, equal to 35 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Two or more studies combined.

[d] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.02 mg/kg bw

Estimate of acute reference dose

0.2 mg/kg bw

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

Data from ongoing studies on the effect of flubendiamide on the developing eye, and results from epidemiological, occupational health and other such observational studies of human exposure

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

Absorption, distribution, excretion and metabolism in mammals

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Rate and extent of absorption	Relatively slow, incomplete oral absorption (23–34% at 2 mg/kg bw)
Distribution	Extensive (rats)
Potential for accumulation	At 2 mg/kg bw, low in both sexes; at 200 mg/kg bw, low in males and moderate in females (rats)
Rate and extent of excretion	Plasma half-lives: males, 12.6 h; females, 37.6 h
	At 2 mg/kg bw: 1.7% and 0.4% in urine of males and females, respectively (rats)
Metabolism in animals	Extensive, by oxidation of the methyl groups linked to the aniline ring and at the alkyl bridge between amide and sulfonyl functions in mice, male rats, dogs and humans. As female rats have very limited capability to oxidize these methyl groups, they metabolize flubendiamide by direct conjugation of flubendiamide with glutathione.
Toxicologically significant compounds	Flubendiamide

Acute toxicity

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Rat, LD_{50}, oral	> 2000 mg/kg bw

Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 0.0685 mg/L (highest achievable concentration)
Rabbit, dermal irritation	Not an irritant
Rabbit, ocular irritation	Not an irritant
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test)

Short-term studies of toxicity

Target/critical effect	Liver (rat, dog), thyroid (rat), red blood cell system (rat), adrenals (dog)
Lowest relevant oral NOAEL	2 mg/kg bw per day (rat), 2.2 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	100 mg/kg bw per day (rat)
Lowest relevant inhalatory NOAEC	No data

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Liver, thyroid, kidney, skin (rat)
Lowest relevant NOAEL	1.7 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic (mouse, rat)

Genotoxicity

	Not genotoxic

Reproductive toxicity

Reproduction target/critical effect	None
Lowest relevant reproductive NOAEL	162 mg/kg bw per day, highest relevant dose tested (rat)
Developmental target	Eye effects in reproductive toxicity studies and developmental neurotoxicity studies (rat)
Lowest relevant developmental NOAEL	15 mg/kg bw per day (rat)

Neurotoxicity/delayed neurotoxicity

Neurotoxicity	No neurotoxic effects
Developmental neurotoxicity	No neurotoxic effects

Other toxicological studies

Immunotoxicity	No immunotoxic effects

Medical data

	Occupational medical surveillance of workers exposed to flubendiamide has not revealed any adverse effects

Summary

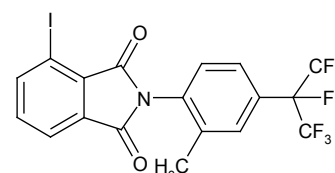|	Value	Study	Safety factor
ADI	0–0.02 mg/kg bw	Two-year study in rat, one-year study in dog	100
ARfD	0.2 mg/kg bw	One- and two-generation studies of reproductive toxicity, developmental neurotoxicity study in rat	100

RESIDUE AND ANALYTICAL ASPECTS

Flubendiamide is an insecticide for use in a broad number of annual and perennial crops against a wide range of lepidopteran pests. The compound is being evaluated by the 2010 JMPR as a new compound, for both residue and toxicological aspects. Data was provided on metabolism of flubendiamide in farm animals and plants, methods of analysis, GAP information, supervised residue trials on various crops, storage stability, processing and animal feeding studies. Below are the chemical structures of flubendiamide and its major metabolites in plant (des-iodo) and animals (iodophthalimide).
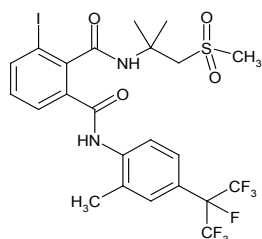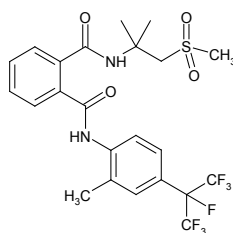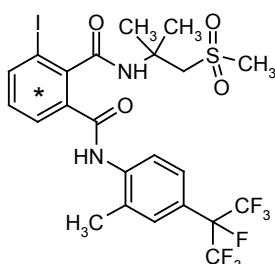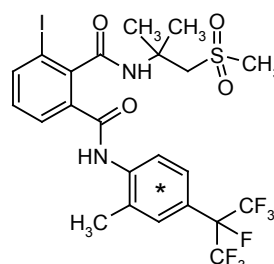

Flubendiamide   Flubendiamide-des-iodo   Flubendiamide-iodophthalimide

Metabolism in animals

The metabolism of flubendiamide in <u>rats</u> was evaluated by the WHO panel of the JMPR at the present Meeting.

The positions of the radiolabels are shown in the figures below.

[phthalic acid ring-UL-^{14}C] flubendiamide   [aniline ring-UL-^{14}C] flubendiamide

Two metabolism studies were conducted on <u>laying hens</u> using similar experimental designs. In each study, radio-labelled doses were orally administered to six birds for 14 days. In one study, the hens were dosed with [phthalic acid ring-UL-^{14}C]flubendiamide at 1.0 mg/kg bw/day (16.95 ppm in the diet) and in the second study with [aniline ring-UL-^{14}C] flubendiamide at 0.71 mg/kg bw/day (8.86 ppm in the diet). Eggs and excreta were collected once daily and hens were sacrificed 24 hours after the last dose.

About 91 and 98% of the administered cumulative dose of [phthalic acid ring] and [aniline ring-UL-^{14}C]flubendiamide, respectively, was recovered from organs, tissues, eggs, and excreta. The majority of the radioactivity (62–66%) was detected in the excreta, 24.4% in tissues and 5.1–7.7% in eggs. In tissues, residues concentrated in fat (18–12.2 mg/kg eq.), followed by liver (4.0–3.0 mg/kg eq.) and muscle (2.9–2.6 mg/kg eq.). Residues in eggs increased during the experiment, from 0.15–0.33 mg/kg eq. in the first 4 days to 2.9–2.6 mg/kg eq. towards the end of the dosing period. Flubendiamide accounted for 92–93% TRR in eggs, 95% TRR in muscle, 98–97% TRR in fat and 82% TRR in liver. The metabolite flubendiamide-benzyl alcohol was present in eggs and tissues, accounting for less than 10% TRR. Traces of flubendiamide-iodophtalimide was found in eggs and

tissues from the [phthalic acid ring] dosing, and accounted for 1.6% TRR (0.20 mg/kg eq.) in fat from the [aniline acid ring] experiment.

In the goat metabolism studies, a single goat received daily for 4 days by gavage either [phthalic acid ring-UL-^{14}C]flubendiamide at a mean dose rate of 4.83 mg/kg bw/day (176 ppm in the diet) or [aniline ring UL-^{14}C] flubendiamide at a daily dose rate of 5 mg/kg bw/day (370 ppm in the diet). Each goat was milked in the morning immediately prior to each administration, 8, 24, 32, 48, 56, 72, and 77 hours (at sacrifice) after the first dose and excreta were collected in intervals of 24 hours and at sacrifice, when tissues were sampled.

Until sacrifice, 53.7% of the administered [phthalic acid ring-UL-^{14}C]flubendiamide was recovered, mostly in the faeces (44.2%). Tissues accounted for 8.7% of the dose and milk 0.5%. The highest residue levels were observed in fat (9.9 mg/kg eq.) and liver (10.1 mg/kg eq.), followed by kidney (2.4 mg/kg eq.), muscle (0.83 mg/kg eq.) and milk (0.70 mg/kg eq.). The parent compound accounted for 78.3–90.6% of TRR. Flubendiamide-iodophthalimide was detected in milk and tissues, the highest levels found in fat (1.0 mg/kg eq and 11% TRR) and liver (0.24 mg/kg eq. and 2.4% TRR). Liver contained six other metabolites (< 5%TRR) at levels ranging from 0.053 (F-iodo-alkylphthalimide) to 0.39 (F-hydroxy) mg/kg eq. About 25% of the totally administered dose of [aniline ring UL ^{14}C]flubendiamide, was excreted until sacrifice with 24% in the faeces. Milk accounted for 0.4% and tissues for 15% of the totally administered doses. The highest radioactivity was measured in fat (21 mg/kg eq.), followed by liver (13.5 mg/kg eq.), kidney (4.4 mg/kg eq.), muscle (1.5 mg/kg eq.) and milk (1.5 mg/kg eq.). The parent compound was the main residue component (72 to 93%TRR). The major metabolite, flubendiamide-iodophthalimide accounted for approx. 17% of the TRR in milk (0.24 mg/kg eq), 24% in fat (5 mg/kg eq) and 8.4% TRR in muscle (0.13 mg/kg eq). Minor identified metabolites accounted for less than 6% TRR each. The major metabolic pathway of flubendiamide in hens and goats was the oxidation of the methyl groups to form a primary alcohol (hydroxylation), further oxidation of the aliphatic alcohol to a carboxylic acid group followed by conjugation with glucuronic acid, which was exclusively found in the excreta and in the bile. A minor reaction was the cleavage of the respective amide bond of flubendiamide and the cyclisation to flubendiamide-iodophthalimide and flubendiamide-iodo-alkylphthalimide.

Metabolism in plants

All plant metabolism studies involved foliar application of flubendiamide to reflect the intended field use patterns. Additionally, the greenhouse metabolism studies for cabbages and tomatoes both made use of a quartz-ceiling greenhouse to make light irradiation conditions similar to field conditions: photolytic studies demonstrating a mean photolytic half-life of 5.5 days support this decision. A metabolism study was conducted on cabbages in a greenhouse using [phthalic acid ring-UL-14C]- and [aniline ring-UL-14C]-flubendiamide applied to immature plants at 300 μg/plant. Samples were collected 3 weeks and 6 weeks after application (maturity). Residues in cabbage heads represented < 0.1% of the applied radioactivity, AR. Flubendiamide was the main compound detected in the loose outer leaves (> 90% AR), and flubendiamide-des-iodo and flubendiamide-3-OH were the main metabolites, reaching up to 1.7% AR.

Cherry tomato plants were either treated in a glasshouse with [phthalic acid ring-UL-^{14}C] or [aniline ring-UL-^{14}C]-labelled flubendiamide at 125 μg/branch of fruits (25 μg/fruit) and 800 μg/branch of leaves. Samples were collected at day 0, and 1, 2 and 4 weeks after application. Total radioactivity decreased during the experiment, from about 3.3 to 1.4 mg/eq. in fruits (99–67% TRR) and 44–45 to 16.5–14.9 mg/kg eq. in leaves (100–67% TRR). The surface rinsate contained most of the radioactive residues. Analysis of untreated plant parts four weeks after treatment showed less than 0.5% of the AR. Flubendiamide was the main component detected in fruits and amounted to 1.27 and 1.43 mg/kg eq. after four weeks for the phthalic acid and aniline label, respectively (63.4 and 66.3% AR). Flubendiamide-des-iodo accounted for up to 0.3% TAR (up to 0.007 mg/kg eq.) and flubendiamide-3-hydroxy for up to 0.2% AR. Flubendiamide was also the main component found in leaves (over 80% TAR after 4 weeks).

The metabolism of flubendiamide in <u>apples</u> was studied by applying [phthalic acid ring-UL-^{14}C]- and [aniline ring-UL-^{14}C] flubendiamide as an EC formulation to two apple trees (one for each label) at 0.11 kg ai/ha. Samples of apples and leaves were collected at 0, 7, 14, 28, and 56 days after treatment. About 100% of TRR was recovered from the fruits, with residues below 0.05 mg/kg at each harvest date for each label, mostly present in the apple rinses (over 60% TRR at 14 days PHI). Residues in fruit pellets were < 0.005 mg/kg eq. Residues in leaves dropped from 4.5 to about 1.5 mg/kg eq. at day 56, mostly recovered in the ACN leaf extracts. Residues in the leaf pellets increased during the experiment to about 10% TRR. Flubendiamide was the major compound detected in both label experiments, accounting for about 70% TRR at 14 days PHI in fruit (0.014 mg/kg eq.) and 78% TRR in leaves. Flubendiamide-des-iodo was at ≤ 0.002 mg/kg in fruit in all sampling times. In leaves, the levels were below 0.5 mg/kg (< 5%TRR).

The metabolism of flubendiamide in <u>sweet corn</u> was investigated using [phthalic acid ring-UL-^{14}C] and [aniline ring-UL-^{14}C] flubendiamide applied four times at 0.16 kg ai/ha. Forage (includes husks) and sweet corn samples were collected one day after the fourth treatment. TRR of forage and fodder was within the range of 0.29 to 0.60 mg/kg eq., with over 85% TRR found in the acetonitrile/water extracts. TRR derived by combustion of sweet corn and corn grain samples from phthalic acid ring label experiments were 0.01 and 0.02 mg/kg eq., respectively, and < 0.005 mg/kg eq. in samples from the aniline ring label experiment. ACN/water extracts of sweet corn and corn grain of the phthalic acid label represented 37 and 15% TRR, respectively; methanol under reflux and alkaline conditions extracted an additional 20 and 13% TRR. Over 75% TRR found in forage and fodder was flubendiamide (0.21 to 0.51 mg/kg eq.). Flubendiamide-des-iodo was detected at levels from 0.03 to 0.05 mg/kg eq, representing up to 18% TRR (forage).

The metabolism of flubendiamide in <u>rice</u> was investigated by applying a [phthalic acid ring-UL-^{14}C]flubendiamide suspension (49.6 ± 0.5 μg eq./mL) to plants just before ear emergence. After drying of the droplets on the plant surface, the plants (four pots) were transferred to the greenhouse. Samples were taken at time zero, four and nine weeks after application. The higher radioactive residues were found in leaves and stems, decreasing from 2.1 mg/kg eq. at time zero to around one third of the initial value four weeks after application (immature plant), mainly due to plant growth, and increased to 1.4 mg/kg eq., probably due to loss of moisture. The TRRs in seed after 9 weeks was 0.023 mg/kg eq., mostly recovered from the solids. Flubendiamide was the predominant constituent of the residue in stems and leaves for all sampling times (over 90%TRR). Flubendiamide-des-iodo accounted for 4.1% of TRR and fubendiamide-3-OH was identified as a minor constituent. Flubendiamide-benzylalcohol and flubendiamide-benzoic acid were also identified. Hulls from the 9 week sampling contained 0.05 mg/kg eq., 88% as parent compound and 4% as the des-iodo metabolite.

In summary, the metabolism of flubendiamide after foliar application on plants involved mostly the des-iodination of the parent compound to yield flubendiamide-des-iodo followed by hydroxylation to flubendiamide-3-OH and the stepwise oxidation of the methyl group at the aniline ring leading to flubendiamide-benzylalcohol and flubendiamide-benzoic acid. In tomatoes, the label-specific metabolite flubendiamide-des-anilino was also observed. In apple fruits, a third route was also observed, involving the elimination of the amino-ethyl-sulfonyl substituent leading to flubendiamide-iodophthalimide and the label-specific metabolite flubendiamide-3-iodo-phthalic acid. In corn, the only metabolic reaction observed was the reductive deiodination to yield flubendiamide-des-iodo. These studies indicate little evidence of residue translocation within the plant; thus, surface residues may be expected in the crop field trial studies.

Environmental fate

The supported uses of flubendiamide concern foliar application only. Based on the 2009 FAO Manual, no studies on the fates and behaviour in soil are required for this type of use. Any metabolite from a field dissipation study that may have an impact on plant residues is covered by the rotational crop study.

Hydrolysis

Flubendiamide comprised more than 95% of the residue at 25 ± 1 °C in pH 4.0, 5.0, 7.0 and 9.0 buffer solutions over a 30 day study period; and more than 95% of the residue at 50.0 ± 0.1 °C in pH 4.0, 7.0 and 9.0 buffer solutions over a 5 day study period. Therefore, flubendiamide is considered hydrolytically stable from pH 4.0 to 9.0.

Photolysis

Flubendiamide was irradiated in distilled water, natural water, and distilled water containing 1% acetone with artificial light for up to 168 hours. An average half-life of 5.5 days was determined in distilled water and distilled water with acetone, while a half-life of 4.3 days was reported in natural waters. The results of the environmental fate studies indicate that degradation of flubendiamide is more likely to occur by photolysis than hydrolysis.

Residues on succeeding crops

The metabolism of flubendiamide after spray application onto bare soil was investigated in spring wheat, Swiss chard and turnips. [Phthalic acid ring-UL-^{14}C]flubendiamide and [aniline ring-UL-^{14}C]flubendiamide were applied by spray application (day 0) at a rate of 0.44 kg ai/ha, based on the projected annual field rate of 0.42 kg ai/ha. Crops of the first, second and third rotation were sown at day 29, day 135 and day 274, respectively. Plants of the first rotation were grown under natural temperature and light conditions and for the second and third rotation, in the greenhouse.

The maximum TRR (0.07 mg/kg) in plants treated with [phthalic acid ring-UL-^{14}C]flubendiamide was observed in wheat straw of the first rotation, which decreased to 0.05 mg/kg eq. in the third rotation. During this period, residues in forage increased from 0.013 to 0.016 mg/kg and remained practically constant in grain (0.003 mg/kg eq.). Residues in Swiss chard decreased from 0.022 to 0.015 mg/kg eq. In turnip leaves and roots, residues in the first rotation were 0.011 and 0.006 mg/kg, respectively, remaining practically constant at the second and third rotation (0.005–0.006 mg/kg eq. and 0.002 mg/kg eq., respectively). The maximum TRR (0.137 mg/kg) in plants treated with [aniline ring-UL-^{14}C]flubendiamide was observed in wheat straw of the first rotation, decreasing to 0.068 and 0.039 mg/kg in the second and third rotation. Similarly, the TRRs in wheat hay decreased from 0.045 mg/kg (first rotation) to 0.021 mg/kg (third rotation). The TRRs in forage and Swiss chard ranged from 0.009 mg/kg to 0.019 mg/kg for all rotations. The lowest residues were present in grain, turnip leaves and turnip roots amounting to ≤ 0.006 mg/kg for all rotations.

About 80–90% of the TRR was extracted from the majority of samples using acetonitrile/water in both experiments. Wheat grain of the first rotation accounted for 62 to 70% TRR, which decreased to about 14% TRR after enzymatic treatment (< 0.001 mg/kg). Unchanged parent compound was the main component of all plant samples and accounted for 22–88% of the TRR, except for grain. In grain, only 4% to 8% (< 0.001 mg/kg) of the TRR (0.003 mg/kg) was due to flubendiamide in the first rotation, decreasing to 2.2 and 0.5% TRR in the second and third rotations. The main portion of the TRR in grain was due to very polar radioactivity found in aqueous phases following conventional and enzymatic extraction. A major metabolite in confined rotational crops in the phthalic acid ring experiment was flubendiamide-des-iodo, accounting for up to 10.8% of the TRR in Swiss chard of the second rotation. The highest absolute amount of flubendiamide-des-iodo-alkylphthalimide was 0.01 mg/kg in straw of the second rotation, corresponding to 16.0% of the TRR. In the aniline ring experiment, flubendiamide-benzyl alcohol and benzoic acid were detected in some of the plant samples up to 1.4% TRR, each accounting for 0.001 mg/kg as a maximum.

The main metabolic reaction of flubendiamide in confined rotational crops was the reduction of the parent compound by elimination of the iodine-substituent. Other metabolic reaction include the elimination of the N-aryl-moiety, hydroxylation of the parent compound to form flubendiamide-benzyl alcohol which was further oxidised to the carboxylic acid, probably in soil.

In summary, total residues in the rotated crops of wheat grain, turnip leaves and roots were < 0.01 mg/kg. The rotated crop matrix with the highest level of flubendiamide was wheat straw, which contained a maximum level of 0.10 mg/kg flubendiamide in the reported studies. The highest reported level of flubendiamide in any human food item in the rotational crop studies was Swiss chard, where a maximum level of 0.015 mg/kg flubendiamide was found.

Methods of analysis

The analytical method developed for the determination of flubendiamide and flubendiamide-des-iodo residues in/on <u>plant material</u> (00816/M001), involves two successive microwave extractions, the first with acetonitrile/0.01% HCl and the second with acetonitrile/0.01% HCl/water. Following column clean-up the residues are eluted with cyclohexane/ethyl acetate, and dissolved in acetonitrile/water for quantification by LC-MS/MS. Oil of plant origin samples are dissolved in hexane, extracted with acetonitrile and partitioned with hexane before LC-MS/MS. Two MRM transitions for quantitation and confirmation were monitored for each analyte (flubendiamide: m/z 681→254 and m/z 681→274; flubendiamide-des-iodo: m/z 555→254 and m/z 555→274). The method was validated for a variety of crops, including tomatoes, grains, beans, cabbages and cotton and submitted also to independent laboratory validation. The limit of quantification (LOQ) for both analytes is 0.01 mg/kg for all sample materials.

The extraction efficiency of microwave and shaker procedures was evaluated using data from radiovalidation of method 00816/M002 with corn (microwave) and the metabolism study with [phthalic acid ring-UL-^{14}C]flubendiamide onto corn plants (blender). The microwave and the blender procedures extracted 100 and 86% TRR, respectively. The method that used the shaker extraction was validated for a LOQ of 0.02 mg/kg for flubendiamide and its des-iodo metabolite.

A HPLC/UV method (C18 column/ 260 nm) was developed to analyse flubendiamide and the des-iodo and 3-OH metabolites in tea samples. The samples were homogenized with ACN/0.1N HCl, extract with n-Hexane/EtOAc and cleaned up with graphite carbon, C18 and NH2 SPE. To analyse flubendiamide and the des-iodo metabolite, an addition clean-up step using silica SPE was included before HPLC/UV. The method was validated for flubendiamide at a LOQ of 0.01 mg/kg.

Method 00912 was developed for the determination of flubendiamide and the metabolite flubendiamide-iodophthalimide in <u>animal commodities</u> (muscle, liver, kidney, milk, fat and egg). The residues are extracted with acetonitrile/water and flubendiamide-iodophthalimide is completely converted to flubendiamide-des-alkylamino and its isomer under mild alkaline conditions. The residues are subjected to column clean-up and analysed by LC-MS/MS. The method uses matrix-matched standards for calibration or internal deuterated standards for calibration. LOQ for flubendiamide and its metabolite was 0.01 mg/kg and for flubendiamide-iodophthalimide was 0.013 mg/kg, expressed as parent equivalents compound. The transition for quantification was m/z 681→ 254 for flubendiamide and m/z 548 → 504 for the flubendiamide-des-alkylamino. Another transition for confirmation was monitored for each analyte.

Due to thermolability of flubendiamide, GC-based multiresidue methods are not recommended. HPLC-based multiresidue methods may be applicable, but no information addressing this approach were submitted.

Stability of residues in analytical samples

Flubendiamide and its des-iodo metabolite residues were shown to be stable in samples of tomatoes, oranges, beans, grapes, olive oil, must grapes and cabbages fortified at 0.10 mg/kg and stored under frozen conditions up to 18 months. Another study conducted with cotton seed and processed commodities, wheat and processed commodities, wheat forage and straw, potatoes and tomato paste fortified at 0.15 mg/kg, the compounds showed stability over one year periods.

No stability studies were conducted with flubendiamide in animal commodities, but information from the animal feeding studies showed that the samples were analysed less than a month after collection.

Definition of the residue

Metabolism studies conducted with flubendiamide in laying hens showed that the highest residues are found in fat and liver. TRR in fat (17.7 mg/kg eq) were higher than in muscle (1 mg/kg eq). The parent compound is the main residues found in edible commodities, accounting for 80 to 95% TRR. The main metabolite detected, flubendiamide-benzylalcohol, accounted for less than 10% TRR, mainly found in liver.

Goat metabolism studies also showed the highest residues in fat and liver. The ratio of flubendiamide residues in muscle vs fat was 1:12. The parent compound accounted for over 70% TRR and the main metabolite, flubendiamide-iodophthalimide, accounted for up to 24% TRR in fat and up to 17% TRR in milk, but less than 10% TRR in other tissues.

Plant metabolism studies conducted on plants have shown that flubendiamide accounted for over 90% of the residues. The main metabolite, flubendiamide-des-iodo, accounts for less than 10% TRR. Succeeding crop studies have shown that, with the exception of flubendiamide-des-iodo-alkylphthalimide present in straw of the second rotation (0.01 mg/kg eq., 16.0% TRR), no other metabolite exceeded 11% TRR.

Proposed definition of the residue (for compliance with the MRL and for estimation of dietary intake) for plant commodities: *flubendiamide*

As the flubendiamide-iodophthalimide metabolite was found in human foods (fat and milk), the Meeting determined that it was appropriate to include this metabolite in the dietary risk assessment.

Definition of the residue (for compliance with the MRL) for animal commodities: *flubendiamide.*

Definition of the residue (for estimation of dietary intake) for animal commodities: *flubendiamide and flubendiamide-iodophthalimide.*

Results of the poultry and bovine feeding studies were consistent with the metabolism studies in showing significantly higher residue levels in fat than muscle. Flubendiamide has a Log K_{ow} of 4.2. Based on this information, the Meeting concluded that flubendiamide is fat soluble.

The residue is fat-soluble.

Residues of supervised trials on crops

With the data gathering methods that were used, residues of both flubendiamide and flubendiamide-des-iodo were analysed in all supervised trials, except tea trials. Flubendiamide des-iodo, was detected only in animal feed commodities and in some processed commodities.

Greece and the Netherlands submitted GAP for tomato and pepper uses. This was the only GAP submitted by any European countries for flubendiamide. Therefore, except for tomatoes and peppers, no European residue data were directly used for maximum residue level estimations.

In the USA, trials were conducted side-by-side applying the pesticide in concentrated and high volume spray in pome fruits and stone fruits. Generally the high volume application gave rise to higher residues. These trials were not considered independent and the higher residues were used for estimation of residue levels.

Pome fruits

Residue trials were conducted on <u>apples</u> and <u>pears</u> in Europe, Canada and the USA. Flubendiamide is registered in the USA in pome fruits with a GAP of 3 × 0.14–0.175 kg ai/ha (minimum of 93.4 L water/ha) and 14 days PHI.

In 12 trials conducted in the USA and Canada in <u>apples</u> at GAP rate, using diluted (1800 to 3000 L/ha) or concentrated sprays (360 to 700 L/ha), residues of flubendiamide within 14 days PHI were 0.13, 0.18 (2), 0.19, 0.21, 0.23 (2), 0.27, 0.30, 0.41, 0.47, and 0.48 mg/kg.

In six trials conducted in the USA in <u>pears</u> at GAP rate, also using diluted and concentrated sprays, residues of flubendiamide at 14 days PHI were 0.09, 0.23, 0.33, 0.36, 0.37, and 0.59 mg/kg.

Residues of flubendiamide in 18 trials conducted on <u>apples</u> and <u>pears</u> in the USA and Canada according to GAP for pome fruit in the USA belong to the same population and can be combined as follow: 0.09, 0.13, 0.18 (2), 0.19, 0.21, <u>0.23 (3)</u>, <u>0.27</u>, 0.30, 0.33, 0.36, 0.37, 0.41, 0.47, 0.48, and 0.59 mg/kg.

Based on the USA and Canada trials conducted on apples and pears according to USA GAP for pome fruit, the Meeting estimated a maximum residue level of 0.8 mg/kg, a STMR of 0.25 mg/kg, and a HR of 0.59 mg/kg for flubendiamide in pome fruits.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.8 mg/kg.

Stone Fruit

Cherries

Flubendiamide is registered in the USA in <u>stone fruits</u> with a GAP of 3 × 0.14 kg ai/ha (minimum of 93.4 L water/ha) and 7 days PHI.

Eight trials were conducted in the USA and Canada in <u>cherries</u> according to US GAP. Residues of flubendiamide at 7 days PHI were 0.19, 0.25, 0.48, <u>0.57</u>, <u>0.60</u>, 0.63, 0.99 and 1.0 mg/kg.

Peaches and Nectarines

Nine trials were conducted in the USA and Canada in <u>peaches</u> according to US GAP. Residues of flubendiamide at 7 days PHI were 0.20 (2), 0.23, 0.24, 0.30, 0.32, 0.35, 0.39 and 0.40 mg/kg.

Plums

Six trials were conducted according to GAP in the USA in <u>plums</u>. Residues of flubendiamide found in plums at a 7 day PHI were: 0.02, 0.03, 0.05, 0.09, 0.14, and 0.50 mg/kg.

The Meeting recommended a group maximum residue level for stone fruit, based on the cherry data. The Meeting estimated a maximum residue level of 2 mg/kg, a STMR of 0.585 mg/kg and a HR of 1.0 mg/kg for flubendiamide in stone fruit.

Grapes

Twelve trials were conducted on <u>grapes</u> in the USA at GAP (3 × 0.14 kg ai/ha and 7 days PHI). Residues were 0.12 (2), 0.19 (2), 0.22, <u>0.40, 0.43</u>, 0.47, 0.67, 0.68, 0.69 and 0.81 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg, a STMR of 0.415 mg/kg and a HR of 0.81 mg/kg for flubendiamide in grapes. The maximum residue level estimate derived from use of the NAFTA statistical calculator was 1.8 mg/kg.

Brassica vegetables

   Broccoli

Flubendiamide is registered in <u>Brassica vegetables</u> in Australia at a maximum rate of 3 ×
0.048 kg ai/ha (0.0048 kg ai/hL) and 3 days PHI. Nine residue trials were conducted in Australia in
2006 with <u>broccoli</u>; three trials conducted at GAP gave residues of flubendiamide of 0.13, 0.22 and
0.25 mg/kg.

   Three trials were conducted on broccoli in the USA at 3 × 0.034 kg ai/ha, giving residues at a
1 day PHI and a 3 day retreatment interval (RTI) of 0.12, 0.16, and 0.23 mg/kg. GAP in the USA for
Brassicas is 2 × 0.034 kg ai/ha. A broccoli residue decline study in California revealed negligible
decline over a 7 day period, making it likely that the additional treatment would result in residues
> 25% higher than would be expected from two treatments as allowed by GAP. Therefore, the
broccoli trials in the USA were not considered further for MRL setting purposes.

   Cauliflower

Three trials were conducted in the USA at 3 × 0.034 kg ai/ha, with residues at 1 day PHI of < 0.01,
0.02 and 0.03 mg/kg.

   Cabbages

Eighteen trials were conducted on <u>cabbages</u> in Australia in 2006/2007. In six trials conducted
according to GAP for Brassicas, residues of flubendiamide at 3 days PHI were 0.19, 0.20, <u>0.27</u>, <u>0.43</u>,
0.92 and 2.7 mg/kg. Twelve trials conducted at higher rates (0.072 to 0.1 kg ai/ha) gave residues
within the same range.

   Six trials were conducted on cabbages in the USA at 3 × 0.034 kg ai/ha, 1 day PHI, and 3 day
RTI. Available residue decline data did not allow the Meeting to conclude that the initial treatment
would not contribute significantly to the residue level at harvest. Therefore, the cabbage trials in the
USA were not considered further for MRL setting purposes.

   Brussels sprouts

Twelve trials were conducted on <u>Brussels sprouts</u> in Australia in 2006. In four trials conducted
according to GAP residues of flubendiamide at 3 days PHI were 0.08, <u>0.23</u>, <u>0.50</u> and 1.1 mg/kg. In
eight trials conducted at higher rate gave residues at 3 days PHI ranging from 0.09 to 1.5 mg/kg.

   The Meeting decided it was appropriate to recommend a group MRL for Brassica vegetables.
Based on the cabbage data from Australia, the Meeting estimated a maximum residue level of
4 mg/kg, a STMR of 0.365 mg/kg and a HR of 2.7 mg/kg for flubendiamide in Brassica vegetables.

Fruiting vegetables, Cucurbits

Flubendiamide is registered in the USA for <u>cucurbit vegetables</u> at 3 × 0.05 kg ai/ha, 7 day RTI, and 1
day PHI. A total of seventeen field trials were conducted with cucumbers (six), summer squash (five)
and melons (six) using five spray applications rather than three as specified by GAP. Residue levels
in all cucurbit vegetables were so low that it is unlikely that residues from the first two spray
treatments had any significant affect on the residue levels that would have been measured after three
spray treatments. Accordingly, the Meeting decided to accept these trials for the purpose of MRL
estimation.

   Cucumber residues were as follows: < 0.01 (2), 0.01 (2), and 0.03 (2) mg/kg. Summer squash
residues were as follows: < 0.01, 0.01 (2), 0.02, and 0.04 mg/kg. Melon residues were as follows:
0.02 (2), <u>0.04</u>, <u>0.05</u>, 0.07, and 0.09 mg/kg.

   Noting the similarity in residue levels among cucumbers, summer squash, and melons, the
Meeting recommended a group maximum residue level for cucurbit vegetables based on the melon

data. The Meeting estimated a maximum residue level of 0.2 mg/kg, a STMR of 0.045 mg/kg and a HR of 0.09 mg/kg for flubendiamide in cucurbit vegetables.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.18 mg/kg.

Fruiting vegetables, other than Cucurbits

Peppers

Flubendiamide is registered in Australia in tomatoes and peppers at a maximum rate of 0.072 kg ai/ha (0.0072 kg ai/hL). Twenty four field trials were conducted on peppers in Australia in 2007. In seven trials conducted according to GAP, residues at a 1 day PHI were: 0.04, 0.06 (2), 0.09, 0.16, 0.21 and 0.37 mg/kg.

Flubendiamide is registered in the USA for use in fruiting vegetables (except cucurbits) at a maximum rate of 3 × 0.05 kg ai/ha. Eleven trials conducted on peppers in the USA at 5 × 0.05 kg ai/ha (1 day PHI and a 3 day retreatment interval) gave residues ranging from < 0.01 to 0.14 mg/kg. As these trials were not in accord with GAP, they were not considered further.

Flubendiamide is registered to be used in Greece and the Netherlands for use in greenhouses on peppers at 2 × 0.006 kg ai/hL (0.096 kg ai/ha) with 1 day PHI. Fourteen glasshouse trials were conducted on peppers in France, Germany, Italy and the Netherlands using two or three spray treatments. Only four of these trials were according to GAP, giving residues as follows: 0.05, 0.06, 0.07, and 0.11 mg/kg.

The trials conducted on peppers in Australia and Europe according to GAP gave different residue populations. The Australian data gave the higher residues and were used as the basis for the estimations.

The Meeting estimated a maximum residue level of 0.7 mg/kg, a STMR of 0.09 mg/kg and a HR of 0.37 mg/kg for flubendiamide in peppers.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.7 mg/kg.

Chili pepper, Dry

Using the default dehydration factor of 10 to extrapolate from peppers to dried chilli peppers, the Meeting estimated a maximum residue level of 7 mg/kg and a STMR of 0.9 mg/kg for flubendiamide in dry chilli peppers.

Tomatoes

Field trials were conducted in Australia on tomatoes. In five trials conducted according to Australian GAP, residues at a 1 day PHI were: 0.04, 0.07, 0.35 (2) and 0.63 mg/kg. The trials conducted at higher and lower rates gave residues within the same range.

In eight field trials conducted on tomatoes in the USA in 2004 using five spray applications instead of three as specified by USA GAP (1 day PHI and 3 day RTI), residues ranged from 0.01 to 0.16 mg/kg. These trials were not considered further for MRL estimates because they do not reflect USA GAP and show residue levels lower than those conducted in Australia.

Flubendiamide is registered to be used in Greece in greenhouses in tomatoes at 2 × 0.006 kg ai/hL (0.12 kg ai/ha) with a 3 day PHI. In the Netherlands, GAP rate is the same, but the PHI is 1 day. Trials were conducted for greenhouse tomatoes in France, Germany, Italy, the Netherlands, Portugal and Spain using the GAP application rate. However, the trials conducted with three applications are not in accord with GAP, and should not be directly used for MRL-estimating purposes.

Five trials conducted in Germany, Spain and Portugal evaluated against Netherlands GAP gave residues at 1 day PHI of 0.06 (2), 0.09, 0.10, 0.11 (2) and 0.12 mg/kg.

The trials from Australia resulted in higher residues than those conducted in Europe and are appropriate for use in MRL estimations.

The Meeting estimated a maximum residue level of 2 mg/kg, a STMR of 0.35 mg/kg and a HR of 0.63 mg/kg for flubendiamide in tomatoes.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 2.9 mg/kg.

Sweet corn

Flubendiamide is registered in the USA in <u>sweet corn</u> at a maximum rate of 4 × 0.10 kg ai/ha with a 1 day PHI. In 11 trials conducted according to GAP, residues in corn-on-the-cob were < 0.01 (10) and 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.02 mg/kg, a STMR and a HR of 0.01 mg/kg for flubendiamide in sweet corn (corn-on-the-cob).

Leafy vegetables

Lettuce, Head

Flubendiamide is registered in Australia for leafy vegetables, including <u>leaf and head lettuce</u>, at a maximum rate of 3 × 0.048 kg ai/ha and a 1 day PHI.

In six Australian trials conducted on 2006 according to GAP, residues of flubendiamide at 1 day PHI were 0.16, 0.32, <u>0.78, 0.97</u>, 1.0 and 2.2 mg/kg. The Meeting estimated a maximum residue level of 5 mg/kg, a STMR of 0.875 mg/kg and a HR of 2.2 mg/kg for flubendiamide in head lettuce.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 5.8 mg/kg.

Lettuce, Leaf

In six Australian <u>leaf lettuce</u> trials conducted in 2006 according to GAP, residues of flubendiamide at a 1 day PHI were 0.95, <u>1.6 (2), 1.8</u>, 2.7 and 4.0 mg/kg.

The Meeting estimated a maximum residue level of 7 mg/kg, a STMR of 1.7 mg/kg and a HR of 4 mg/kg for flubendiamide in leaf lettuce.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 6.0 mg/kg.

Spinach

Five trials were conducted in the USA using 5 × 0.05 kg ai/ha (GAP for leafy vegetables allow up to three applications, with a 3 day RTI). Residues at 1 day PHI ranged from 3.1 to 6.7 mg/kg.

As no residue trials were conducted according to GAP, and no residue decline data were available to indicate the rate of residue dissipation, the Meeting could not estimate a maximum residue level for flubendiamide in spinach.

Legume vegetables

Beans with pods

Flubendiamide is registered in Australia in <u>legume vegetables</u> at a maximum rate of 3 × 0.072 kg ai/ha and 1 day PHI. Residues at 1 day PHI in four trials conducted on 2006/2007 according to GAP were 0.11, 0.20 (2) and 0.22 mg/kg in <u>green beans</u>.

Trials were conducted with <u>beans</u> and <u>peas</u> in the USA according to the legume vegetable GAP (2×0.1 kg ai/ha). Residues at 1 day PHI in six USA trials were 0.03, 0.07, 0.09 (2), 0.14, and 0.17 mg/kg in beans with pods.

Peas with pods

Residues at 1 day PHI in five trials conducted in Australia according to GAP were 0.38, 0.39, <u>0.43</u>, 0.45, and 0.90 mg/kg in <u>peas with pods</u>.

Residues at 1 day PHI in three trials conducted in the USA according to GAP were 0.14, 0.22, and 0.21 mg/kg in peas with pods.

Succulent shelled beans and peas

Soya bean, green seed

Twenty trials were conducted on <u>soya beans</u> in the USA according to GAP of 2×0.10 kg ai/ha. Residues in green seeds at 1 day PHI were 0.02, 0.03 (2), 0.04 (4), 0.05, 0.07, <u>0.08</u> (2), 0.09, 0.10, 0.12, 0.20 (2), 0.21, 0.22, 0.29 and 0.40 mg/kg;

Shelled beans and peas

Twelve trials were conducted in the USA according to the USA legume vegetable GAP on <u>shelled beans</u> (six trials) and <u>shelled peas</u> (six trials). Residues in shelled beans were < 0.01 (4), 0.01 and 0.03 mg/kg and in shelled peas < 0.01 (4), 0.01 and 0.03 mg/kg. Residues in shelled beans and peas can be combined as < 0.<u>01</u> (8), 0.01 (2) and 0.03 (2) mg/kg.

The Meeting decided it was appropriate to make a commodity group recommendation for legume vegetables. The results from the peas with pods trials from Australia were used to make the estimations. The Meeting estimated a maximum residue level of 2 mg/kg, and a STMR of 0.43 mg/kg, and a HR of 0.90 mg/kg for flubendiamide in legume vegetables.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 1.2 mg/kg.

Pulses

Soya beans, dry

In dry soya bean seeds, residues at 14 days PHI were < 0.01, 0.01 (4), 0.02 (2), 0.03 (5), 0.04, 0.06, 0.07 (2), 0.09, 0.14, 0.25 and 0.30 mg/kg.

Dry peas and cowpeas

Fourteen trials were conducted with <u>cowpeas</u> and <u>dry peas</u> in the USA according to GAP of 2×0.1 kg ai/ha and 14 days PHI. Residues in cowpeas were < 0.01, 0.01 (2), 0.02, 0.04 (3), 0.06 and 0.20 mg/kg. Residues in dry peas were 0.08, 0.11, <u>0.18</u> (2) and 0.59 mg/kg.

Based on the data set for dry peas, the Meeting recommended establishing a group MRL for pulses. The Meeting estimated a maximum residue level of 1 mg/kg and a STMR of 0.18 mg/kg for flubendiamide in pulses.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 1.0 mg/kg.

Celery

Flubendiamide is registered in the USA in leafy vegetables at a maximum rate of 3×0.05 kg ai/ha and 1 day PHI. In six US trials conducted using five applications at the GAP rate with a 3 day RTI, residues at a 1 day PHI in celery stalks were: 0.81, 1.2, <u>1.3</u>, <u>2.1</u>, 2.3, and 2.6 mg/kg.

Although the number of spray applications (five) exceeded that specified by GAP (three), a residue decline study shows substantial reductions in residue levels over three days, the RTI for use in celery. The Meeting concluded that the first two sprays are unlikely to contribute more than 20% to the residue levels at harvest. Consequently, the celery results may be used to estimate maximum residue levels. The Meeting estimated a maximum residue level of 5 mg/kg a STMR of 1.7 mg/kg, and a HR of 2.6 mg/kg for flubendiamide in celery.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 4.6 mg/kg.

Corn (maize)

Flubendiamide is registered in the USA in field corn at a maximum rate of 4 × 0.10 kg ai/ha and 28 day PHI. Nineteen trials were conducted in Canada and the USA according to this GAP giving residues within 28 days PHI of < 0.01 (17) and 0.01 (2) mg/kg. The Meeting estimated a maximum residue level of 0.02 mg/kg and a STMR of 0.01 mg/kg for flubendiamide in maize grain.

Rice

Flubendiamide is registered in India in rice with a GAP of 3 × 0.024 kg ai/ha with a PHI of 40 days. Ten trials were conducted in Thailand and two in India using the GAP rate, but at a PHI of 30 days or less. Nine trials from Thailand conducted with PHIs of 27–30 days gave residues from < 0.01 to 0.11 mg/kg. Two trials conducted in India with 28 day PHIs gave residues of 0.06 and 0.20 mg/kg. One Thai trial with a 13 day PHI gave residues of 0.30 mg/kg.

As no residue trials were conducted according to GAP, the Meeting could not estimate a maximum residue level for flubendiamide in rice.

Tree nuts

Flubendiamide is registered in the USA in tree nuts at 3 × 0.14 kg ai/ha and 14 days PHI. Twenty trials were conducted in the country in almonds and pecans according to GAP. Residues in almonds were < 0.01 (4), 0.01, 0.02 (3), 0.04 and 0.05 mg/kg. Residues in pecans were < 0.01 (6), 0.01 (2), 0.02, and 0.03 mg/kg.

Based on the almond data, the Meeting estimated a maximum residue level of 0.1 mg/kg, a STMR of 0.015 mg/kg and a HR of 0.05 mg/kg for flubendiamide in tree nuts.

Cotton

Flubendiamide is registered in the USA in cotton with a GAP of 3 × 0.10 kg ai/ha with a PHI of 28 days. Residue levels found from 12 trials conducted according to GAP, were: < 0.01, 0.02, 0.03, 0.11, 0.12 (2), 0.18, 0.19, 0.25, 0.28, 0.37 and 1.0 mg/kg.

The Meeting estimated a maximum residue level of 1.5 mg/kg and a STMR of 0.15 mg/kg for flubendiamide in cotton seed.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.91 mg/kg.

Tea

Flubendiamide is registered in Japan in dry tea at 1 × 0.40 kg ai/ha and 7 days PHI. Six trials were conducted in the country according to GAP, giving residues at 7 days PHI of 11, 17, 22, 24, 28 and 29 mg/kg.

The Meeting estimated a maximum residue level of 50 mg/kg, a STMR of 23 mg/kg and a HR of 29 mg/kg for flubendiamide in tea.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 49 mg/kg.

Animal feeds

The individual residue values that are reported in this section have not been adjusted for dry matter content. However, maximum residue levels were corrected for dry matter content as listed in the OECD feed tables.

Soya bean forage and hay

Twenty trials were conducted on <u>soya bean forage and hay</u> in the USA according to the GAP of that country (2 × 0.10 kg ai/ha). Residues in forage at a 3 day PHI were: 4.3, 6.0, 6.1, 6.7, 6.8, 7.1, 7.2, 7.6, 7.7, <u>7.9, 8.0</u>, 9.1, 9.9, 10 (3), 11 (2), 13 and 15 mg/kg.

The Meeting estimated a STMR of 7.95 mg/kg and a highest residue of 15 mg/kg for flubendiamide in soya bean forage (green).

In hay, residues at 3 days PHI were 12, 13, 14, 15, 17, 22, 23, 24, 25, <u>26, 29</u> (2), 30, 32, 33, 34, 35, 39 and 41 (2) mg/kg.

The Meeting estimated an MRL of 60 mg/kg, a STMR of 27.5 mg/kg and a highest residue of 41 mg/kg for flubendiamide in soya bean fodder.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 62 mg/kg.

Cowpea and pea forage and hay

Twenty two trials were conducted on <u>forage and hay from cowpeas</u> and <u>vines and hay from peas</u> in the USA according to GAP.

Residues at 3 days PHI from six trials in cowpea forage were: 3.9, 4.2, <u>5.5, 6.6</u>, 9.0 and 14 mg/kg.

The Meeting estimated a STMR of 6.05 mg/kg and a highest residue of 14 mg/kg for flubendiamide in cowpea forage.

Residues in pea vines at 3 days PHI from five trials were: 2.4 (2), <u>3.1</u>, 3.6 and 5.5 mg/kg. The Meeting estimated a STMR of 3.1 mg/kg and a highest residue of 5.5 mg/kg for flubendiamide in pea vines.

Residues from six trials in cowpea hay at 3 days PHI were: 8.3, 15, 16, 25 and 26 mg/kg. Residues from five trials in pea hay at 3 days PHI were: 4.2, 9.1, 9.9, 12 and 20 mg/kg.

The Meeting decided that residues from trials conducted on cowpeas and pea hay belonged to the same population and could be combined for mutual support as: 4.2, 8.3, 9.1, 9.9, <u>12, 15</u>, 16, 20, 25 and 26 mg/kg

The Meeting therefore, estimated an MRL of 40 mg/kg, a STMR of 13.5 mg/kg and a highest residue of 26 for flubendiamide in pea fodder.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 47 mg/kg.

Maize forage

In 31 trials conducted on field corn in Canada and the USA according to US GAP, residues in <u>maize forage</u> at 1 day PHI were 1.0, 1.7, 1.8 (2), 2.0, 2.2, 2.5, 3.4, 3.5, 3.6 (3), 3.7 (2), <u>3.8</u> (3), 3.9 (3), 4.2,

4.6 (2), 4.8, 5.0, 5.3, 5.5, 5.6 (2), 6.7 and 8.4, mg/kg. The Meeting estimated a STMR of 3.8 mg/kg and a highest residue of 8.4 mg/kg for flubendiamide in maize forage.

Almond hulls

In ten trials conducted on <u>almonds</u> in the USA according to GAP, residues in <u>almond hulls</u> at 14 days PHI were 0.98, 1.4, 1.4, 2.1, <u>2.4, 2.5</u>, 2.9, 3.3, 4.7 and 5.2 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg, and a STMR of 2.45 mg/kg for flubendiamide in almond hulls.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 8.3 mg/kg]

Cotton gin trash

In six trials conducted in the USA according to GAP, residues in <u>cotton gin trash</u> at a 28 day PHI were 2.3, 3.5, <u>6.8, 8.1</u> and 25 (2) mg/kg.

The Meeting estimated a STMR of 7.45 mg/kg for flubendiamide in cotton gin trash.

Processing studies

Effects on the nature of residues

[Phthalic-acid ring-UL-^{14}C]flubendiamide (0.2 mg ai/L water containing 1% acetonitrile) was incubated in buffered drinking water at three representative sets of conditions: pasteurization at 90 °C/20 min at pH 4; baking, brewing, boiling at 100 °C/60 min at pH 5; sterilization (autoclave) at 120 °C/20 min at pH 6. Radioactivity was determined by LSC and HPLC/MS for confirmation of the identity of the test compound. Radioactivity balances were in a range of 99.8 to 101.0% of applied radioactivity. In all three processing scenarios, no degradates were observed in any of the samples, and flubendiamide was the only compound in all HPLC profiles.

Fate of residues in processing

Processing studies were conducted on apples, peaches, plums, grapes, tomatoes, cucurbits (cucumbers, melons and summer squash), cabbages, broccoli, lettuce, cotton, soybean, corn and rice. In all studies, residues of flubendiamide and its metabolite flubendiamide-des-iodo were determined by HPLC-MS/MS. Processing factors are only shown for flubendiamide.

A summary of processing factors (PF) calculated based on the data provided is shown on Table 1. Based on the estimations made on the crops, a STMR-P was estimated by multiplying the STMR of the raw commodity for the PF. As no recommendations were made for rice, no further estimations were made for processing commodities of this crop. Maximum residue levels (MRLs) were only estimated for commodities with a Codex code and of importance to international trading.

Table 1 Summary of processing factors and estimations for processing commodities

Commodity	STMR, mg/kg	HR, mg/kg	PF, mean or best estimate	STMR-P, mg/kg
Pome fruit	0.25	0.59		
Dried fruit			0.51	0.13
Apple juice			0.06	0.015
Plum	0.585	1.0		
Prunes			0.9	0.53
Grape	0.415	0.81		
Grape juice			0.13	0.054

Commodity	STMR, mg/kg	HR, mg/kg	PF, mean or best estimate	STMR-P, mg/kg
Wine			0.19	0.079
Raisin			1.7	0.70
Grape pomace, dry			5.9	2.45
Brassica vegetables	0.365	2.7		
Tomato	0.35	0.63		
Tomato peeled			0.3	0.105
Tomato juice			0.49	0.17
Tomato preserve/canned			0.29	0.10
Tomato paste			4	1.4
Lettuce	0.875	2.2		
Soybean	0.08	0.40		
Refined oil			< 0.04	0.001
Aspirated grain fraction			358	28.6
Soybean meal			0.12	0.01
Soybean hulls			2.7	0.22
Corn (maize)	0.01	0.01		
Corn flour			2.1	0.021
Corn meal			0.93	0.009
Corn oil, refined			0.45	0.0045
Corn aspirated grain fractions			318	3.18
Cotton	0.15	1.0		
Cotton oil crude			6.1	0.92
Cotton meal			0.22	0.08

Residues in the dried commodity were lower than in fresh grapes: as a consequence the meeting decided a maximum residue level need not be recommended.

The Meeting decided to estimate a maximum residue level of 0.05 mg/kg for corn flour based on a mean residue of 0.01 mg/kg for maize and a processing factor of 2.1 (0.01 × 2.1 = 0.021 mg/kg).

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of flubendiamide in farm animals on the basis of the diets listed in Appendix IV of the 2009 Manual on the Submission and Evaluation of Pesticide Residues Data and the STMR or highest residue levels estimated at the present Meeting. Dietary burden calculations are provided in Annex 5.

Table 2 Animal dietary burden for flubendiamide, ppm of dry matter diet

		US/CAN	EU	Australia	Japan
Beef cattle	max	4.9	32.1	47.9[a]	0.039
	mean	3.1	14.7	29.9[b]	0.039
Dairy cattle	max	25.0	32.6	47.3[c]	10.5
	mean	13.7	15.0	25.0[d]	4.78

		US/CAN	EU	Australia	Japan
Poultry broiler	max	0.07	0.09	0.19	0.008
	mean	0.07	0.09	0.19	0.008
Poultry layer	max	0.07	9.6[e]	0.19	0.009
	mean	0.07	5.3[f]	0.19	0.009

[a] Highest maximum beef or dairy cattle dietary burden suitable for maximum residue level estimates for mammalian meat

[b] Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.

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

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

[e] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.

[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

The flubendiamide burdens for animal commodity MRL estimation (residue levels in animal feeds expressed on dry weight) reached a maximum of 47.3 ppm for cattle and of 9.6 ppm for poultry. The flubendiamide dietary burdens for animal commodity STMR estimation (residue levels in animal feeds expressed on dry weight) reached a maximum of 29.9 ppm for cattle and of 5.3 ppm for poultry.

Animal feeding studies

<u>Laying hens</u> were fed for 28 consecutive days with feed containing flubendiamide at 0.02, 0.10, or 0.50 ppm. Eggs were collected daily. Additionally, two groups of laying hens were fed at 0.5 ppm feed for 28 consecutive days in order to investigate the depuration of flubendiamide and its metabolite in eggs and tissues (up to 14 days after the last dose). Samples were analysed by HPLC-MS/MS for flubendiamide and flubendiamide-iodophthalimide. Flubendiamide was detected in eggs at the second dosing level from day 13 (0.01 mg/kg) and it reached 0.06 mg/kg at the highest dose. No residues of flubendiamide-iodophthalimide were detected in any egg sample at any dose. The highest flubendiamide residues in tissues were observed in fat, showing evidence of a dose response (0.01, 0.07 and 0.25 mg/kg in the first, second and third dose, respectively). Flubendiamide-iodophthalimide was found only at the highest dose level in fat (0.02 mg/kg). Flubendiamide was not present in egg samples 14 days after the last dose and decreased in fat from 0.27 mg/kg at the end of the dosing period to 0.04 mg/kg 7 days after the last dose to 0.01 mg/kg after 14 days (only one fat sample).

<u>Lactating cows</u> were dosed orally for 29 consecutive days with flubendiamide at 2.5, 7.5, 30 or 50 mg/kg feed/day (nominal dosing rates). Milk was collected twice daily during the dosing period, and a portion of the 25 day sample from the highest dose group was separated into milk fat and skim milk whey. Additionally, two cows were fed at 50 mg/kg for 29 consecutive days in order to investigate the depuration of residues in milk (up to 21 days after the last dose) and tissues (at 7 and 21 days after the last dose). Tissue and milk samples were analysed for residues by HPLC-MS/MS for flubendiamide and flubendiamide-iodophthalimide. For the low and medium dose levels, residues of flubendiamide in milk remained very low throughout the dosing periods at the low and medium dose levels (up to 0.03 mg/kg). At higher dose levels (30 and 50 mg/kg), residues in milk reached a plateau level after 7–8 days of dosing (approximately 0.11 mg/kg). Flubendiamide residues were 0.02 mg/kg in milk whey and 1.5 mg/kg in "milk fat (cream)", with an apparent processing factor for milk to milk fat of 13.6. However, no information on the lipid content of the milk fat (cream) sample was provided. The iodophthalimide metabolite was only detected in milk fat (0.23 mg/kg). Residues of flubendiamide were observed in tissues of all animals in all dose groups, with the lowest levels in muscle (0.01 to 0.12 mg/kg), followed by liver and kidney (0.04 to 0.46 mg/kg) and fat (from 0.06 to 0.65 mg/kg in subcutaneous fat, 0.08 to 1.0 mg/kg in omental and perirenal fat). Flubendiamide was detected in fat at a mean level up to 0.17 mg/kg. During the depuration phase, residues in milk decline from 0.16 mg/kg in the last dosing day to 0.02 mg/kg after 19 to 21 days. Residues in tissues

declined to 31 to 46% of the last dosing day level in the first week of depuration and from 23 to 32% after 14 days.

Animal commodity maximum residue levels

Poultry

The dietary burdens for the estimation of maximum residue levels and STMR values for flubendiamide in <u>poultry</u> commodities are 9.6 and 5.3 ppm, respectively. Because the poultry dietary burden exceeds the highest dosing level in the poultry feeding study by more than 30%, no attempt was made to estimate maximum residue levels, STMR or HR values for poultry tissues and eggs.

Dosing levels in the bovine feeding study are adequate for the purposes of estimating residue levels in mammals, and the relevant data are summarized in Table 3.

Table 3 Estimations of residues in mammalian commodities

Dietary burden (mg/kg) Feeding level [ppm]		Flubendiamide and flubendiamide-iodophthalimide residues, mg/kg					
		Milk	Milk fat	Muscle	Liver	Kidney	Fat
MRL cattle beef, highest residue	(47.9) [38] [60]			(0.13) [0.09] [0.16]	(0.56) [0.53] [0.59]	(0.57) [0.55] [0.59]	(1.2) [0.93] [1.47]
MRL milk, highest residue	(47.3) [69]	(0.16) [0.17]	(4.0) [4.25][a]				
STMR cattle beef and dairy, mean residue	(29.9) [38]			(0.06) [0.07]	(0.31) [0.39]	(0.32) [0.41]	(0.62) [0.79]
STMR milk, mean residue	(25.0) [38]	(0.066) [0.10]	(1.6) [2.50][a]				

[a] Although a residue concentration factor was provided for "milk fat (cream)", no lipid content was provided for this sample. Assuming that whole milk is 4% milk fat, and assuming all flubendiamide and flubendiamide-iodophthalimide residues partition into the fat, a milk fat residue was estimated by applying the maximum concentration factor for milk to milk fat of 25×.

The data from the cattle feeding studies were used to support the estimation of maximum residue levels for flubendiamide in mammalian meat, edible offal, and milk.

The Meeting estimated STMR values of 0.06 mg/kg for mammalian muscle and 0.62 mg/kg for mammalian fat, and a maximum residue level of 2 mg/kg for mammalian meat. The HRs were 0.13 mg/kg and 1.2 mg/kg for muscle and fat, respectively.

The Meeting estimated an STMR value of 0.32 mg/kg and a maximum residue level of 1 mg/kg for mammalian edible offal, based on liver and kidney data. The HR was 0.57 mg/kg.

The Meeting estimated an STMR value of 0.066 mg/kg and a maximum residue level of 0.2 mg/kg for flubendiamide in milks.

The Meeting estimated an STMR value of 1.6 mg/kg and a HR of 4.0 mg/kg for milk fat. The Meeting estimated a maximum residue level of 5 mg/kg for milk fat.

DIETARY RISK ASSESSMENT

Long-term intake

The ADI for flubendiamide is 0–0.02 mg/kg bw. The International Estimated Daily Intakes (IEDI) for flubendiamide was estimated for the 13 GEMS/Food cluster diets using the STMR or STMR-P

values estimated by the current Meeting. The results are shown in Annex 3. The IEDI ranged from 3 to 20% of the maximum ADI. The Meeting concluded that the long-term intake of residues of flubendiamide from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The ARfD for flubendiamide is 0.2 mg/kg bw. The International Estimated Short Term Intake (IESTI) for flubendiamide was calculated for the plant commodities for which STMRs and HRs were estimated and for which consumption data were available. The results are shown in Annex 4. The IESTI ranged from 0 to 40% of the ARfD for the general population and from 0 to 60% of the ARfD for children.

The Meeting concluded that the short-term intake of residues from the uses of flubendiamide considered by the Meeting is unlikely to present a public health concern.