

## 5.16 METAFLUMIZONE (236)

### TOXICOLOGY

Metaflumizone is the ISO approved common name for (EZ)-2'-[2-(4-cyanophenyl)-1-( $\alpha,\alpha,\alpha$ -trifluorom-tolyl)ethylidene]-4-(trifluoromethoxy)carbanilohydrazide (CAS No. 139968-49-3), which is a mixture of E and Z isomers (ratio, approximately 9: 1). Metaflumizone is a novel insecticide of the semicarbazone class, which acts by blocking voltage-dependent sodium channels of the nervous system, causing paralysis of the insect. Metaflumizone was evaluated at the request of CCPR and was not evaluated previously by JMPR.

All pivotal studies were certified as complying with GLP or an approved quality-assurance programme.

#### *Biochemical aspects*

In rats given [ $^{14}$ C]benzotrile-ring (B)-labelled or [ $^{14}$ C]trifluoromethoxyphenyl-ring (T)-labelled metaflumizone orally by gavage, absorption was up to 17% of the administered dose after a single dose at 6 mg/kg bw, and up to 7% after a single dose at 30 or 1000 mg/kg bw. Absorption may be higher by dietary administration (23% at 0.76 mg/kg bw) or by gavage in Cremophor, an emulsifying agent (33% at 6 mg/kg bw). The maximum plasma concentrations were reached after 10–48 h, depending on the dose and the radiolabel tested. Increasing the dose by a factor of 33 resulted in an increase in AUC of about 10-fold, correlating with the lower absorption of metaflumizone at the higher dose. Radiolabel was widely distributed throughout the body. Residues in tissues at 168 h after a single dose at 6 or 30 mg/kg bw accounted for approximately 15% or approximately 2–3% of the administered dose, respectively, with fat, liver, kidney, muscle and blood containing the highest concentrations of residues. The major route of excretion of radiolabel was via the faeces (mainly unabsorbed substance; < 5% in bile) while only < 3% of the administered dose was excreted via the urine. The elimination half-lives depended on the position of the radiolabel, ranging from 27–48 h to 139–402 h for the B-labelled and the T-labelled metaflumizone, respectively.

Metaflumizone was metabolized via hydroxylation of the aniline or benzotrile ring, hydrolysis of the central hydrazine carboxamide group and conjugation with sulfate, glucuronic acid, glycine or glutathione. Unchanged parent compound was the major component of the residues extracted in tissues and plasma, while no parent was found in the urine and bile.

#### *Toxicological data*

Metaflumizone was of low toxicity in rats exposed orally or dermally ( $LD_{50} > 5000$  mg/kg bw) and caused neither mortality nor systemic toxicity at this limit dose. Metaflumizone was also of low toxicity in rats exposed by inhalation ( $LC_{50} > 5.2$  mg/L).

Metaflumizone was not a skin irritant in rabbits, was non-to-slightly irritating to rabbits' eyes, and was not a skin sensitizer in the guinea-pig maximization test.

After repeated administration of metaflumizone, decreased food consumption, decreased body-weight gain or body-weight loss and subsequent poor general state of health at higher doses were observed in all species tested. These effects were observed regardless the route of administration, i.e., after oral, dermal or inhalation exposure. Data also indicated that females, both rats and dogs, are relatively more sensitive to intoxication than are males.

The poor palatability of the test substance at dietary concentrations of  $\geq 50$  ppm was considered to significantly affect food consumption in short-term feeding studies, and consequently in all further studies (including short-term studies of toxicity, long-term studies of toxicity and carcinogenicity, two-generation study of reproductive toxicity) the test substance was administered

via gavage (rats) or in capsules (dogs). However, similar effects (such as decreased food consumption and body-weight gain) were observed with all methods of administration, but occurred at markedly lower doses with dietary administration.

A clear mode of action for the toxicity of metaflumizone in mammals has not been identified. Many of the effects observed after repeated dosing were consistent with decreased food consumption and body-weight loss but do not appear to be induced by the insecticidal mode of action (i.e., specific receptor affinity, blocking of sodium channels).

The short-term toxicity of metaflumizone was investigated in mice, rats and dogs. In two 28-day range-finding feeding studies in mice, the NOAEL was 40 ppm, equal to 8.2 mg/kg bw per day, on the basis of decreased food consumption and body-weight gain at dietary concentrations of 200 ppm and above. Effects at higher doses included body-weight loss, clinical signs of toxicity (ataxia, convulsions) and mortality.

In 28-day and 3-month feeding studies in rats, the NOAEL was 20 ppm, equal to 2.2 mg/kg bw per day, on the basis of decreased food consumption and body-weight gain at 40 ppm, equal to 4.3 mg/kg bw per day, and above. Effects at higher doses ( $\geq 1000$  ppm, equal to 83 mg/kg bw per day) included body-weight loss and poor general state (emaciation, hair loss, pallor, hunched posture). In subsequent 28-day and 3-month studies in rats treated by gavage, the NOAEL was 60 mg/kg bw per day on the basis of reduced food consumption and body-weight gain in females at 300/200 mg/kg bw per day.

In a combined 3-month/1-year study of toxicity in dogs given metaflumizone in capsules, the NOAEL was 12 mg/kg bw per day on the basis of clinical signs of poor general state of health and premature sacrifice, decreased food consumption, reduced body-weight gain and body-weight loss and changes in haematological parameters at doses of 30 mg/kg bw per day and above.

Metaflumizone was tested in an adequate battery of assays for genotoxicity in vitro and in vivo. Negative results were obtained in the tests in vitro, except for a positive result in a test for chromosomal aberration in the absence of metabolic activation. In vivo, an assay for micronucleus formation in mice and a test for unscheduled DNA synthesis in rats gave negative results.

The Meeting concluded that metaflumizone was unlikely to be genotoxic.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In an 18-month study of carcinogenicity in mice treated by gavage, the NOAEL was 250 mg/kg bw per day on the basis of decreased body weight/body-weight gain and increased incidences of brown pigment in the spleen at 1000 mg/kg bw per day, the highest dose tested. There was no evidence for carcinogenicity with metaflumizone in this study.

In a 2-year study of toxicity and carcinogenicity in rats treated by gavage, the NOAEL was 30 mg/kg bw per day on the basis of increased incidences of centrilobular hepatocellular hypertrophy and hepatocellular basophilic alteration in males at 60 mg/kg bw per day. There was no evidence for carcinogenicity up to the highest doses tested (300 or 200 mg/kg bw per day for males or females, respectively).

On the basis of the absence of carcinogenicity in mice and rats and the absence of genotoxicity, the Meeting concluded that metaflumizone is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats treated by gavage, the highest dose tested (75 mg/kg bw per day) induced excessive parental toxicity, resulting in reduced fertility and high pup mortality. Consequently, the highest dose was reduced from 75 to 50 mg/kg bw per day and the intermediate dose from 30 to 20 mg/kg bw per day for the next two successive parental generations. The NOAEL for parental toxicity was 20 mg/kg bw per day on the basis of increased incidences of poor general state of health of females at doses of 30 mg/kg bw per day and above. The NOAEL for offspring toxicity was 20 mg/kg bw per day on the basis of increased incidences of stillborn pups and increased pup mortality at doses of 50 mg/kg bw per day and above. The NOAEL

for effects on fertility was 50 mg/kg bw per day on the basis of a reduction in the male and female fertility index at 75 mg/kg bw per day.

In a study of prenatal developmental toxicity in rats, the NOAEL for maternal toxicity was 40 mg/kg bw per day on the basis of reduced food consumption and decreased body-weight gain at 120 mg/kg bw per day. The NOAEL for developmental toxicity was 120 mg/kg bw per day, the highest dose tested.

In a study of prenatal developmental toxicity in rabbits, the NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of clinical signs of toxicity (poor general state, including ataxia) and abortion at 300 mg/kg bw per day. The NOAEL for developmental toxicity was 100 mg/kg bw per day on the basis of decreased fetal body weights and an increased rate of incomplete ossification of the sternebrae at 300 mg/kg bw per day.

The Meeting concluded that metaflumizone caused developmental toxicity only at doses that were maternally toxic but that it was not teratogenic.

In a study of acute neurotoxicity in rats, metaflumizone did not induce signs of systemic toxicity or neurotoxicity at up to the highest dose tested (2000 mg/kg bw). In a short-term study of neurotoxicity in rats treated by gavage, the NOAEL for neurotoxicity was 300 and 150 mg/kg bw per day in males and females, respectively, the highest doses tested. The NOAEL for systemic toxicity was 36 mg/kg bw per day on the basis of poor general state, including mortality and impairment of food consumption and body-weight gain at 150 mg/kg bw per day.

In a range-finding study of developmental neurotoxicity in rats treated by gavage, the NOAEL for systemic toxicity and reproductive performance was 80 mg/kg bw per day on the basis of clinical signs of poor general state and litter loss at 120 mg/kg bw per day. The concentrations of metaflumizone in milk and pup plasma were up to 15 mg/kg and up to 4 mg/kg, respectively. A full study of developmental neurotoxicity was not performed since young rats were not more sensitive than adults to the effects of metaflumizone and no evidence of neurotoxicity was seen in standard studies of toxicity or in studies of acute or subchronic neurotoxicity.

The Z-isomer of metaflumizone (M320I02) was of low acute oral toxicity in rats ( $LD_{50} > 5000$  mg/kg bw) and was not mutagenic in an assay for reverse mutation in bacteria. In a short-term study of toxicity in rats treated by gavage, the NOAEL was 100 mg/kg bw per day on the basis of decreased body-weight gain, reduced motor activity and histopathological findings in mesenteric lymph nodes and adrenal cortex in females at doses of 300 mg/kg bw per day and above.

The main plant and soil metabolite of metaflumizone (Reg. No. 4984051; M320I23), was of low acute oral toxicity in rats ( $LD_{50} > 2000$  mg/kg bw). It was not genotoxic in assays for gene mutation in vitro, but induced chromosomal aberrations in the presence of metabolic activation in vitro. A test for micronucleus formation in mice gave negative results. In a short-term study of toxicity in rats treated by gavage, the NOAEL was 200 mg/kg bw per day on the basis of increased salivation in both sexes and increased relative liver weights and centrilobular hepatocellular hypertrophy in females at 1000 mg/kg bw per day.

An additional soil metabolite of metaflumizone (Reg. No. 43455; M320I29), was not genotoxic in assays for gene mutation and chromosomal aberration in vitro.

There were no reports of adverse health effects in manufacturing-plant personnel. Also, there were no reports of poisonings with metaflumizone.

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

#### *Toxicological evaluation*

The Meeting established an ADI for metaflumizone of 0–0.1 mg/kg bw based on a NOAEL of 12 mg/kg bw per day for clinical signs of poor general state of health, decreased food consumption,

reduced body-weight gain and body-weight loss, and changes in haematological parameters at 30 mg/kg bw per day and above in a 1-year study in dogs, and using a 100-fold safety factor.

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

A toxicological monograph was prepared.

### *Levels relevant to risk assessment*

Species	Study	Effect	NOAEL	LOAEL
Mouse	18-month study of carcinogenicity <sup>a</sup>	Toxicity	250 mg/kg bw per day	1000 mg/kg bw per day
		Carcinogenicity	1000 mg/kg bw per day <sup>c</sup>	—
Rat	Three-month study of toxicity <sup>a</sup>	Toxicity	60 mg/kg bw per day	200 mg/kg bw per day
		Carcinogenicity	200 mg/kg bw per day <sup>c</sup>	—
	Two-year study of toxicity and carcinogenicity <sup>a</sup>	Toxicity	30 mg/kg bw per day	60 mg/kg bw per day
		Carcinogenicity	200 mg/kg bw per day <sup>c</sup>	—
		Fertility	50 mg/kg bw per day	75 mg/kg bw per day
	Multigeneration study of reproductive toxicity <sup>a</sup>	Parental toxicity	20 mg/kg bw per day	30 mg/kg bw per day
		Offspring toxicity	20 mg/kg bw per day	50 mg/kg bw per day
		Developmental toxicity <sup>a</sup>	Maternal toxicity	40 mg/kg bw per day
	Acute neurotoxicity <sup>a</sup>	Embryo- and fetotoxicity	120 mg/kg bw per day <sup>c</sup>	—
		Neurotoxicity	2000 mg/kg bw per day <sup>c</sup>	—
Subchronic neurotoxicity <sup>a</sup>	Neurotoxicity	150 mg/kg bw per day <sup>c</sup>	—	
Developmental neurotoxicity <sup>a</sup>	Maternal toxicity	80 mg/kg bw per day	120 mg/kg bw per day	
	Offspring toxicity	80 mg/kg bw per day	120 mg/kg bw per day	
Rabbit	Developmental toxicity <sup>a</sup>	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Embryo- and fetotoxicity	100 mg/kg bw per day	300 mg/kg bw per day
Dog	One-year study of toxicity <sup>b</sup>	Toxicity	12 mg/kg bw per day	30 mg/kg bw per day

<sup>a</sup> Gavage administration.

<sup>b</sup> Capsule administration.

<sup>c</sup> Highest dose tested.

### *Estimate of acceptable daily intake for humans*

0–0.1 mg/kg bw

*Estimate of acute reference dose*

Unnecessary

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

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

***Critical end-points for setting guidance values for exposure to metaflumizone****Absorption, distribution, excretion and metabolism in animals*

Rate and extent of oral absorption	≤ 17% at 6 mg/kg bw; ≤ 7% at 30 or 1000 mg/kg bw
Distribution	Widely; highest concentrations in fat, liver, kidney, muscle and blood
Rate and extent of excretion	≥ 90% within 168 h for a single dose of ≥ 30 mg/kg bw, mainly via faeces (< 5% in bile), < 3% via urine; elimination half-life, 27–48 h or 139–402 h, depending on position of radiolabel
Potential for accumulation	Evidence of accumulation in fat after repeated exposure (steady state after 21–28 days; terminal half-life, 15–17 days)
Metabolism in mammals	Extensive; hydroxylation (aniline and benzonitrile rings), hydrolysis (hydrazine carboxamide group), conjugation (sulfate, glucuronic acid, glycine, glutathione); in tissues, mainly unchanged parent.
Toxicologically significant compounds (animals, plants and the environment)	Parent compound

*Acute toxicity*

Rat, LD <sub>50</sub> , oral	> 5000 mg/kg bw
Rat, LD <sub>50</sub> , dermal	> 5000 mg/kg bw
LC <sub>50</sub> inhalation	> 5.2 mg/L air (4-h, nose-only exposure)
Rabbit, dermal irritation	Not an irritant
Rabbit; ocular irritation	Not or slightly irritating
Guinea-pig, dermal sensitization	Not sensitizing (Magnussen & Kligman test)

*Short-term studies of toxicity*

Target/critical effect	Decreased food consumption and body-weight gain; clinical signs of poor general state, mortality or premature sacrifice; changes in haematological parameters
Lowest relevant oral NOAEL	12 mg/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	100 mg/kg bw per day (3-month study in rats)
Lowest relevant inhalation NOAEC	0.03 mg/L air (28-day study in rats)

*Genotoxicity*

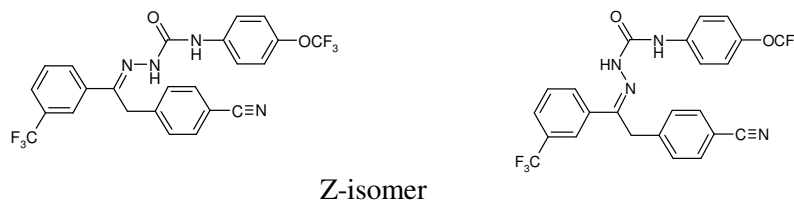
No genotoxic potential

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Liver (hepatocellular hypertrophy, basophilic alteration) in rats; spleen (pigment deposition), decreased body-weight gain in mice		
Lowest relevant NOAEL	30 mg/kg bw per day (2-year study in rats)		
Carcinogenicity	No evidence for carcinogenicity in rats and mice		
<i>Reproductive toxicity</i>			
Reproductive target/critical effect	Reduced male & female fertility in the presence of severe systemic toxicity  Increased incidences of stillborn pups and pup mortality at parentally toxic dose		
Lowest relevant reproductive NOAEL	50 mg/kg bw per day for effects on fertility (two-generation study in rats)  20 mg/kg bw per day for systemic toxicity in parents and offspring		
Developmental target/critical effect	No developmental toxic effects at maternally toxic dose in rats; decreased fetal weights, incomplete ossification of sternebrae at maternally toxic dose in rabbits		
Lowest relevant developmental NOAEL	100 mg/kg bw per day (rabbits)		
<i>Neurotoxicity</i>			
Acute neurotoxicity	No evidence of neurotoxicity; NOAEL: 2000 mg/kg bw (highest dose tested)		
Subchronic neurotoxicity	No evidence of neurotoxicity; NOAEL: 300/150 mg/kg bw per day (highest dose tested; 90-day study in rats)		
<i>Other toxicological studies</i>			
Studies on Z-isomer (M320I02)	Rat, oral LD <sub>50</sub> , > 5000 mg/kg bw;  Rat, 90-day study, NOAEL: 100 mg/kg bw per day (reduced body-weight gain, histopathological changes in lymph nodes and adrenal cortex);  No genotoxic potential		
<i>Studies on metabolites:</i>			
Reg. No. 4984051 (M320I23, plant & soil metabolite)	Rat, oral LD <sub>50</sub> , > 5000 mg/kg bw;  Rat, 90-day study: NOAEL 200 mg/kg bw per day (salivation, increased relative liver weight, hepatocellular hypertrophy);  No genotoxic potential		
Reg. No. 43455 (M320I29, soil metabolite)	No genotoxic potential		
<i>Medical data</i>	Limited data; no adverse health effects reported in manufacturing plant personnel		
<b>Summary</b>			
	<b>Value</b>	<b>Study</b>	<b>Safety factor</b>
ADI	0–0.1 mg/kg bw	Dog; 1-year study	100
ARfD	Unnecessary	—	—

### RESIDUE AND ANALYTICAL ASPECTS

The insecticide metaflumizone is a broad-spectrum semicarbazone composed of two optical isomers in the ratio E:Z of 90:10 and was considered for the first time by the JMPR.



E-isomer

Z-isomer

The manufacturer submitted studies on physical and chemical properties, animal and plant metabolism, environmental fate in soil, rotational crops, analytical methods, freezer storage stability, use patterns, supervised field trials on plants, processing and residues in animal commodities.

#### List of metabolites and degradation products

M3210I04	4-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}benzotrile
M3210I05	trifluoromethoxy aniline
M3210I06	4-cyanobenzoic acid
M3210I07	(EZ)-2-{2-(4-cyanophenyl)-2-hydroxy-1-[3-(trifluoromethylphenyl)ethylidene]-N-[4-(trifluoromethoxy)-phenyl]hydrazinecarboxamide
M3210I08	N-[4-(trifluoromethoxy) phenyl]hydrazinecarboxamide
M3210I09	4-{(2E)-2-hydrazono-2-[3-(trifluoromethyl)phenyl]ethyl} benzotrile
M3210I10	(2S,3S,4S,5R,6R)-6-[2-(4-cyano-phenyl)-1-(3-trifluoromethyl-phenyl)-ethoxy]-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid
M3210I13	glycine conjugate of M3210I06
M3210I22	metaflumizone hydroxylated at the 3-fluoromethoxyphenyl ring
M3210I23	4-{5-hydroxy-3-oxo-4-[4-(trifluoromethoxy)phenyl]-6-[3-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,2,4-triazin-5-yl}benzotrile
M3210I24	glucuronic acid conjugate of M3210I22
M3210I25	4-{2-hydroxy-2-[3-(trifluoromethyl) phenyl]ethyl}benzotrile
M3210I26	2-amino-pentanedioic acid 1-[2-(4-cyano-phenyl)-1-(3-trifluoromethyl-phenyl)-ethyl]ester
M3210I27	metaflumizone hydroxylated at the 3-fluoromethylphenyl ring
M3210I28	N-[4-(trifluoromethoxy) phenyl]acetamide
M3210I29	m-trifluoromethyl benzoic acid

#### Animal metabolism

The Meeting received animal metabolism studies with metaflumizone in rats, lactating goats and laying hens. The metabolism and distribution of metaflumizone in animals was investigated using the trifluoromethoxyphenyl-U-[<sup>14</sup>C] and benzotrile-U-[<sup>14</sup>C]-labelled compound, referred as T- and B-label.

Metaflumizone was found to be metabolised in the rat via hydroxylation of the aniline ring or benzonitrile ring and hydrolysis of the central hydrazine carboxamide group to yield the aniline and phenacylbenzoylnitrile derivatives. The trifluoromethoxyaniline group was shown to conjugate with malonic and oxalic acids. Ring hydroxylated derivatives of metaflumizone were readily conjugated with sulphate or glucuronic acid. Glycine conjugation occurred at the carboxyl group of the cyanobenzoic acid, whereas glutathione conjugation occurred by displacement of one of the fluorine atoms of the trifluoromethyl or trifluoromethoxy groups. Analysis of tissues after a single oral dose revealed that the major residue was unchanged metaflumizone. Evaluation of residues in adipose tissue following repeated dosing demonstrated that unchanged metaflumizone was the only significant residue.

When lactating goats received a nominal oral dose of 12 ppm of [<sup>14</sup>C]metaflumizone for 14 consecutive days in the feed, most of the absorbed radioactive material was excreted through the faeces (66–79%). About 2.5–5% of the initial dose was excreted via urine. Milk accounted for 0.87–1.47% of the initial radioactive dose, though the radioactive concentration in milk increased throughout the application period. TRR were 0.2 mg/kg in milk, 1.3 mg/kg in liver, 0.21 mg/kg in kidney, 0.068 mg/kg in muscle, and 0.73 mg/kg in fat from goats dosed orally with T-label [<sup>14</sup>C]metaflumizone. TRR were 0.53 mg/kg in milk, 2.8 mg/kg in liver, 0.38 mg/kg in kidney, 0.18 mg/kg in muscle, and 2.9 mg/kg in fat from goats dosed orally with B-label [<sup>14</sup>C]metaflumizone. Metaflumizone (sum of E- and Z-isomers) were found to be the major residue in all matrices, with 31–108% TRR (highest level at 3.1 mg/kg in fat). The metabolites M320I04, M320I07, M320I13, M320I23, M320I24, M320I25 and M320I26 were identified in liver. Furthermore, the non-extracted residues of liver (T-label) could be converted into the hydrolysis product M320I28 after mixing with acetonitrile and acetic acid and treated by micro-wave for 30 minutes at 150 °C. M320I24 was identified in kidney.

Metabolism of metaflumizone in goats followed two different paths. One route was cleavage of the molecule at the imine-bridge resulting in the formation of M320I04 and the trifluoromethoxyaniline (M320I05). M320I04 was cleaved, oxidized and conjugated with glycine to M320I13 or reduced and conjugated with glucuronic acid (M320I10) or glutamic acid (M320I26). The main route involved hydroxylation of the parent compound at the trifluoromethoxyaniline ring, followed by conjugation to glucuronic acid. The hydroxylation at the benzyl-position of the molecule was followed by oxidation and ring formation to M320I23. In extracts of edible portions of the goat the parent compound is the main residue.

After 14 consecutive daily oral administrations of [<sup>14</sup>C]metaflumizone at nominal dose level of 12 ppm feed to laying hens, considerable retention in organs and tissues, especially in adipose tissue, was measured. Depending on the label used, radioactivity in eggs amounted to 5.75–6.35% of the total radioactivity administered. The relevant residue in organic extracts of egg, liver, muscle and fat was the parent compound with 56–106% TRR (highest level at 28 mg/kg in fat) in extractable fractions. The metabolite M320I04 was found at low levels (1.5% TRR, 0.042 mg/kg) in extracts of egg and excreta (B-label). Additionally, considerable amounts of the hydroxylated metabolite M320I27 were detected in excreta. The metabolites M320I25 and M320I26 were identified in liver.

Furthermore, the non-extracted residues of liver could be converted into the detectable hydrolysis products M320I28 for T-label and M320I04 for B-label after mixing with acetonitrile and acetic acid and treated by micro-wave for 30 minutes at 150 °C.

The active substance was metabolized in hens via two routes: the cleavage of the molecule at the imine-bridge resulted in the formation of M320I04, which was further converted to M320I25 and M320I26. The hydroxylation of the parent compound at the 3-trifluoro-methylphenyl moiety resulted in the formation of the metabolite M320I27. In edible portions of poultry the parent compound is the main residue.

In summary, the metabolic pathways in rats, goats and poultry were generally similar. Metaflumizone is metabolized in livestock via the following reactions:



- hydroxylation at the 3-trifluoromethylphenyl ring forming M320I27
- hydroxylation at the trifluoromethoxyaniline ring forming M320I22 followed by conjugation to glucuronic acid to form M320I24
- hydroxylation of metaflumizone at the benzyl position to form M320I07 followed by oxidation and ring formation yielding M320I23
- cleavage at the imine bridge, resulting in the formation of M320I04 and a metabolite containing the trifluoromethoxyaniline moiety
- cleavage of M320I04 to form M320I06 which is conjugated with glycine to form M320I13; and/or reduction of M320I04 to form M320I25 which is conjugated with glucuronic acid to form M320I10 or conjugated with glutamic acid to form M320I26.

In edible portions the parent compound is the main residue.

### *Plant metabolism*

Plant metabolism studies were performed on white cabbage (sampling at 0, 3 and 7 days PHI), tomato (sampling at 0 and 7 days PHI) and cotton (sampling at 21 days PHI) using the benzonitrile- and trifluoromethoxyphenyl-U-[<sup>14</sup>C]labelled metaflumizone (B- and T-label). The cabbage study was conducted at 4 × 0.28 kg ai/ha. The rates of application for the cotton and the tomato study (under both field and glasshouse conditions) were 6 × 0.34 kg ai/ha.

In cabbage, TRR were 11.7, 11.2, and 10.0 mg/kg in cabbage leaves harvested 0, 3, and 7 days, respectively, following application of B-label metaflumizone, and 12.4, 11.8, and 11.3 mg/kg in cabbage leaves harvested 0, 3, and 7 days, respectively, following application of T-label metaflumizone. The E- and Z-isomers of metaflumizone were the major identified residues in both B- and T-label cabbage. The E-isomer constituted 60–81% TRR and the Z-isomer 6–18% TRR at 3 or 7 days PHI. The E:Z isomer ratio decreased from the 3 to the 7 day sampling interval. Metabolite M320I04 was also a significant residue identified in B-label cabbage (up to 16% TRR, 2.1 mg/kg). Two additional metabolites, M320I07 and M320I23, were identified as minor residues in cabbage (both labels, maximum of 3.2% TRR).

In tomatoes, TRR were found at up to 0.6 mg/kg for the field (0 day PHI) and 0.78 mg/kg for the glasshouse (0 day PHI). At day 7, residues up to 0.52 mg/kg were found. In field-grown tomatoes, the E- and Z-isomers of metaflumizone were the major identified residues in tomatoes from both labels and both sampling intervals.

In field grown B-label tomatoes, the E- and Z-isomers of metaflumizone, respectively, accounted for 29% TRR (0.17 mg/kg) and 34% TRR (0.20 mg/kg) in the 0 day PHI samples, and in samples from a 7 day PHI 25% TRR (0.083 mg/kg) and 35% TRR (0.12 mg/kg). In T-label tomatoes, the E- and Z-isomers, respectively, accounted for 35% TRR (0.14 mg/kg) and 44% TRR (0.18 mg/kg) from 0 days PHI samples, and 32% TRR (0.096 mg/kg) and 49% TRR (0.15 mg/kg) from 7 day PHI samples. Metabolite M320I04 was also a residue in B-label tomatoes at 12% TRR (0.04–0.08 mg/kg). Two additional metabolites were identified: M320I23 at 2.7–3.6% TRR (0.01–0.02 mg/kg) in B- and T-label samples, and M320I06 at < 1% TRR (0.003–0.004 mg/kg) in B-label samples.

The E- and Z-isomers of metaflumizone were also the major identified residues in tomatoes grown under protected cropping conditions (green-house) from both labels and both sampling intervals. In B-label tomatoes, the E- and Z-isomers, respectively, accounted for 44% TRR (0.35 mg/kg) and 29% TRR (0.22 mg/kg) in samples from a 0 day PHI, and 32% TRR (0.17 mg/kg) and 40% TRR (0.21 mg/kg) in 7 day PHI samples. In T-label tomatoes, the E- and Z-isomers, respectively, accounted for 47% TRR (0.18 mg/kg) and 37% TRR (0.14 mg/kg) in samples from the 0 day PHI, and 38% TRR (0.11 mg/kg) and 45% TRR (0.13 mg/kg) from the 7 day PHI. Metabolite M320I04 was also a residue in B-label tomatoes at 11.5–15.7% TRR (0.06–0.12 mg/kg). Two

additional metabolites were identified: M320I23 at 1–3% TRR (0.007–0.011 mg/kg) in B- and T-label samples, and M320I06 at < 1% TRR (0.003–0.005 mg/kg) in B-label samples.

In cotton seed, TRR were up to 0.37 mg/kg of which 56–64% of them were identified. The E- and Z-isomers of metaflumizone and metabolite M320I04 were the major identified residues, with the E- and Z-isomers accounting for 16.8% TRR (0.063 mg/kg) and 16.9% TRR (0.063 mg/kg), respectively, in B-label cotton seed, and 20.8% TRR (0.029 mg/kg) and 25.6% TRR (0.036 mg/kg), respectively, in T-label cotton seed; metabolite M320I04 was identified at 16.6% TRR (0.059 mg/kg) in B-label cotton seed. Three additional metabolites were identified in cotton seed: M320I23 at 7.1% TRR (0.026 mg/kg) and 8.4% TRR (0.011 mg/kg) in B- and T-label cotton seed, M320I06 at 6.4% TRR (0.024 mg/kg) in B-label cotton seed, and M320I05 at 1.5% TRR (0.002 mg/kg) in T-label cotton seed.

Total radioactive residues were up to 29 mg/kg in cotton gin by-products. The E- and Z-isomers of metaflumizone were the major identified residues, accounting for 19% TRR (5.58 mg/kg) and 29% TRR (8.50 mg/kg), respectively, in B-label gin by-products, and for 26% TRR (4.97 mg/kg) and 38.9% TRR (7.49 mg/kg), respectively, in T-label gin by-products. Three additional metabolites were identified in cotton gin by-products: M320I23 at 6.4% TRR (1.9 mg/kg) and 8.3% TRR (1.6 mg/kg) in B- and T-label samples, and M320I04 and M320I06 at 13.1% TRR (3.83 mg/kg) and 7.2% TRR (2.11 mg/kg) in B-label samples.

In the plant metabolism studies on cabbage, tomato and cotton, the same metabolic pathway was observed. In all plant metabolism studies the parent compound metaflumizone was identified as the most prominent component (E- and Z-isomers; 34–98% TRR; E:Z ratio of about 1:1 to 12:1). The major degradation product is M320I04, accounting for 12–17% of TRR. The cyclic derivative M320I23, arising from M320I07 by ring closure, was detected in concentrations < 10% of TRR in all three plant metabolism studies. M320I07 was only found at low levels in cabbage samples (2–3% of TRR). Metabolite M320I05 also formed by cleavage of the parent compound was only found in cotton seed and in low amounts, accounting for 1.5% of TRR. Metabolite M320I06 is formed by cleavage of M320I04. This metabolite accounted for 7% of the TRR in cotton seed and < 1% in tomato samples. Based on these data, it appears that metaflumizone is metabolized in plants via the following reactions:

- isomerisation of the metaflumizone E-isomer to the Z-isomer,
- cleavage of the parent molecule to form M320I04,
- ring closure to form metabolite M320I23,
- cleavage of M320I23 to form M320I05
- cleavage of M320I23 and/or M320I04 to form M320I06.

### *Environmental fate in soil*

#### *Aerobic degradation*

Two studies were carried out to investigate the degradation of metaflumizone under aerobic conditions. In the first study benzonitrile- and trifluoromethoxyphenyl-U-[<sup>14</sup>C]labelled metaflumizone (B- and T-label) was used. Metaflumizone degraded and mineralized in soil with a DT<sub>50</sub> of 186–209 days. CO<sub>2</sub> (8–29% of total applied radioactivity) and non extracted residues (21–38% of total applied radioactivity) were the major degradation products. Several metabolites were observed, but only metabolite M320I23 exceeded 5% of total applied radioactivity, showing maximum amounts of 7–8% of total applied radioactivity during the incubation period.

In the second study the [<sup>14</sup>C]trifluoromethylphenyl-labelled compound was used to get information on the fate of the third ring system of the metaflumizone molecule. The results show that the parent is slowly degraded in soil with half-lives of 202, 328, and 423 days for the three tested soils, respectively. In all three soils numerous minor metabolites appeared during the course of the study. However, all metabolites detected were formed only in very small amounts and none exceeded 3.8% of the applied radioactivity. The mineralization rate reached 2–15% of the applied radioactivity after 122 days of incubation, whereas the non-extracted residues amounted to 6–13% of the applied radioactivity at the end of the study.

The degradation of metaflumizone in soil is characterized by a breakdown of the molecule leading to several intermediate products representing the various aromatic ring moieties of the parent compound. In all tested soils, in principle the same routes of degradation are followed. Metaflumizone can be oxidized at the benzyl group between the trifluoromethylphenyl ring and the benzonitrile ring (M320I07), which further leads to the cyclic product (M320I23). Metaflumizone can also split up into two moieties, one representing the trifluoromethoxyphenyl ring (M320I08 or M320I05), the other one still consisting of benzonitrile and trifluoromethylphenyl ring (M320I09 or M320I04). The two aromatic rings in metabolites M320I09 and M320I04 can be split up forming the single ring structures M320I29 (trifluoromethyl benzoic acid) and M320I06 (cyano benzoic acid). All intermediates are further degradable to finally form CO<sub>2</sub> and non-extracted residues.

#### *Rotational crops*

A field-based rotational crop study was not conducted. Two confined rotational crop metabolism studies were undertaken to consider the uptake of residues in rotational crops. Both studies were conducted using B- and T-label [<sup>14</sup>C]metaflumizone applied to bare soil. The first study involved considering a range of replanting intervals, where rotational lettuce, radish, and spring wheat were planted 30, 60/62, 120, and 365 days after treatment. The application rate of the first study was 2 × 0.56 kg ai/ha/application (20 days between applications). The second study involved a 30 days replant interval only, and a single application of 1.2 kg ai/ha, and again lettuce, radish and spring wheat were planted.

For all plant back intervals (PBI) of the first study, the residue levels in lettuce leaf were very low and remained at the same level (≤ 0.01 mg/kg). The concentration of TRR in radish leaves and roots were only slightly higher (max. 0.036 mg/kg) than in lettuce and declined with subsequent plant back periods. In the wheat matrices hay and grain the initial TRR values were clearly higher, with highest values in wheat hay of 0.67 mg/kg and in grain of 0.17 mg/kg, but they also declined with longer PBI. In wheat straw, the initial TRR (0.11–0.14 mg/kg) were higher than in lettuce, radish and wheat forage at a PBI of 30 days. The TRR in straw increased in the 60 day PBI (0.24–0.27 mg/kg) and declined again in the samples at 120 (0.11–0.12 mg/kg) and 365 PBI (0.04–0.05 mg/kg). There were no major differences in radioactivity levels between the two labels.

In the second rotational crop metabolism study, TRR were comparable in both labels, with the exception of wheat straw and grain, where the B-label showed higher residues. The TRR in lettuce leaf were low (0.02 mg/kg) and had a range similar to radish roots (0.01 mg/kg), but were slightly higher in radish leaves (0.04 mg/kg). In wheat matrices, residues were generally higher than in other matrices with highest values in wheat hay (0.8 mg/kg). In grain and straw, TRR of 0.04 and 0.1 mg/kg were found. The extractability of the different matrices (with the exception of grain) had a range of 54–95% TRR. In grain samples only 11–15% of TRR was extractable.

In the second study, HPLC analysis of the methanol extracts showed that the unchanged parent compound was present in all matrices (with the exception of wheat grain) as a minor component of the radioactive residue with levels of < 0.001–0.015 mg/kg. In radish roots and wheat grain, the radioactivity was mainly in the polar region. In all other matrices, the metabolite patterns of the methanol extracts were quantitatively comparable. The radioactivity was divided into a range of peaks, mainly in the polar and medium polar fraction. M320I04 and M320I06 could be identified as minor components in the radioactive residues. HPLC analysis of all other extractable radioactive

residues showed that these split up in a variety of polar and medium polar peaks that can all be considered as minor. Bound residues that could be released by treatments with aqueous ammonia solution, NaOH and different enzymes also split up in various fractions with TRR at a maximum level of 0.014 mg/kg.

The data submitted on rotational crop metabolism suggest there are no residues of significance that are expected to arise in crops planted in the rotation following primary crop use of metaflumizone according to GAP. Besides the parent, two other metabolites, M320I04 and M320I06, could be detected in low levels (< 5% TRR).

### *Environmental fate in water-sediment systems*

#### *Hydrolysis*

In the hydrolysis study with [<sup>14</sup>C]metaflumizone conducted using sterile buffer solutions at 25 °C, the hydrolytic half-lives were found to be about 6 days at pH 4 and about 27–31 days at pH 5. No degradation of metaflumizone occurred in the pH 7 and pH 9 buffer solutions. At pH 4 and pH 5, the hydrolysis products M320I04 and M320I08 were identified, reaching maximum amounts of up to 90% and 68% TAR, respectively. A number of minor unidentified components were also detected (individually mostly < 5%).

#### *Photolysis*

The results showed that metaflumizone is extensively degraded in water under photolytic conditions. A DT<sub>50</sub> value of 2–3 days of continuous irradiation was calculated. Isomerisation of the metaflumizone E-isomer to the Z-isomer occurred. There were several major and minor photoproducts appearing in the water phase identified as M320I04, M320I06, M320I09, and M320I08, representing the different ring moieties of the parent after cleavage of the molecule. One degradation product, M320I05, proved to be volatile and was trapped in the ethylene glycol trapping solution. Additionally, numerous minor non-identified photoproducts (n > 50) were formed. With both B- and T-label it was shown that even under sterile conditions, metaflumizone was completely degraded forming finally CO<sub>2</sub>.

### *Methods of analysis*

Metaflumizone and its metabolites M320I04 and M320I23 are extracted from the following plant matrices; white cabbage, tomato, cotton seed, lettuce, potato tuber, lemon, gin trash, wheat grain and potato crisps using a mixture of methanol and water. For clean-up a liquid/liquid partition against dichloromethane was used. The final determination of metaflumizone, M320I04 and M320I23 was performed by HPLC-MS/MS. For cotton seed no clean-up was done.

The LC-MS/MS method of analysis for a range of plant products was acceptably validated as method 531/0 over the concentration range of 0.01 to 0.1 mg/kg. Independent laboratory validation (ILV) data were available as method 531/1 and the individual recoveries were all within a good range.

The LC-MS/MS method of analysis of metaflumizone (E- and Z-isomer) for animal products as muscle (bovine, hen), liver (bovine, hen), kidney (bovine) and fat (bovine) together with intra-laboratory validation was acceptably validated as method 528/0 over the concentration range 0.01 to 0.20 mg/kg. The methods for the determination of metaflumizone (E- and Z-isomer) in bovine milk and hen eggs were validated over the concentration range 0.005 to 0.10 mg/kg.

In general, for residues methods of analyses in plants and animal products, the following criteria were fulfilled:

- adequate limit of quantification

- mean recovery 70–110%
- relative standard deviation of recovery rates < 20%
- interfering blanks lower than 30% of the limit of quantification

The GC-MS multiresidue method DFG method S19 was tested for both the E- and the Z-isomer and was found not to be applicable to the analysis of metaflumizone.

### *Stability of residues in stored analytical samples*

The Meeting received information on the storage stability of residues in extracts available from metabolism studies, in fortified samples and incurred residues.

Extracts available from metabolism studies in lactating goats, laying hens, white cabbage and tomatoes were used to estimate the stability of [<sup>14</sup>C]metaflumizone residues in stored analytical samples. It was shown, that the chromatographic pattern of the stored extract was comparable with the pattern of the first extract. It can be concluded that residues are stable in methanol extracts of animal matrices (eggs, milk, liver, kidney, muscle and fat) and in plant matrices (methanol extracts of white cabbage, acetonitrile extracts of tomato) for at least 18 and 12 months, respectively.

The Meeting received information on the stability of metaflumizone E- and Z-isomer, M320I04 and M320I23 in fortification experiments on tomato, cotton seed, potato, white cabbage and lettuce at –20 °C in the dark.

Both isomers of the parent were stable for up to two years in potato tuber, white cabbage and lettuce. Storage stability for one year was demonstrated for the metaflumizone E-isomer in tomato and the E- and Z-isomer in cotton seed. The metaflumizone Z-isomer was unstable in tomatoes stored for greater than 28 days.

For the metabolite M320I04, freezer storage stability was adequately demonstrated in tomato and cotton seed but not in potato, white cabbage and lettuce. The calculation of the 70% stability for potato, white cabbage and lettuce gave results of 23, 15 and 2 days respectively.

For the metabolite M320I23, freezer storage stability was adequately demonstrated in tomato, cotton seed, potato, white cabbage and lettuce for one year.

Incurred residues of the E-isomer of metaflumizone were stable at –20 °C in the dark in tomatoes, cabbage, broccoli, lettuce, celery and mustard greens for at least one year. The metaflumizone Z-isomer was stable in cabbage, broccoli, lettuce, celery and mustard greens for at least 290 days. In tomatoes there was a loss of the parent Z-isomer, but an increase in concentration of M320I04 was noted, indicating a possible degradation of parent to M320I04.

### *Definition of the residue*

#### *Plants*

The main residues found in the crop metabolism studies are the E- and Z-isomers of metaflumizone. In tomatoes, the metabolite M320I04 constituted up to 16% TRR in the fruit. This metabolite was also found in cotton seed and cabbage at up to 17% of TRR. Other metabolites were found in lower amounts, e.g., M320I23 was found at up to 8% TRR in the cotton study, up to 4% TRR in tomatoes, and up to 1% TRR in cabbage.

In metabolism studies and residues trials, where positive residues were found, evidence of isomerisation from the E- to the Z-isomer was shown. As a consequence both isomers should be included into the residue definition.

The metabolite M320I23 was not identified in the rat metabolism study done with metaflumizone. A separate toxicity study of metabolite M320I23 shows that it is of lower toxicity than the parent. Residues of M320I23 were consistently absent in supervised residue trials but were found in the outer leaves of cabbage at 0.02 to 0.06 mg/kg. This was about 0.5% of the applied concentration of metaflumizone. Because of its general absence, it was concluded that this component does not need to be accommodated in the residue definition.

The metabolite M320I04 was identified in the rat metabolism study done with metaflumizone and its toxicity is covered by the derived ADI. Storage stability studies with incurred metaflumizone residues indicate that the concentration of M320I04 may increase during freezer storage, but the concentrations were at low levels. M320I04 was not detected in most of the supervised residue trials. However, in processing studies on tomatoes it was found in juice, purée, paste and wet pomace in equal or higher concentrations than the parent. Based on the very low or non-detectable residues of M320I04 in samples of supervised residue trials, this component does not need to be taken into account in the residue definition for enforcement and dietary risk assessment. However, the Meeting was aware, that the metabolite M320I04 may arise in processed products from acidic raw agricultural commodities in concentrations that may be of interest for dietary intake estimation. This should be taken into account for future uses.

### *Animals*

The main residues found in the farm animal metabolism studies are the E- and Z-isomers of metaflumizone. Both isomers should be included into the residue definition.

The component that was identified in liver hydrolysates in the highest amount was M320I28 at 9% TRR (0.11 mg/kg) for goat and 18% TRR (0.66 mg/kg) for hen. As this component was only built under strong hydrolysis its inclusion in the residue definition was considered unnecessary.

The octanol/water coefficient ( $\log P_{ow}$ ) of 4.4 for the Z-isomer and 5.1 for the E-isomer, and the distribution of residues between muscle and fat in metabolism studies indicate that the residue is fat soluble.

The Meeting recommended the following residue definition:

Definition of the residue for compliance with MRLs and estimation of dietary intake for plants and animals: *Metaflumizone, sum of E-isomer and Z-isomer.*

The residue is fat-soluble.

### ***Results of supervised residue trials on crops***

The Meeting received supervised trials data for the foliar application of metaflumizone as a suspension concentrate formulation (SC) to a variety of fruit, and vegetable crops. The Meeting also received supervised trials data for the application of a granular bait (GB) formulation to the soil of citrus orchards, grape vineyards, and tree nut orchards.

The NAFTA calculator was used as a tool in the estimation of maximum residue levels from the selected residue data set obtained from trials conducted according to GAP. As a first step, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level. Then, the NAFTA calculator was employed. If the statistical calculation spreadsheet suggested a different value from that recommended by the JMPR, a brief explanation of the deviation was supplied. Some common factors that may lead to rejection of the statistical estimate include when the number of data points in a data set is < 15 or when there are a large number of values < LOQ.

*Citrus*

Trials from the USA on grapefruit, lemons, and oranges were reported for soil treatment using a granular formulation to control fire ants. However, the GAP/label had not been approved by the national authority as of the time of the current Meeting. As there was no GAP provided to support the trials, the Meeting could not estimate a maximum residue level for citrus.

*Berries and others small fruits*

Trials from the USA on grapes were reported for the application to the soil of a granular formulation. However, the GAP/label had not been approved by the national authority as at the time of the current Meeting. As there was no approved GAP provided to support the trials, the Meeting could not estimate a maximum residue level for berries and other small fruits.

*Brassica vegetables*

Trials for the foliar application of an SC formulation of metaflumizone to head cabbage were reported for the USA, Japan, Germany, Denmark, Spain, France, United Kingdom, Greece, Sweden, and China. The proposed GAP has been withdrawn in the USA.

No label was presented for Japan, and the trials are evaluated against the GAP of Taiwan ( $3 \times 0.029$  kg as/hL, SC, 9 day PHI). The ranked order of residues from the Japan trials (n=4) were: 0.19, 0.20, 0.21, 0.25 mg/kg.

The GAP was made available for use on cabbage for Italy ( $2 \times 0.24$  kg ai/ha or  $2 \times 0.024$  kg as/hL, SC, 3 day PHI) and Macedonia ( $4 \times 0.24$  kg ai/ha or  $4 \times 0.06$  kg as/hL, SC, PHI not specified). Using the GAP of Italy, the ranked order of residues in the southern European trials (n=4) were:  $< 0.02$  (2), 0.05, 0.06 mg/kg. The ranked order of residues in the northern European trials (n=8) were:  $< 0.02$  (2), 0.04, 0.06, 0.08, 0.15, 0.39, 0.48 mg/kg. The trials from the North and the South do not appear to be from the same populations and should not be combined. Four trial results (from the South and under the GAP of Italy) were not considered sufficient to estimate a maximum residue level for cabbage.

The GAP for use on cabbage in China is  $3 \times 0.29$  kg ai/ha or  $3 \times 0.048$  kg as/hL, SC, 3 day PHI. The residue values in ranked order (n=4) were: 4.5, 4.7, 4.9, 5.5 mg/kg. Four trial results were not considered sufficient to estimate a maximum residue level for cabbage.

Trials were reported from the USA for the foliar application of an SC formulation to broccoli. However, the proposed GAP/label has been withdrawn in the USA. Trials were also presented from Belgium, United Kingdom, France, Germany, Italy, and Spain. No label/GAP was available for a European country.

Trials were reported from Taiwan for Chinese Broccoli. The ranked order of trial results for trials conducted according to the maximum GAP of Taiwan, China ( $3 \times 0.20$  kg as/hL, SC, 9 day PHI) is: 1.2, 1.3 mg/kg. The Meeting considered two trials insufficient for the estimation of a maximum residue level and STMR.

Trials were reported for Brussels sprouts from Germany, Spain, France, Sweden, Italy, the United Kingdom, and the Netherlands. A label was available for Italy ( $2 \times 0.24$  kg ai/ha, SC, 3 day PHI). Four trials were conducted in the southern Europe (0.10, 0.12, 0.35, 0.39) mg/kg, and eight trials were conducted in the northern Europe (0.07 (2), 0.10, 0.11, 0.13, 0.16, 0.22, 0.60 mg/kg). The data sets are not from different populations and could be combined for evaluation against the GAP of Italy. The residue values (n=12) in ranked order were: 0.07 (2), 0.10 (2), 0.11, 0.12, 0.13, 0.16, 0.22, 0.35, 0.39, 0.60 mg/kg.

The Meeting estimated an STMR of 0.125 mg/kg. The Meeting estimated a maximum residue level of 0.8 mg/kg. The maximum residue level estimate derived from use of the NAFTA calculator was 0.76 mg/kg. The normal JMPR procedure is to use one significant figure for maximum residue

levels below 10 mg/kg. With rounding the value derived from use of the calculator corresponded to the Meeting's recommendation, i.e., 0.8 mg/kg rounded.

#### *Fruiting vegetables, Cucurbits*

Melon field trials were reported from Greece and Spain. No label/GAP is available for melons or cucurbits. As there was no GAP provided to support the trials, the Meeting could not estimate a maximum residue level for melons.

#### *Fruiting vegetables other than Cucurbits*

Chilli pepper field trials were reported from South Korea and the USA. However, the proposed label in the USA has been withdrawn. The ranked order of trials from South Korea that approximate the maximum GAP of South Korea ( $3 \times 0.016$  kg as/hL, SC, 2 day PHI) was: 0.10 and 0.12 mg/kg. The Meeting noted that two trials were insufficient to estimate a maximum residue level, HR, and STMR.

Field trial studies for peppers (bell or sweet) were reported from the USA. However, the proposed label in the USA was withdrawn.

Glasshouse trial studies on peppers were reported from Germany, the Netherlands, France, Italy, Spain, and Greece. Relevant labels were available for Germany, Italy, and Austria. The labels specify  $2 \times 0.024$  kg as/hL, 3 day PHI in Germany and Italy, 1 day PHI in Austria. Residue data for a 1 day PHI were not supplied. The GAPs of Germany and Italy were utilized, and the residue values in ranked order (n=15) were: 0.10 (2), 0.16, 0.18 (5), 0.24 (2), 0.30, 0.34 (2), 0.35 (2) mg/kg.

The Meeting estimated a STMR of 0.18 mg/kg. The Meeting estimated a maximum residue level of 0.6 mg/kg. The maximum residue level estimate derived from use of the NAFTA calculator was 0.56 mg/kg. The normal JMPR procedure is to use one significant figure for maximum residue levels below 10 mg/kg. With rounding, the value derived from use of the calculator corresponded to the Meeting's recommendation, i.e., 0.6 mg/kg rounded.

Tomato field trial studies were reported from the USA. However, the proposed label in the USA has been withdrawn.

Tomato field trial studies were reported from Spain and Italy. The GAP/label of Italy specifies  $2 \times 0.24$  kg ai/ha, SC, and a 3 day PHI. The ranked order of trial results (n=10) were: 0.03 (4), 0.04 (2), 0.07, 0.10 (2), 0.14 mg/kg.

Tomato glasshouse studies were reported from Germany, the Netherlands, Spain, France, Italy, and Greece. Labels for use in glasshouses were available from Austria, Germany, and Italy. All specify  $2 \times 0.24$  kg ai/ha. There is a 1 day PHI in Austria and a 3 day PHI in Germany and Italy. Residue data were not available for a 1 day PHI. The labels for Germany and Italy were utilized to arrive at the ranked order of residue values (n=10) of: < 0.02, 0.08, 0.09, 0.10, 0.11, 0.13 (2), 0.17, 0.25, 0.36 mg/kg. The Meeting noted that the tomatoes from glasshouses generated a higher residue value set than those from field trials in Europe.

Using the glasshouse trials from Europe, the Meeting estimated an STMR of 0.18 mg/kg. Noting the similarity of the residue populations for peppers and tomatoes, the Meeting estimated a maximum residue level of 0.6 mg/kg was appropriate for tomatoes.

The maximum residue level estimate derived from use of the NAFTA calculator was 0.69 mg/kg. The normal JMPR procedure is to use one significant figure for maximum residue levels below 10 mg/kg. With rounding the value derived from use of the calculator was 0.7 mg/kg rounded. The Meeting noted the similarity of the tomato and pepper data sets and the 0.6 mg/kg estimate for peppers was selected for tomatoes



The Meeting agreed to use the tomato and pepper data as support for egg plant (aubergine) and estimated a STMR and a maximum residue level of 0.18, and 0.6 mg/kg, respectively, for egg plant.

Using the default dehydration factor of 10, the meeting estimated an STMR of 1.8 and a maximum residue level of 6 mg/kg for dried chilli peppers.

#### *Leafy vegetables*

Chinese cabbage field trials were reported from Japan, South Korea, and Taiwan, China. No label was available for Japan, and the Japanese trials were evaluated against the label of Taiwan ( $3 \times 0.029$  kg as/hL, SC, 18 day PHI). Results in ranked order are: < 0.10 (2), 0.76, 0.77 mg/kg. Two trials from Taiwan match the Taiwan label: 1.4, 1.6 mg/kg. One trial from South Korea matches the South Korea label ( $2 \times 0.016$  kg as/hL, 7 day PHI): 2.1 mg/kg. The trials matching Taiwan GAP were combined: < 0.10 (2), 0.76, 0.77, 1.4, 1.6 mg/kg. The Meeting utilized the trials from Japan and Taiwan to estimate an STMR of 0.765. The Meeting estimated a maximum residue level of 6 mg/kg appropriate.

The maximum residue level estimate derived from use of the NAFTA calculator was 5.97 mg/kg. With rounding the value derived from use of the calculator corresponded to the Meeting's recommendation, i.e., 6 mg/kg.

Field trial studies were reported from the USA for lettuce, spinach, and mustard greens. However, the proposed labels in the USA had been withdrawn.

Trials for head lettuce were reported from the Netherlands, Spain, Germany, France, Greece, Denmark, and Italy. A label was available for Italy ( $3 \times 0.24$  kg ai/ha, SC, 3 day PHI). The residue values in ranked order (n=8) for the trials from southern Europe were: 0.76, 1.8, 2.7, 2.8, 3.0 (2), 3.6, 5.0 mg/kg. The residue values in ranked order (n=8) for trials from northern Europe were: 1.0, 1.2, 1.4, 1.5, 1.7, 2.0 (3). The Meeting agreed that the data from the northern and southern European trials appear to be from similar populations and could be combined (n=16): 0.76, 1.0, 1.2, 1.4, 1.5, 1.7, 1.8, 2.0 (3), 2.7, 2.8, 3.0 (2), 3.6, 5.0 mg/kg.

Trials for head lettuce grown in glasshouses were reported from Germany, France, the Netherlands, Italy, Greece and Spain. However, the only available approved label, from Italy, specified field use only.

The Meeting estimated an STMR of 2.0 mg/kg for head lettuce based on the field trials in Europe. The Meeting estimated a maximum residue level of 7 mg/kg. The maximum residue level estimate derived from use of the NAFTA calculator was 6.24 mg/kg. With rounding the value derived from use of the calculator was 7 mg/kg.

#### *Legume vegetables*

The Meeting received a field trial study report for soya beans from Taiwan, China. However, only two trials were reported (0.30, 0.45 mg/kg) conducted at the maximum GAP of Taiwan (0.033 kg as/hL, 15 day PHI). The Meeting considered two trials an insufficient number for the estimation of a maximum residue level, HR, and STMR.

#### *Root and tuber vegetables*

Potato field trial studies were reported from the USA. However, the pending label has been withdrawn.

Potato field trial studies were reported from the United Kingdom, the Netherlands, Spain, Germany, France and Italy. Relevant labels were provided for Austria, Croatia, Germany, Hungary, Italy, Macedonia, Romania and Serbia. The application rate is 0.06 kg ai/ha (except in Macedonia at 0.072 kg ai/ha) and 2 treatments (except 3 in Italy and 4 in Macedonia), and a PHI of 14 days (except

3 days in Romania and not specified in Hungary and Germany). Using the GAP of Italy, the residue values in ranked order were: < 0.02 (11) mg/kg. One trial conducted at an exaggerated rate ( $3 \times 1$  kg ai/ha) also yielded < 0.02 mg/kg. It was also noted that in thirty-three trials conducted in the USA at  $4 \times 0.3$  kg ai/ha, PHI 7 days, all residue values were < 0.02 mg/kg. Samples from four of these trials were < 0.02 mg/kg at a 1 day PHI. Four trials were conducted in the USA at a total seasonal rate of 5.8 kg ai/ha ( $4 \times 1.45$  kg ai/ha). Two of the trials revealed the E and/or Z isomer at 0.01 mg/kg each.

The Meeting estimated an STMR of 0 and a maximum residue level of 0.02(\*) mg/kg for potato.

The use of the NAFTA statistical calculation spreadsheet was not considered applicable as all data points were below the LOQ.

#### *Stalk and stem vegetables*

A report on celery field trials was received from the USA. However, the proposed label in the USA has been withdrawn. As there was no GAP provided to support the trials, the Meeting could not estimate a maximum residue level for celery.

#### *Tree nuts*

A report on almond and pecan field trials was received from the USA, for the application of a granular formulation to the soil. However, the label is pending in the USA at the time of this Meeting. As there was no approved GAP available to support the trials, the Meeting could not estimate a maximum residue level for tree nuts.

#### *Cotton seed*

Study report on cotton field trials in the USA, Spain and Greece were available. However, the relevant pending label in the USA has been withdrawn and no additional approved labels were made available. As there was no GAP information available to support the trials, the Meeting could not estimate a maximum residue level for cotton seed.

#### ***Fate of residues during processing***

A nature of the residue under simulated processing conditions study was received. Hydrolyses of benzonitrile ring-U-[<sup>14</sup>C]metaflumizone and trifluoromethoxyphenyl ring-U-[<sup>14</sup>C]metaflumizone were conducted at 90 °C in pH 4 aqueous buffer for 20 minutes (pasteurization simulation), at 100 °C in pH 5 aqueous buffer for 60 minutes (baking, brewing, boiling simulation), and at 120 °C in pH 6 aqueous buffer for 20 minutes (sterilization simulation). Metaflumizone was not stable at pH 4 and pH 5 (90 °C–100 °C). Metaflumizone loss was as much as 40%. The hydrolysis products were M320I04 and M320I08.

Processing studies were provided for tomato, cabbage, lettuce, potato, and cotton seed. The potato processing studies could not be used to derive processing factors, as the RAC contained no residues above LOQ and all processed fraction residues were below the LOQ.

The processing factors and the derived STMR-P and HR-P values relevant to proposed maximum residue levels are summarized as follows:

RAC	Processed Commodity	Processing Factor <sup>a, b</sup>	RAC maximum residue level	RAC STMR	Processed Commodity STMR-P
Tomato	Juice	< 0.33 < 0.14	0.6	0.125	0.020

RAC	Processed Commodity	Processing Factor <sup>a, b</sup>	RAC maximum residue level	RAC STMR	Processed Commodity STMR-P
		< 0.19 < 0.046			
	Wet pomace	Median 0.16 1.5 2.4 3.1 1.1	0.6	0.125	0.25
	Puree	Median 2.0 0.48 0.20 0.42 0.23	0.6	0.125	0.040
	Paste	Median 0.32 1.5 0.80 0.89 0.54	0.6	0.125	0.10
	Canned	Median 0.84 < 0.33 < 0.14 < 0.19 < 0.046	0.6	0.125	0.020
		Median 0.16			

<sup>a</sup> Each value represents a separate study. The factor is the ratio of the total residue in the processed item divided by the total residue in the RAC. The total residue is the parent metaflumizone (E isomer + Z isomer).

<sup>b</sup> Processing studies were conducted for potatoes. However, RAC samples were at or below the LOQ (0.04 mg/kg), and no residues were found in any processed commodity (< 0.04 mg/kg).

**Residues in animal commodities**

The Meeting received reports of lactating cow and laying hen feeding studies.

*Laying hens*

Hens were dosed orally for 55 days at levels of 0.1, 0.3, and 1 ppm based on feed consumption. Residues reached a plateau in eggs between day 21 and day 25. For the 0.1 ppm feeding regime, total residues of metaflumizone in eggs, muscle, liver, and fat at day 55 were 0.038–0.061 mg/kg, < 0.02–0.021 mg/kg, 0.029–0.033 mg/kg, and 0.30–0.34 mg/kg, respectively. Residue levels were approximately linear with dose.

*Lactating dairy cattle*

Holstein cows were dosed orally for 45 days at levels of 0.2, 1.0, 5.5, and 16.2 ppm in the feed. Total metaflumizone residues were below the LOQ (< 0.01) in whole milk at the 0.2 and 1.0 ppm feeding levels. Cream (Day 40) from the 1.0 ppm level contained 0.047–0.052 mg/kg metaflumizone (E + Z).

At the 5.5 ppm feeding level, metaflumizone in milk reached a plateau of 0.02–0.03 mg/kg between day 21 and day 25. Liver, kidney, and muscle contained no residue (< 0.02 mg/kg) at the 0.2, 1.0, and 5.5 ppm levels; fat contained residue at the LOQ (0.02 mg/kg) at the 1.0 ppm level. At the 5.5 ppm feeding level, residues were 0.12–0.18 mg/kg in fat.

### *Estimated maximum and mean dietary burdens of farm animals*

Dietary burden calculation results for beef cattle and dairy cattle are provided below. The calculations are in Annex 6 and were made according to the animal diets from Canada-USA, EU, and Australia in the Table of OECD Feedstuffs Derived from Field Crop (Annex 6 of the 2006 JMPR Report).

There are no potential poultry feed items. Potential cattle feed items include: potato culls and pulp and waste, and tomato pomace.

		Animal dietary burden, metaflumizone total residue, ppm of dry matter diet		
		US-Canada	EU	Australia
Beef cattle	max	0.00	0.00	0.13 <sup>a</sup>
	mean	0.00	0.00	0.13 <sup>b</sup>
Dairy cattle	max	0.00	0.00	0.13 <sup>a</sup>
	mean	0.00	0.00	0.13 <sup>b</sup>

<sup>a</sup> Highest maximum beef or dairy cattle dietary burden suitable for maximum residue level estimates for mammalian meat and milk.

<sup>b</sup> Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat and milk.

### *Animal commodity maximum residue levels*

#### *Cattle*

In the table below, dietary burdens are shown in round brackets (), feeding levels and residue concentrations from the feeding study are shown in square brackets [], and estimated concentrations related to the dietary burdens are shown without brackets.

Dietary Burden (ppm) Feeding Level [ppm]	Cream	Milk	Muscle	Liver	Kidney	Fat
MRL	Mean	Mean	Highest	Highest	Highest	Highest
MRL beef cattle (0.13) [ 0.2]			0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]
MRL dairy cattle (0.13) [ 0.2]	0.0065 [< 0.01]	0.0065 [< 0.01]	0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]
STMR	Mean	Mean	Mean	Mean	Mean	Mean
STMR beef cattle (0.13) [0.2]			0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]
STMR dairy Cattle (0.13) [0.2]	0.0065 [< 0.01]	0.0065 [< 0.01]	0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]	0.013 [< 0.02]

The data from the lactating dairy cow feeding study was used to support mammalian (except marine) milk and meat maximum residue levels.

The Meeting estimated the following STMR values: milk 0.007; milk fat 0.013; muscle 0.013; edible offal 0.013; fat 0.013 mg/kg. Cream was assumed to contain 50% fat.

The Meeting estimated the following maximum residue levels for mammalian commodities (except marine): milk 0.01(\*); milk fat 0.02; meat (fat) 0.02(\*); edible offal 0.02(\*).

## **DIETARY RISK ASSESSMENT**

### ***Long-term intake***

The International Estimated Daily Intakes of metaflumizone, based on the STMRs estimated for the 12 commodities, for the 13 GEMS/Food Consumption Cluster Diets, were in the range 0–1% of the maximum ADI of 0.1 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of metaflumizone from uses that have been considered by the JMPR is unlikely to present a public health concern.

### ***Short-term intake***

The 2009 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of metaflumizone residues is unlikely to present a public health concern.

